FORMULARY SUBMISSION DOSSIER
FOR
LATUDA® (LURASIDONE HCL) TABLETS

Prepared by:
Sunovion Pharmaceuticals Inc., a U.S. subsidiary of Dainippon Sumitomo Pharma Co. Ltd.
March 2012

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 10
1. EXECUTIVE SUMMARY 14
1.1. Clinical Benefits 14
1.1.1. Pharmacology 15
1.1.2. Humanistic Benefits 15
1.2. Economic Benefits 16
1.2.1. CVD Incidence Related Cost-Consequence Model 16
1.2.2. Relapse and Relapse-related Hospitalization Cost Model 16
1.2.3. Budget Impact Model 17
1.3. Conclusions 17
2. PRODUCT INFORMATION AND DISEASE DESCRIPTION 19
2.1. Product Description 20
2.1.1. Generic Name, Brand Name, and Therapeutic Class 20
2.1.2. Dosage Forms, Including Strengths and Package Sizes 20
2.1.3. National Drug Code (NDC) for All Formulations 21
2.1.4. Copy of the Official Product Labeling/Literature 21
2.1.5. Average Sales Price (ASP), Wholesale Acquisition Cost (WAC), and Payers' Contract Price 21
2.1.6. American Hospital Formulary Service (AHFS) or Other Drug Classification 21
2.1.7. Indications and Usage 21
2.1.8. Other Potential Indications and Off-Label Use 22
2.1.9. Pharmacology 22
2.1.10. Pharmacokinetics/Pharmacodynamics 22
2.1.11. Contraindications 22
2.1.12. Warnings/Precautions/Adverse Events 22
2.1.13. Instructions 22
2.1.14. Dosing and Administration 22
2.1.15. Access 22
2.1.16. Co-Prescribed/Concomitant Therapies 22
2.1.17. Comparison of Select Prescribing Information for Lurasidone, Aripiprazole, Olanzapine, Quetiapine XR, and Asenapine 22
2.2. Place of Product in Therapy 68
2.2.1. Disease Description 68
2.2.2. Approaches to Treatment 71

2.2.3. Relevant Treatment Guidelines and Consensus Statements 74
2.2.4. Evidence for Pharmacogenomic Tests and Drugs 75
3. SUPPORTING CLINICAL EVIDENCE 76
3.1. Overview of Key Clinical Efficacy and Safety Studies 77
3.1.1. Methodological Overview of D1050006, D1050049, D1050196, D1050229, D1050231, D10502333 82
3.1.2. Results of Completed Short-term Lurasidone Safety and Efficacy Trials 85
3.1.3. Results of Longer-term Studies 116
3.1.4. Ongoing Lurasidone Clinical Trials 143
3.2. Clinical Evidence Table Spreadsheets 145
3.2.1. Short-Term (6-week) Studies 145
3.2.2. Longer-term Studies 157
4. ECONOMIC VALUE AND MODELING REPORTS 167
4.1. CVD Incidence Related Cost-Consequence Model 168
4.1.1. Overview and Objectives 168
4.1.2. Model Type and Time Horizon 168
4.1.3. Methodological Overview 168
4.1.4. Model Structure 168
4.1.5. Patient Characteristics 169
4.1.6. Cardiometabolic Treatment Effect 170
4.1.7 Cardiometabolic Events 171
4.1.8 Costs 171
4.1.9 Assumptions 172
4.1.10 Results: Base Case Analysis 173
4.1.11 Results: Sensitivity Analyses 175
4.1.7. Limitations 180
4.1.8. Discussion and Conclusions 181
4.2. Relapse and Relapse-Related Hospitalization Cost Model 182
4.2.1. Model Overview and objectives 182
4.2.2. Methods 182
4.2.3. Model Structure 182
4.2.4. Treatment Options 183
4.2.5. Patient Population 183
4.2.6. Perspective and Time Horizon 184
4.2.7. Model Inputs 184

4.2.8. Calculation of Model Outcomes 186
4.2.9. Sensitivity Analysis 187
4.2.10. Assumptions 187
4.2.11. Results 187
4.2.12. Univariate Sensitivity Analysis 190
4.2.13. Strengths & Limitations 195
4.2.14. Discussions and Conclusions 195
4.3. Budget Impact Model 196
4.3.1. Overview and Objectives 196
4.3.2. Methodological Overview 196
4.3.3. Model Structure 196
4.3.4. Population Inputs 197
4.3.5. Market Dynamics 198
4.3.6. Drug Treatment Costs 198
4.3.7. Model Assumptions 199
4.3.8. Results 199
4.3.9. Limitations 200
4.3.10. Conclusions 201
5. OTHER SUPPORTING EVIDENCE 202
5.1. Early Clinical Development Studies (Phase I/Ib Studies) 203
5.1.1. Food Effect Study – (D1050267) 203
5.1.2. QTc Study – (D1050249) 205
5.1.3. Phase Ib Study – (D1050254) 207
5.2. Humanistic Benefits (Post-Hoc/Secondary Analyses) 212
5.2.1. Cognition 212
5.2.2. Quality-of-Life 213
5.2.3. Epworth Sleepiness Scale (ESS) 213
6. APPENDIX 1 PACKAGE INSERT 215
7. APPENDIX 2 MELTZER 2011 REPRINT 216
8. APPENDIX 3 NAKAMURA 2009 REPRINT 217
9. REFERENCES 218

LIST OF TABLES

Table 1: List of Abbreviations 10
Table 2: National Drug Code (NDC) for All Formulations 21
Table 3: Comparison of Select Prescribing Information for Lurasidone, Aripiprazole, Olanzapine, Quetiapine XR, and Asenapine 24
Table 4: Comparative Risk of Adverse Effects of Atypical Antipsychotics 72
Table 5: Receptor Binding Affinities for Atypical Antipsychotics 73
Table 6: Choice of Medication in the Acute Phase of Schizophrenia Based on Patient Profiles 75
Table 7: Treatment Arms in D1050006, D1050049, D1050196, D1050229, D1050231, D1050233 82
Table 8: Summary of Inclusion and Exclusion Criteria (D1050006, D1050049, D1050196, D1050229, D1050231, D1050233) 83
Table 9: Summary of Efficacy Endpoints in D1050006, D1050049, D1050196, D1050229, D1050231, D1050233 84
Table 10: Baseline Characteristics, Study D1050233, Safety Population 85
Table 11: Summary of Primary and Secondary Endpoints, Repeated Measures Model or ANCOVA Model, Study D1050233, ITT Population 86
Table 12: Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050233, Safety Population 88
Table 13: Summary of Prolactin Levels, Study D1050233, Safety Population 89
Table 14: Summary of Metabolic Endpoints, Study D1050233, Safety Population 89
Table 15: Baseline Characteristics, Study D1050231, Safety Population 91
Table 16: Summary of Primary and Secondary Endpoints, Repeated Measures Model, Study D1050231, ITT Population 92
Table 17: Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050231, Safety Population 94
Table 18: Summary of Prolactin Levels, Study D1050231, Safety Population 95
Table 19: Summary of Metabolic Endpoints, Study D1050231, Safety Population 95
Table 20: Baseline Characteristics, Study D1050229, Safety Population 98
Table 21: Summary of Primary and Secondary Endpoints, Repeated Measures Model, Study D1050229, ITT Population 98
Table 22: Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050229, Safety Population 100
Table 23: Summary of Prolactin Levels, Study D1050229, Safety Population 101
Table 24: Summary of Metabolic Endpoints, Study D1050229, Safety Population 101
Table 25: Baseline Characteristics, Study D1050006, Safety Population 103

Table 26: Summary of Primary and Secondary Endpoints, Study D1050006, ITT LOCF-3 Population 104
Table 27: Number (%) of Patients Reporting the Most Common Adverse Events (Incidence ≥5%), Study D1050006, Safety Population 105
Table 28: Summary of Prolactin Levels, Study D1050006, Safety Population 106
Table 29: Summary of Metabolic Endpoints, Study D1050006, Safety Population 106
Table 30: Baseline Characteristics, Study D1050196, Safety Population 107
Table 31: Summary of Primary and Secondary Endpoints, Study D1050196, Day 42 LOCF 108
Table 32: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050196, Safety Population 109
Table 33: Summary of Prolactin Levels, Study D1050196, Safety Population 109
Table 34: Summary of Metabolic Endpoints, Study D1050196, Safety Population 110
Table 35: Baseline Characteristics, Study D1050049, Safety Population 111
Table 36: Summary of Primary and Secondary Endpoints to Week 6 LOCF, Study D1050049, ITT-LOCF Population 112
Table 37: Number (%) of Patients Reporting the Most Common Adverse Events (Incidence ≥5%), Study D1050049, Safety Population 113
Table 38: Summary of Prolactin Levels, Study D1050049, Safety Population 115
Table 39: Summary of Metabolic Endpoints, Study D1050049, Safety Population 115
Table 40: Baseline Characteristics, Study D1050234, Safety Population 117
Table 41: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050234, Safety Population 120
Table 42: Change from Core Baseline to Month 12 and LOCF Endpoint in Prolactin Levels, Study D1050234, Safety Population 121
Table 43: Change from Core Baseline to Month 12 and LOCF Endpoint in Metabolic Endpoints, Study D1050234, Safety Population 121
Table 44: Summary of Inclusion and Exclusion Criteria (D1050237) 123
Table 45: Baseline Characteristics, Study D1050237, Safety Population 123
Table 46: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050237, Safety Population 124
Table 47: Change from Baseline to Month 12 and LOCF Endpoint in Prolactin Levels, Study D1050237, Safety Population 125
Table 48: Change from Baseline to Month 12 and LOCF Endpoint in Metabolic Endpoints, Study D1050237, Safety Population 125
Table 49: Secondary Efficacy Endpoints, Repeated Measures Model, Study D1050237, ITT Population 127
Table 50: Baseline Characteristics, Study D1050231E, Safety Population 128

Table 51: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050231E, Safety Population 129
Table 52: Summary of Prolactin Levels, Study D1050231E, Safety Population 130
Table 53: Summary of Metabolic Endpoints, Study D1050231E, Safety Population.....130
Table 54: Summary of Efficacy Endpoints, Study D1050231E 132
Table 55: Baseline Characteristics, Study D1050229E, Safety Population.....134
Table 56: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050229E, Safety Population 135
Table 57: Summary of Prolactin Levels, Study D1050229E, Safety Population 136
Table 58: Change from OL Baseline to Month 24 in Metabolic Endpoints, Study D1050229E, Safety Population 136
Table 59: Summary of Efficacy Endpoints – Observed Change from Open-Label Baseline, Study D1050229E.....138
Table 60: Summary of Inclusion and Exclusion Criteria (D1001048) 140
Table 61: Baseline Characteristics, Study D1001048, Safety Population 141
Table 62: Summary of Efficacy Endpoints, Study D1001048 141
Table 63: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1001048, Safety Population.....142
Table 64: Summary of Prolactin Levels, Study D1001048 Safety Population.....142
Table 65: Summary of Metabolic Endpoints, Study D1001048, Safety Population 143
Table 66: Ongoing Lurasidone Clinical Trials for Schizophrenia.....144
Table 67: Study D1050233 145
Table 68: Study D1050231 147
Table 69: Study D1050229 149
Table 70: Study D1050006 151
Table 71: Study D1050196 153
Table 72: Study D1050049 155
Table 73: Study D1050234 157
Table 74: Study D1050237 159
Table 75: Study D1050231E.....161
Table 76: Study D1050229E.....163
Table 77: Study D1001048 165
Table 78: Baseline Patient Characteristics from Patients Used in the Simulation (Pooled Across Studies D1050231 and D1050229, Safety Population) 170
Table 79. Cardiometabolic Treatment Effect: Mean Change from Baseline After One Year..171
Table 80. Costs Inputs ($2011).....172
Table 81. Model Results: Estimated Outcomes and Costs for Lurasidone and Comparators ..174

Table 82. Model Results: Estimated Net Savings in Costs and Outcomes Between Lurasidone and Comparators 175
Table 83. Observed Relapse Rates from Study 234 184
Table 84. Observed Rehospitalization Rates from Study 234 184
Table 85. Cost Inputs in 2000 USD (Ascher-Svanum et al., 2010) 185
Table 86. 2011 Inflation Adjusted Cost Inputs: Relapsing and Non-relapsing Patients 186
Table 87. Estimated Per Patient Per Year Costs (All Patients; Relapse Rates) 188
Table 88. Estimated Per Patient Per Year Costs (All Patients; Hospitalization Rates) 189
Table 89. Estimated Per Patient Per Year Costs (Clinical Responders; Relapse Rates) 189
Table 90. Estimated Per Patient Per Year Costs (Clinical Responders; Hospitalization Rates) 190
Table 91. Plan Inputs – Default Values 197
Table 92. Market Share Inputs – Default Values 198
Table 93. Dosing and Unit Prices 198
Table 94. Estimated Annual Budgetary Impact of Latuda® Treatment 199
Table 95: Meal Conditions and Meal Composition 203
Table 96: Ratios (with 90%-CIs) for Lurasidone PK Parameters Under Fed/Fasted Conditions 205
Table 97: Summary of Clinically Noteworthy QTcI and dQTcI (msec) 207
Table 98: Baseline Characteristics, Study D1050254, Safety Population 208
Table 99: Incidence of TEAEs in ≥5% of Patients, Safety Population 209
Table 100: LS Mean Change at LOCF-endpoint from Baseline to Week 3 (ANCOVA Analysis) 211

LIST OF FIGURES

Figure 1: Time to Relapse for Lurasidone vs. Quetiapine XR 118
Figure 2: Time to Rehospitalization, Study D1050234 119
Figure 3: Least Square Mean Change in PANSS Total Score (MMRM) from Core Baseline to Month 12 (ITT Population) 119
Figure 4: Model Structure 169
Figure 5: Univariate Sensitivity Analysis of Various Parameters 177
Figure 6: Study Design 182
Figure 7: Model Structure 183
Figure 8: Univariate Sensitivity Analyses for 4 Model Scenarios 191
Figure 9: Budget Impact Model Structure 197
Figure 10. Univariate Sensitivity Analysis of Various Parameters for the Overall Population. 200
Figure 11: Mean Lurasidone Concentration-time Profiles After Multiple-dose Administration of Lurasidone 120 mg Under Fasted and Fed Conditions 204
Figure 12: Least-squares Mean dQTcI with 90% CI for Each Treatment 206
Figure 13: Mean Change from Baseline in PANSS Total Score (MMRM Analysis Weeks 1-3; LOCF endpoint Change Based on ANCOVA) 210

LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Description/Definition
ADA	American Diabetes Association
AE	Adverse Event(s)
AHFS	American Hospital Formulary Service
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APA	American Psychiatric Association
ASHP	American Society of Health-System Pharmacists
ASP	Average Sales Price
AST	Aspartate Transaminase
ATP	Adult Treatment Pane
AUC	Area under the concentration-time curve
BAS	Barnes Akathisia Scale
BIM	Budget Impact Model
BMI	Body Mass Index
bpm	Beats per minute
BPRS	Brief Psychiatric Rating Scale
BPRSd	Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CGI-I	Clinical Global Impression Improvement scale
CGI-S	Clinical Global Impression Scale – Severity of Illness
CHD	Coronary Heart Disease
cm	Centimeter
C_{max}	Maximum plasma concentration
CMS	Centers for Medicare & Medicaid Services
CNS	Central Nervous System
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CV	Cardiovascular
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders,* fourth edition

Abbreviation	Description/Definition
ECG	Electrocardiogram(s)
EPS	Extrapyramidal symptoms
ESS	Epworth Sleepiness Scale
FDA	US Food and Drug Administration
FG	Fasting glucose
FHS	Framingham Heart Study
g	Gram(s)
GGT	Gamma-glutamyltransferase
H	Hour(s)
HbA1c	Hemoglobin A1c
HCl	Hydrochloride
HCUP	Healthcare Cost and Utilization Project
HDL	High Density Lipoprotein
HI	Hepatic Impairment
HIV	Human Immunodeficiency Virus
IR	Immediate Release
ITT	Intent-to-Treat
kg	Kilogram(s)
L	Liter(s)
lb	Pound(s)
L40	Lurasidone 40 mg in double-blind treatment phase
L120	Lurasidone 120 mg in double-blind treatment phase
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
LS	Least Square(s)
LUR	Lurasidone
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MMRM	Mixed Model for Repeated Measures
msec	Millisecond(s)
N	Number of patients
NCEP	National Cholesterol Education Program
NDC	National Drug Code
NMDA	N-methyl d-aspartate
NMS	Neuroleptic malignant syndrome

Abbreviation	Description/Definition
NOS	Not Otherwise sSpecified
NR	Not Reported
NS	Not Significant
OC	Oral Contraceptive
OGTT	Oral Glucose Tolerance Test
OL	Open-label
OLZ	Olanzapine 15 mg in double-blind treatment phase
PANSS	Positive and Negative Syndrome Scale
PBO	Placebo
PI	Prescribing Information
PORT	Patient Outcomes Research Team
PMPM	Per Member Per Month
PMPY	Per Member Per Year
PR interval	Time from the onset of the P wave to the beginning of the QRS complex
PTMPM	Per treated member per month
QD	Once a day
QRS	Q, R, and S waves in an ECG
QT	QT interval
QTc	Corrected QT interval
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SCID-CV	Structured Clinical Interview for the DSM-IV Disorders-Clinician's Version
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form (36) Health Survey
$t_{½}$	Half-life
TC	Total Cholesterol
TEAE	Treatment-emergent Adverse Event(s)
TESAE	Treatment-emergent Serious Adverse Event
TMAP	Texas Medication Algorithm Project
ULN	Upper limit of normal
US	United States
USD	United States dollars
WAC	Wholesale Acquisition Cost

Abbreviation	Description/Definition
WBC	White blood cell(s)
w/	With
w/o	Without
XR	Extended release

1. EXECUTIVE SUMMARY

1.1. Clinical Benefits

Lurasidone is an atypical antipsychotic agent indicated for the treatment of adult patients with schizophrenia (indication status accurate as of February 2012). The recommended starting dose of lurasidone is 40 mg once daily. Lurasidone has been shown to be effective in a dose range of 40 mg/day to 120 mg/day. In the 6-week controlled trials submitted for approval, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 80 mg/day.[1]

At the time of FDA approval, the efficacy and safety of lurasidone was established in four, 6-week, placebo-controlled trials in adult patients who met DSM-IV criteria for schizophrenia. In addition, a fifth study was not considered for efficacy comparisons as the active control used to assess assay sensitivity, haloperidol, failed to show statistically significant differences vs. placebo on the primary efficacy endpoints. Therefore, only the study's safety outcomes were included in pooled safety assessments. Results from the four positive studies, listed in the package insert, demonstrated the superiority of lurasidone compared with placebo in clinical assessments of psychopathology and positive and negative psychotic symptoms, as measured by the Positive and Negative Symptoms Scale (PANSS) or the Brief Psychiatric Rating Scale derived from the PANSS (BPRSd). In these studies, improvements were observed as early as within the first week of treatment, with improvements continuing through study endpoint at week 6.[1,2, 3, 4]

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with lurasidone were somnolence, akathisia, nausea, parkinsonism, and agitation. Based on the pooled data from these five studies, among the adverse reactions that occurred with a greater than 5% incidence in patients treated with lurasidone, the apparent dose related adverse reactions were akathisia and somnolence. A total of 9.4% of lurasidone-treated patients and 5.9% of placebo treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in patients treated with lurasidone that were at least 2% and at least twice the placebo rate. Lipid parameters, glucose, weight, and body mass index changes were generally similar to placebo. The mean weight gain was 0.75 kg for lurasidone-treated patients compared to 0.26 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at endpoint) was 5.6% for lurasidone-treated patients and 4.0% for placebo-treated patients.[1]

As stated in the Prescribing Information, additional safety data were also obtained from 11 uncontrolled, primarily open-label extension studies. In these studies, lurasidone was associated with a: mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236), and +1.2 mg/dL at week 52 (n=244); mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, 1.9 (n=238) and -3.5 (n=238) mg/dL at week 36, and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively; mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303), and -0.71 kg at week 52 (n=244); and median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189), and -3.3 ng/mL at week 52 (n=243).[1]

Following FDA approval, a six-week, placebo and active-controlled trial, demonstrated the efficacy of lurasidone at daily doses of 80 and 160 mg/day. Quetiapine XR 600 mg/day was included as an active control to confirm assay sensitivity. Patients who completed the six-week double-blind study were eligible for participation the 12 month, double-blind, parallel group comparison of flexibly dosed lurasidone (40 to 160 mg/day) and quetiapine XR (200-800 mg/day). The primary endpoint,

the time to relapse at Month 12 endpoint, showed a hazard ratio (HR) of 0.728 [95%CI:0.410,1.295], indicating a 27% lower risk of relapse for lurasidone vs. quetiapine XR. The probability of relapse at Month 12 endpoint (based on Kaplan-Meier survival analysis) was 23.7% for lurasidone and 33.6% for quetiapine XR.[5,6]

Additional longer-term studies have also been completed following FDA approval. A one-year, double blind trial demonstrated the long term safety and tolerability of lurasidone (flexibly dosed 40 to 120 mg/day), in the treatment of schizophrenia or schizoaffective disorder and included risperidone (flexibly dosed 2 to 6 mg/day), as an active comparator. Additionally, safety and tolerability of flexibly dosed lurasidone (40 to 120 mg/day) was demonstrated in treating patients with schizophrenia during a six month and a 22 month open-label extension study.[7, 8, 9]

1.1.1. Pharmacology

The mechanism of action of lurasidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.[1]

In vitro receptor binding studies revealed that lurasidone is an antagonist with high affinity at dopamine D_2 receptors (K_i = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors $5\text{-}HT_{2A}$ (K_i = 0.47 nM) and $5\text{-}HT_7$ (Ki = 0.495 nM), is an antagonist with moderate affinity at human α_{2C} adrenergic receptors (K_i = 10.8 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (K_i = 6.38 nM) receptors, and is an antagonist at α_{2A} adrenergic receptors (K_i = 40.7 nM). Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors ($IC_{50} \geq 1{,}000$ nM and > 1,000 nM, respectively).[1]

1.1.2. Humanistic Benefits

Lurasidone also has demonstrated effect on humanistic benefits in terms of overall quality of wellbeing, daytime sleepiness, and cognition as it relates to Study 233. In study 233, lurasidone in once-daily doses of 80 mg and 160 mg, was associated with improvements in health-related quality of life and day-time sleepiness in patients with an acute exacerbation of schizophrenia as measured by the self-administered Quality of Well-Being Scale (QWB-SA) and Epworth Sleep Scale (ESS), respectively.

- QWB-SA is a preference-weighted measure with a combined score ranging from 0 to 1.0 (death to optimal functioning) assessing community mobility, physical activity, social activity, and subjective symptoms which include somatic, cognitive, and emotional symptoms. On an endpoint ANCOVA analysis, there was significant improvement in the LS mean QWB-SA score compared to placebo (0.631) in the lurasidone 80 mg group (0.672; p=0.049), the lurasidone 160 mg group (0.710; p<0.001), and the quetiapine XR group (0.711; p<0.001).
- Epworth Sleepiness Scale (ESS) is an 8-item patient reported outcome measure that assesses the level of daytime sleepiness. A reduction in ESS scores (less sedation) was observed at LOCF endpoint among patients treated with lurasidone 80 mg (-1.1), lurasidone 160 mg (-0.7) and placebo (-0.9). There was no significant treatment difference in the lurasidone 80 mg group (-0.6; p=0.276) or the lurasidone 160 mg group (0.1; p = 0.784) compared with placebo.
- Cognitive performance was examined with the CogState composite Z-score and domain test Z-scores from the computerized CogState system, which has 7 cognitive tests, including the

domains of episodic memory, processing speed, and social cognition. At Week 6, within group analysis showed a significant increase (LS mean ± SE) in composite scores in the lurasidone 80 mg group (0.18 ± 0.07, p=0.018), the lurasidone 160 mg group (0.14 ± 0.07, p=0.050), and the placebo group (0.17 ± 0.08, p = 0.031), indicating an overall improvement in cognitive function.

1.2. Economic Benefits

Lurasidone's economic value proposition is illustrated from the economic models below demonstrating potential cost-savings compared with other atypicals due to:

- fewer patients requiring treatment for dyslipidemia and hyperglycemia after 1-yr treatment with lurasidone and a lower incidence of CVD events like CHD, stroke, etc (CVD Incidence Related Cost-Consequence Model)
- lower rates of relapse and relapse-related hospitalizations after 1-yr treatment with lurasidone vs. quetiapine XR (Relapse and Relapse-related hospitalization Cost Model)

Additionally, a budget impact model that illustrates the estimated health plan drug budget impact is described below.

1.2.1. CVD Incidence Related Cost-Consequence Model

A cost-consequence model was developed to assess the potential impact of cardio-metabolic parameter changes (incidence of diabetes and cardiovascular (CV) events) after one year of treatment with lurasidone versus other selected atypical antipsychotics among adult patients diagnosed with schizophrenia. Using patient-level data from lurasidone's clinical trials, the analysis demonstrated that fewer lurasidone-treated patients would become eligible for treatment with a glucose-lowering medication (based on American Diabetes Association [ADA] Guidelines) compared to olanzapine, risperidone, or quetiapine XR at one year. Consequent costs for medication management were also lower for lurasidone. Over three years, lurasidone is predicted to result in 119, 15, and seven fewer incident diabetes cases per 1,000 patients when compared with olanzapine, risperidone, and quetiapine XR, respectively. Lurasidone is also expected to be associated with a similar (quetiapine XR) or fewer (olanzapine and risperidone) number of incident cardiovascular events. These differences in cardiometabolic changes are expected to translate to potential net savings within three years: $2,466 per patient compared to olanzapine, $102 compared to risperidone, and $85 compared to quetiapine XR, excluding the cost of antipsychotic treatment, and $15,095 per patient compared to olanzapine, $13,422 compared to risperidone, and $9,693 compared to quetiapine XR, when the costs of antipsychotic treatment. The base-case analysis was conducted using branded products and a sensitivity analysis used generic products.

1.2.2. Relapse and Relapse-related Hospitalization Cost Model

Lurasidone's impact on observed 12-month relapse rates and relapse-related hospitalization rates from Study D1050234 (hereinafter Study 234), a double-blind, parallel group comparison trial of quetiapine XR was used to model a probabilistic simulation of annual direct mental health care cost differences due to differences in relapses and relapse-related hospitalizations based on cost-estimates from a published article (Ascher-Svanum 2010).[47] Total direct mental health care costs (inflated to 2011 USD) for relapsing and non-relapsing patients were calculated for categories including psychiatric hospitalizations, emergency services, medication management, and outpatient individual therapy (Ascher-Svanum 2010).[47] Model robustness was tested using a uni-variate and probabilistic sensitivity analysis.

Annual direct mental health care costs were estimated based on two outcome measures; (i) relapses and (ii) relapse-related hospitalizations for "ALL patients" and "Responder patients" in both treatment groups.

- Relapses: "ALL patients" receiving lurasidone (19.9%, n=151) had lower rates of relapses than quetiapine XR (28.2%, n=85) and "Responder Patients" receiving lurasidone also had (20.9%, n=139) had lower rates of relapses than quetiapine XR (26.6%, n=79) resulting in potential PPPY total direct mental health care cost savings of:
    - $2,702 (95% CI: -4052, -2017) compared with quetiapine XR for "ALL patients"; and
    - $1,914 (95% CI: -2767, -1234) compared with quetiapine XR for Responder patients.

Probabilistic sensitivity analysis suggest that there was a 99.7%, and 96.5% likelihood that the mental health-related direct costs would be less for lurasidone than for quetiapine XR in the ALL and Responder population, respectively.

- Relapse-related hospitalizations: "ALL patients" receiving lurasidone (7.3%, n=151) had lower rates of relapse-related hospitalizations than quetiapine XR (17.6%, n=85) and "Responder patients" receiving lurasidone (7.2%, n=139) also had lower rates of relapse-related hospitalizations than quetiapine XR (16.5%, n=79), resulting in potential PPPY total direct mental-health care-cost savings of:
    - $3,277 (95% CI: -$4,658, -$2,111) compared with quetiapine XR for ALL patients
    - $2,888 (95% CI: -$4,256,-$1,696) compared with quetiapine XR for Responder patients (Rajagopalan APA 2012).

Probabilisitic sensitivity analyses suggest cost savings with lurasidone were primarily driven by cost of hospitalizations and lurasidone had a 100% probability of being a cost saving option due to relapse-related hospitalizations for both ALL and CR patients (Rajagopalan APA 2012).[109]

1.2.3. Budget Impact Model

The impact of adding lurasidone to a formulary was evaluated with a budget impact model (BIM) which found that post introduction of lurasidone in a formulary should not increase total formulary costs. Given lurasidone's competitive and flat pricing, along with a realistic and researched market share estimate, the BIM calculated that for the same fixed budget, the difference in total costs for a current formulary versus a formulary including lurasidone is assumed to be -$16,475 (i.e., cost saving of $16,475), with incremental changes of $0.00 PMPM and -$0.27 and PTMPM. These estimates assume that lurasidone will become one of the alternatives to other currently available branded and generic atypical antipsychotics and will capture market share proportionally from each agent. Overall, the overall pharmacy budget impact analysis indicates that lurasidone should be a cost-saving formulary addition.

Based on the results of these economic analyses, lurasidone represents a budget-conscious and potentially cost-saving alternative compared to other atypical antipsychotics to treat patients diagnosed with schizophrenia.

1.3. Conclusions

Based on the results of short-term and longer-term clinical studies, treatment with lurasidone is expected to significantly reduce symptom severity in adult patients with schizophrenia. Furthermore, a recently completed large one year, double-blind, randomized study of lurasidone vs. quetiapine XR found that treatment with lurasidone was associated with fewer relapses and significantly fewer

relapse-related hospitalizations compared to quetiapine XR. Based on clinical evidence from this and several other longer-term, primarily open-label, studies as well as multiple placebo-controlled short-term studies, treatment with lurasidone is also expected to result in lower incidence of adverse cardiometabolic changes compared to several other, widely used atypical antipsychotics. In particular, the predicted incidence of dyslipidemia, hyperglycemia and diabetes are expected to be lower in patients treated with lurasidone as compared to olanzapine, risperidone, and quetiapine XR.

Due to these expected benefits and outcomes, lurasidone is expected to have a cost-saving impact on predicted pharmacy and medical costs associated with the treatment of adult patients with schizophrenia.

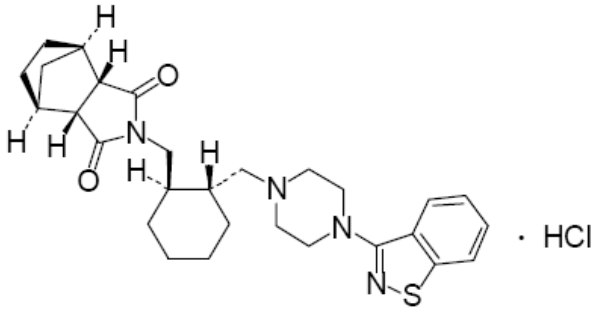
2. PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 Product Description **Page 18**

2.2 Place of Product in Therapy **Page 64**

2.1. Product Description

Lurasidone is a psychotropic agent belonging to the chemical class of benzisothiazol derivatives.[1] Its chemical name is (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride. Its molecular formula is C28H36N4O2S•HCl, and its molecular weight is 529.14. The chemical structure is:



Lurasidone hydrochloride (HCl) is a white-to-off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene, and very slightly soluble in acetone.

Lurasidone tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, or 80 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry®, and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

All information about lurasidone presented in Section 2.1 is contained in the full prescribing information for lurasidone unless otherwise noted.

2.1.1. Generic Name, Brand Name, and Therapeutic Class

Generic name: lurasidone HCl

Brand name: LATUDA®

Therapeutic class: Atypical antipsychotic

2.1.2. Dosage Forms, Including Strengths and Package Sizes

Lurasidone is available as an oral tablet in 20 mg, 40 mg, and 80 mg strengths. The recommended starting dose for lurasidone is 40 mg once daily. Initial dose titration is not required. Lurasidone has been shown to be effective in the dose range of 40 mg/day to 120 mg/day dose. In the 6-week controlled studies, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 80 mg/day. Lurasidone should be taken with food (at least 350 calories).

2.1.3. National Drug Code (NDC) for All Formulations

Table 2: National Drug Code (NDC) for All Formulations

Tablet Strength	Package Configuration	NDC
20 mg	Bottles of 30	63402-302-30
	Bottles of 90	63402-302-90
	Bottles of 500	63402-302-50
	Box 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-302-10 Carton 63402-302-01 Blister
40 mg	Bottles of 30	63402-304-30
	Bottles of 90	63402-304-90
	Bottles of 500	63402-304-50
	Box 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 Blister
80 mg	Bottles of 30	63402-308-30
	Bottles of 90	63402-308-90
	Bottles of 500	63402-308-50
	Box 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-308-10 Carton 63402-308-01 Blister

2.1.4. Copy of the Official Product Labeling/Literature

A copy of the package insert as approved by the US Food and Drug Administration (FDA) is attached (see Appendix 1).

2.1.5. Average Sales Price (ASP), Wholesale Acquisition Cost (WAC), and Payers' Contract Price

The WAC for lurasidone 20, 40, or 80 mg tablets is $15.39 per day.

2.1.6. American Hospital Formulary Service (AHFS) or Other Drug Classification

The AHFS classification for atypical antipsychotics is 28:16:08:04.

2.1.7. Indications and Usage

Lurasidone is indicated for the treatment of patients with schizophrenia.

At the time of FDA approval, the efficacy of lurasidone in schizophrenia was established in four six-week controlled studies of adult patients with schizophrenia.

The effectiveness of lurasidone for longer-term use, that is, for more than six weeks, has not been established in controlled studies. Therefore, the physician who elects to use lurasidone for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

FDA approval of lurasidone was granted on October 28, 2010.

2.1.8. Other Potential Indications and Off-Label Use

Trials are currently being conducted or planned to study the use of lurasidone in bipolar I depression (NCT01284517, NCT00868959, NCT01358357), major depressive disorder with mixed features (NCT01423240, NCT01421134, NCT01423253), and schizophrenia maintenance (NCT01435928).

2.1.9. Pharmacology

Refer to Section 12 of the approved package insert.

2.1.10. Pharmacokinetics/Pharmacodynamics

Refer to Sections 12.2 and 12.3 of the approved package insert.

2.1.11. Contraindications

Refer to Section 4 of the approved package insert.

2.1.12. Warnings/Precautions/Adverse Events

Refer to Sections 5 and 6 of the approved package insert.

2.1.13. Instructions

Refer to Section 7 of the approved package insert.

2.1.14. Dosing and Administration

Refer to Section 2 of approved package insert.

2.1.15. Access

There are no restrictions on distribution, and there are no supply limitations or anticipated shortages.

2.1.16. Co-Prescribed/Concomitant Therapies

Not applicable.

2.1.17. Comparison of Select Prescribing Information for Lurasidone, Aripiprazole, Olanzapine, Quetiapine XR, and Asenapine

The purpose of this table is to provide a side-by-side comparison of product label sections for lurasidone and four other atypical antipsychotics for the adult schizophrenia indication. These four comparators were chosen because they either are current established therapies (olanzapine, quetiapine XR, aripiprazole) or were recently approved (asenapine). Fanapt (iloperidone), another recently approved product, was not included due to its low utilization.[10]

In order to focus the information provided in the table, the scope is limited to information that is pertinent to lurasidone in comparison to the information provided in comparator labels. For instance, the Warnings and Precautions and the Drug Interactions sections of the table are limited to those that are present in the lurasidone label or at least two other product labels. Information contained within only one comparator label and not in the lurasidone label is noted below the table as footnotes. In addition, drugs with no clinically important interactions with the four comparators are also presented separately as footnotes below the table. Finally, the table only compares product labels for the adult schizophrenia indication. The comparators also have the following additional indications below:

- Aripiprazole: Treatment of adolescent (13−17 years) patients with schizophrenia. Indicated for the acute and maintenance treatment of adults and pediatric patients (10−17 years) with manic and mixed episodes associated with bipolar 1 disorder (monotherapy or as an adjunct to lithium or valproate). Indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults. Treatment of irritability associated with autistic disorder in pediatric patients (6−17 years). Acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.[11]
- Olanzapine: Treatment of adolescent (13−17 years) patients with schizophrenia. Indicated for the acute treatment of manic or mixed episodes associated with bipolar 1 disorder in adult and adolescent patients (13−17 years) and maintenance treatment of bipolar 1 disorder. Indicated for the treatment of manic or mixed episodes associated with bipolar 1 disorder as an adjunct to lithium or valproate. Indicated in intramuscular formulation for treatment of acute agitation associated with schizophrenia and bipolar I mania. Treatment of depressive episodes associated with bipolar I disorder and treatment resistant depression in combination with fluoxetine.[12]
- Quetiapine XR: Indicated for the acute treatment of manic or mixed episodes associated with bipolar 1 disorder, both as monotherapy and as an adjunct to lithium or divalproex. Indicated for the acute treatment of depressive episodes associated with bipolar disorder. Indicated for the maintenance treatment of bipolar 1 disorder, as an adjunct to lithium or divalproex. Indicated for use as adjunctive therapy to antidepressants for the treatment of MDD.[13]
- Asenapine: Indicated for the acute and maintenance treatment of adults with manic and mixed episodes associated with bipolar 1 disorder (monotherapy or as an adjunct to lithium or valproate).[14]

A comparison of selected prescribing information for lurasidone, aripiprazole, olanzapine, quetiapine XR, and asenapine is provided in Table 3.

Please see each product's respective Package Insert for complete prescribing information.[1, 11, 12, 13, 14]

Table 3: Comparison of Select Prescribing Information for Lurasidone, Aripiprazole, Olanzapine, Quetiapine XR, and Asenapine

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
Brand Name	**Latuda®**	**Abilify®**	**Zyprexa®**	**Seroquel XR®**	**Saphris®**
Manufacturer	Sunovion Pharmaceuticals Inc.	Bristol-Myers Squibb/Otsuka America Pharmaceutical, Inc.	Eli Lilly and Co.	AstraZeneca	Merck
Therapeutic Class	**Atypical Antipsychotic**				
Description	Psychotropic agent belonging to the chemical class of benzisothiazol derivatives	Psychotropic agent	Psychotropic agent belonging to the thienobenzodiazepine class	Psychotropic agent belonging to chemical class, dibenzothiazepine derivatives	Psychotropic agent available for sublingual administration. Asenapine belongs to the class dibenzo-oxepino pyrroles.
How supplied (tablets)	Tab: 20 mg, 40 mg, 80 mg	Tab, Orally Disintegrating: (Discmelt): 10 mg, 15 mg; Tab: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg; Sol: 1 mg/mL; Inj: 7.5 mg/mL	Inj: 10mg; Tab: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg; Tab, Disintegrating: (Zydis) 5 mg, 10 mg, 15 mg, 20 mg	Tab, Extended release: 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	Tab, Sublingual: 5 mg, 10 mg
Indication	**Treatment of Patients with Schizophrenia**				
Clinical Studies	Efficacy in schizophrenia established in four 6-week controlled studies in adult patients	Efficacy in schizophrenia established in four 4-6 week trials in adults and one 6-week trial in adolescents (13 to 17 years). Maintenance efficacy was demonstrated in one trial in adults and can be extrapolated to adolescents	Efficacy in schizophrenia established in 3 clinical trials in adults: two 6-week trials and one maintenance trial. In adolescent (ages 13-17), efficacy was established in one 6-week trial	Efficacy in schizophrenia was established in one 6-week and one maintenance trial in adults; extrapolation from three 6-week trials in adults from quetiapine	Efficacy in schizophrenia was established in two 6-week trials and one maintenance trial in adults

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
Contraindications	Hypersensitivity to lurasidone HCl or its components; coadministration with a strong CYP3A4 inhibitor (e.g., ketoconazole) and strong inducer (e.g., rifampin)	Hypersensitivity to aripiprazole	None	None	None
Recommended Dosing					
Dosing (Adults)	Starting dose of 40 mg QD (initial dose titration is not required). Shown to be effective in a dose range of 40 mg/day to 120 mg/day; however 120 mg/day dose had no additional benefit. Maximum recommended dose is 80 mg/day.	Starting and target dose is 10 mg/day or 15 mg/day. Highest demonstrated effective dose is 30 mg/day.	Starting dose is 5-10 mg/day, with a target dose of 10 mg/day. Highest demonstrated effective dose is 15 mg/day.	Starting dose is 300 mg/day. Can be titrated to 400 mg-800 mg/day.	Starting and target dose is 5 mg given twice daily.
Administration	QD; with food (at least 350 calories)	QD; without regard to meals	QD; without regard to meals	QD; taken without food or with a light meal (approximately 300 calories)	BID, sublingual. No food or drink for 10 minutes after administration.
Pharmacokinetics					
Mean Half-life (t1/2) (hours)	18 hours	75 hours	30 hours	7 hours	24 hours
Maximum plasma concentration (C_{max})	3.0-times increase in presence of food	Administration of 15 mg tablet with food did not significantly affect C_{max}.	Food does not affect the rate or extent of olanzapine absorption.	Steady-state mean C_{max} of active metabolite norquetiapine is 21-27% of quetiapine. A high-fat meal produced a 52% increase for 300 mg	The mean C_{max} is approximately 4 ng/mL.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
				tablets, while a light meal had no significant effect on C_{max}.	
Time to C_{max}	1–3 hours	3–5 hours	6 hours	6 hours	1 hours
AUC	2.0-times increase in presence of food	Administration of a 15 mg tablet with food did not significantly affect AUC.	Accounted for 12% of the AUC for total radioactivity	Steady-state mean AUC of active metabolite norquetiapine is 45-56% of quetiapine. A high-fat meal produced a 22% increase for the 300-mg tablets, while a light meal had no significant effect on AUC.	NR
Volume of distribution	6,173 L (mean); highly bound (~99%) to serum proteins	404 L; highly bound (>99%) to serum proteins	1,000 L; 93% bound to plasma proteins	10 ± 4 L/kg; 83% bound to plasma proteins	20−25 L/kg; highly bound (95%) to plasma proteins
Absorption	Estimated that 9–19% of administered dose is absorbed. In a food effect study, mean C_{max} and AUC were about three times and two times, respectively, when administered with food compared to the levels observed under fasting conditions.	Aripiprazole tablets are well-absorbed, with an absolute bioavailability of 87%. Aripiprazole may be administered with or without food. Administration of a 15 mg aripiprazole tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC but delayed T_{max} by 3 hours for aripiprazole.	Olanzapine is well-absorbed Olanzapine may be given without regard to meals.	Quetiapine XR should be taken without food or with a light meal. Quetiapine dosed once daily at steady-state has comparable bioavailability to an equivalent total daily dose of quetiapine administered in divided doses, twice daily. A high-fat meal (approximately 800 to 1000 calories) was found to produce statistically significant increases in the quetiapine C_{max} and AUC of 44% to 52%	The absolute bioavailability of sublingual asenapine at 5 mg is 35%. Increasing the dose from 5 mg to 10 mg twice daily results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The absolute bioavailability of when swallowed is low (<2%). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased asenapine exposure. Eating and

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
				and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal (approximately 300 calories) had no significant effect on the C_{max} or AUC of quetiapine.	drinking should be avoided for 10 minutes after administration.
Metabolism	Metabolized mainly via the CYP3A4 enzyme. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation.	The metabolism is mediated primarily by dehydrogenation, hydroxylation, and N-dealkylation. CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4.	Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. CYP2D6-mediated oxidation is a minor metabolic pathway.	Extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. Cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite and in the metabolism of its active metabolite norquetiapine.	Direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2) are the primary metabolic pathways.
Excretion	Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine,	Following a single oral dose of $^{[14C]}$-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively;	Seven percent of a $^{[14C]}$-labeled dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly	Following a single oral dose of $^{[14C]}$-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly	After administration of a single dose of $^{[14C]}$-labeled asenapine, about 90% of the dose was recovered; approximately 50% was recovered in urine, and

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	after a single dose of [14C]-labeled lurasidone.	elimination of aripiprazole occurs primarily via hepatic metabolism involving CYP2D6 and CYP3A4.	metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively.	metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.	40% recovered in feces.
Clearance	3,902 mL/min	NR	12 to 47 L/hr	NR	52 L/hr
Listed Warnings and Precautions*					
Boxed Warning: **Increased mortality in elderly patients with dementia-related psychosis**	**Not approved for the treatment of patients with dementia-related psychosis**				
Body temperature regulation	Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing the drug for patients who experience conditions that may contribute to an elevation in their core body temperature.				
Cerebrovascular adverse reactions, including stroke	In placebo-controlled trials of risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions, including fatalities, compared to placebo-treated patients.	In placebo-controlled clinical studies (two flexible-dose studies and one fixed-dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events, including fatalities, in aripiprazole-treated patients. In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole.	Cerebrovascular adverse events including fatalities were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo.	NR	In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated patients.
Dysphagia	Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients – in particular, those with advanced Alzheimer's dementia. Drug is not approved for the				

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	treatment of patients with dementia-related psychosis and should not be used in patients at risk for aspiration pneumonia.				
	NR	NR	NR	NR	Dysphagia was reported in 0.2% (1/572) of patients treated with therapeutic doses (5−10 mg twice daily) of asenapine as compared to 0% (0/378) of patients treated with placebo in a six-week schizophrenia trial.
Hyperglycemia and diabetes mellitus	Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.				
	Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk. In six-week, placebo-controlled studies the mean	Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk.	Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL,	In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.	Because SAPHRIS was not marketed at the time these studies were performed, it is not known if SAPHRIS is associated with this increased risk.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	changes from baseline in serum glucose were -0.6, 2.5, -0.9, 2.5, and -0.7 mg/dL for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. The proportion of patients with shifts in serum glucose ≥126 mg/dL was 11.7%, 14.3%, 10.0%, 10.0%, and 8.6%, for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. In the uncontrolled, longer-term studies (primarily open-label extension studies), lurasidone was associated with a mean change in glucose of +1.6 mg/dL at week 24 (N =186), +0.3 mg/dL at week 36 (N=236) and +1.2 mg/dL at week 52 (N =244).		nonfasting 140-200 mg/dL). While relative risks estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum, and olanzapine appears to have a greater association than some other atypical antipsychotics. Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the CATIE. The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL. In a study of healthy volunteers, patients who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of	In a 24-week trial (active-controlled, 115 patients treated with quetiapine) that evaluated glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥200 mg/dL was 1.7%, and the incidence of a fasting treatment-emergent blood glucose level ≥126 mg/dL was 2.6%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in two-hour glucose from baseline was -1.8 mg/dL for quetiapine.	

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
			2.3 mg/dL. Placebo-treated patients (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL. In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). Olanzapine-treated		

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
			patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated patients (median exposure 17 days). In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated patients (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated patients (N=599). The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.		
Hyperprolactinemia	As with other drugs that	NR	As with other drugs that	Like other drugs that	Like other drugs that

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	antagonize dopamine D2 receptors, lurasidone elevates prolactin levels. In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for lurasidone-treated patients was 1.1 ng/mL and was -0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose dependent. The proportion of patients with prolactin ≥5 x ULN was 3.6% for lurasidone-treated patients vs. 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5 x ULN was 8.3% for lurasidone-treated patients vs. 1% for placebo-treated female patients. The proportion		antagonize dopamine D2 receptors, olanzapine elevates prolactin levels, which persist during chronic administration. In placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual related events1 (2% [49/3240] of females), sexual function-related events (2% [150/8136] of females and males), and breast-related events3 (0.7% [23/3240] of females, 0.2% [9/4896] of males).	antagonize dopamine D2 receptors, quetiapine elevates prolactin levels in some patients, and the elevation may persist during chronic administration. During clinical trials with quetiapine across all indications, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.	antagonize dopamine D2 receptors, asenapine can elevate prolactin levels, and the elevation can persist during chronic administration. In asenapine clinical trials, the incidences of adverse events related to abnormal prolactin levels were 0.4% vs. 0% for placebo.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	of male patients with prolactin elevations ≥5 x ULN was 1.9% vs. 0.6% for placebo-treated male patients. In the uncontrolled longer-term studies (primarily open-label extension studies), lurasidone was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189), and -3.3 ng/mL at week 52 (n=243).				
Leukopenia, neutropenia, and agranulocytosis	Leukopenia/neutropenia events have been reported temporally related to antipsychotic agents. Patients with a history of a clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy, and discontinuation of drug should be considered at the first sign of a clinically significant decline in white blood cell count in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue drug and have their WBC count followed until recovery.				
Hyperlipidemia	Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from six-week, placebo-controlled studies demonstrated a mean	NR	Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations, in patients using olanzapine is recommended.	Undesirable alterations in lipids have been observed with quetiapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations, in patients using quetiapine is recommended. In some	NR

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	change from baseline in total cholesterol of -12.3, -9.4, -9.8, -3.8, and -8.5 mg/dL, for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. Mean change from baseline in triglycerides was -29.1, -6.2, -14.2, -3.1, and -15.7 mg/dL for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. The proportion of patients with shifts in total cholesterol ≥240 mg/dL was 13.8%, 7.3%, 6.9%, 3.8%, and 6.6%, for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. The proportion of patients with shifts in triglycerides ≥200 mg/dL was 14.3%, 14.0%, 8.7%, 10.5%, and 12.5%, for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. In the uncontrolled,		Clinically significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use. In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences	patients, a worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate. In quetiapine clinical trials for schizophrenia, the percentage of patients with shifts in cholesterol and triglycerides from baseline to clinically significant levels were 18% (placebo: 7%) and 22% (placebo: 16%). From six-week, placebo-controlled studies, the proportion of schizophrenia patients with shifts in total cholesterol ≥240 mg/dL was 9% for quetiapine and 9% for placebo. The proportion of patients with shifts in triglycerides ≥200 /dL was 18% for quetiapine and 5% for placebo. The proportion of	

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	longer-term studies (primarily open-label extension studies), lurasidone was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n=238) and -3.5 (238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.		were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels. In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of	patients with shifts in LDL cholesterol ≥160 mg/dL was 7% for quetiapine and 8% for placebo. The proportion of patients with shifts in HDL cholesterol ≤40 mg/dL was 15% for quetiapine and 12% for placebo.	

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
			therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months. The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. In phase 1 of the CATIE over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.		

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
Neuroleptic malignant syndrome (NMS)	NMS has been reported in association with the administration of antipsychotic drugs. The management of NMS should include: 1. immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2. intensive symptomatic treatment and medical monitoring, and 3. treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored because recurrences of NMS have been reported.				
Orthostatic hypotension	Lurasidone may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from six-week, placebo-controlled studies was: orthostatic hypotension (0.4%, 0.2%) and syncope (<0.1%, 0%) for lurasidone and placebo, respectively. In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with lurasidone 40 mg, 1.4% with lurasidone 80 mg and 1.7% with lurasidone 120 mg compared to 0.9% with placebo. Lurasidone should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose patients	Aripiprazole may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from six-week, placebo-controlled trials of adult patients on oral aripiprazole (N = 2467) included (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo in adult oral aripiprazole-treated patients (4%, 2% for	Olanzapine may induce orthostatic hypotension, probably reflecting its α1-adrenergic antagonistic properties. Initiating therapy with 5 mg QD minimizes the risk of orthostatic hypotension and syncope. In an open-label clinical pharmacology study in non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated (three 10 mg doses administered four hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg). Syncope was reported in 0.6% (15/2500) of olanzapine-treated	Quetiapine may induce orthostatic hypotension, probably reflecting its α1-adrenergic antagonist properties. Syncope was reported in 0.3% (5/1866) of the patients treated with quetiapine XR across all indications, compared with 0.2% (2/928) on placebo. Syncope was reported in 1% (28/3265) of the patients treated with quetiapine, compared with 0.2% (2/954) on placebo. Orthostatic hypotension, dizziness, and syncope may lead to falls. Quetiapine should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that would predispose patients to hypotension. If hypotension occurs during titration to the target dose, a return to	Asenapine may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its α1-adrenergic antagonist activity. In six-week schizophrenia trials, syncope was reported in 0.2% (1/572) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of asenapine, compared to 0.3% (1/378) of patients treated with placebo. Patients should be instructed about nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension. Asenapine should be used with caution in (1) patients with known cardio-vascular disease, cerebro-vascular disease, or conditions that would pre-dispose patients to hypotension

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.	aripiprazole and placebo, respectively). Aripiprazole should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that would presuppose patients to hypertension.	patients in phase 2–3 oral olanzapine studies. Olanzapine should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, and conditions that would predispose patients to hypotension where the occurrence of syncope or hypotension and/or bradycardia might put the patient at increased medical risk. Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory, or CNS depression.	the previous dose in the titration schedule is appropriate.	and (2) the elderly. Asenapine should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, or respiratory or CNS depression. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.
Potential for cognitive and motor impairment	Lurasidone, like other antipsychotics, has the potential to impair judgment or motor skills. In six-week placebo-controlled trials, somnolence was reported in 22.3% of patients treated with lurasidone compared to 9.9% of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence	Aripiprazole, like other antipsychotics, may impair judgment, thinking, or motor skills. In six-week, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (N=2467) treated with oral aripiprazole (11%, 6%). Somnolence (including sedation) led to discontinuation in 0.3%	Somnolence is a common adverse reaction associated with olanzapine treatment and occurred in 26% of olanzapine patients compared to 15% of placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing	Somnolence was a commonly reported adverse event reported in patients treated with quetiapine especially during the 3-day period of initial dose titration. In schizophrenia trials, somnolence was reported in 24.7% (235/951) of patients on quetiapine XR compared to 10.3% (33/319) of placebo	Somnolence was reported in patients treated with asenapine. In six-week, fixed-dose, placebo-controlled schizophrenia trials, somnolence was reported in 15% (41/274) of patients on asenapine 5 mg twice daily and in 13% (26/208) of patients on asenapine 10 mg twice daily compared to 7% (26/378) of placebo

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	was reported in 26.5% of patients receiving lurasidone 120 mg/day. In these six-week trials, somnolence included hypersomnia, hypersomnolence, sedation, and somnolence. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with lurasidone does not affect them adversely.	(8/2467) of adult patients on oral aripiprazole in short-term, placebo-controlled trials. Patients on aripiprazole therapy should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole does not affect them adversely.	database. Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients on olanzapine therapy should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.	patients. Since quetiapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that quetiapine therapy does not affect them adversely. Somnolence may lead to falls.	patients. During pre-marketing clinical trials with asenapine, including long-term trials without comparison to placebo, somnolence was reported in 18% (358/1953) of patients treated with asenapine. Somnolence (including sedation) led to discontinuation in 0.6% (12/1953) of patients in short-term, placebo-controlled trials. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that asenapine therapy does not affect them adversely
QT interval (QT) prolongation	See Adverse Events Section below.	See Adverse Events Section below.	See Adverse Events Section below.	In clinical trials quetiapine was not associated with a persistent increase in QT intervals. However, the QT effect was not	The effects of asenapine on the QT/QTc internal were evaluated in a dedicated QT study. This trial involved asenapine doses of

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
				systematically evaluated in a thorough QT study. In post marketing experience there were cases reported of QT prolongation in patients who overdosed on quetiapine, in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval. The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrythmics (e.g., quinidine, procainamide) or Class III antiarrythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate,	5 mg, 10 mg, 15 mg, and 20 mg twice daily and placebo and was conducted in 151 clinically stable patients with schizophrenia. Asenapine was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo. No patients treated with asenapine experienced QTc increases ≥60 msec from baseline measurements, nor did any patient experience a QTc of ≥500 msec. Electrocardiogram (ECG) measurements were taken at various time points during the asenapine clinical trial program (5 mg or 10 mg twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for asenapine and placebo in these short-term trials. There were no reports of Torsade de Pointes or any other adverse reactions associated with delayed

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
				methadone). Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g. cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).	ventricular repolarization. The use of asenapine should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics or Class 3 antiarrhythmics, antipsychotic medications, and antibiotics. This drug should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.
Seizures and convulsions	Drug should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.				
	In six-week, placebo-controlled trials, seizures/	In six-week, placebo-controlled trials, seizures/convulsions	Olanzapine is not approved for the treatment of patients	During six-week clinical trials with quetiapine, seizures occurred in	Seizures were reported in 0% (0/572) and 0.3% (1/379) patients treated

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	convulsions occurred in <0.1% of patients treated with lurasidone compared to 0.2% of placebo-treated patients.	occurred in 0.1% (3/2467) of adult patients treated with oral aripiprazole.	with Alzheimer's disease. During premarketing testing, seizures occurred in 0.9% of olanzapine-treated patients.	0.05% (1/1866) of patients treated with quetiapine across all indications compared to 0.3% (3/928) on placebo. During clinical trials with quetiapine, seizures occurred in 0.5% (20/3490) of patients treated with quetiapine compared to 0.2% (2/954) on placebo.	with doses of 5 mg and 10 mg twice daily of asenapine, respectively, compared to 0% (0/503) of patients treated with placebo in six-week schizophrenia trials.
Suicide	Close supervision of high-risk patients should accompany drug therapy. Prescriptions for drug should be written for the smallest quantity consistent with good patient management to reduce the risk of overdose.				
	In two six-week placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% for lurasidone-treated patients compared to 0.4% on placebo. No suicide attempts or completed suicides were reported in these studies.	In two six-week placebo-controlled studies of aripiprazole as adjunctive treatment of major depressive disorder, the incidences of suicidal ideation and suicide attempts were 0% (0/371) for aripiprazole and 0.5% (2/366) for placebo.	NR	In three six-week clinical studies in patients with schizophrenia (N=951), the incidence of treatment-emergent suicidal ideation or suicide attempt was 0.6% (N=6) in quetiapine-treated patients and 0.9% (N=3) in placebo-treated patients.	The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for asenapine should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.
Tardive dyskinesia	Tardive dyskinesia is a syndrome that can develop in patients treated with antipsychotic drugs. Antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotic drugs, treatment discontinuation should be considered.				
Weight gain	Weight gain has been	See Adverse Events	Patients receiving	Increases in weight have	Increases in weight have

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	observed with atypical antipsychotic use. In the six-week, placebo-controlled studies the mean change in weight from baseline was -0.15, 0.67, 1.14, 0.68, and 0.26 kg, for lurasidone 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, and placebo, respectively. The mean weight gain was 0.75 kg for lurasidone-treated patients compared to 0.26 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight was 5.6% for lurasidone-treated patients vs. 4.0% for placebo-treated patients. In the uncontrolled, longer-term studies (primarily open-label extension studies), lurasidone was associated with a mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303) and -0.71 kg at week 52 (n=244).	Section below. In four-week to six-week trials in adults with schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)].	olanzapine should have their weight monitored regularly. In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of six weeks. In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb).	been observed in clinical trials. Patients receiving quetiapine should receive regular monitoring of weight. In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate. In schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four three-to-six-week placebo-controlled clinical trials, revealing a statistically significant greater incidence of weight gain for quetiapine (23%) compared to placebo (6%).	been observed in clinical trials. Patients receiving asenapine should receive regular monitoring of weight. In six-week, placebo-controlled schizophrenia trials, the mean weight gain was 1.1 kg for asenapine-treated patients compared to 0.1 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at endpoint) was 4.9% for asenapine-treated patients vs. 2% for placebo-treated patients. In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia or schizoaffective disorder, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a ≥7% increase in body weight (at endpoint) was 14.7%.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
Use in patients with concomitant illness	Clinical experience with drug in patients with certain concomitant systemic illnesses is limited. This drug has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease.				
Drug Interactions, †**					
Centrally acting drugs and alcohol	Given the primary CNS effects of lurasidone, caution should be used when lurasidone is taken in combination with other centrally acting drugs and alcohol.	Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with other centrally acting drugs. There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy patients. As with most psychoactive medications, patients should be advised to avoid alcohol while taking aripiprazole.	Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol. Multiple doses of olanzapine did not influence the kinetics of ethanol.	Given the primary CNS effects of quetiapine, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in patients with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine.	Given the primary CNS effects of asenapine, caution should be used when it is taken in combination with other centrally acting drugs or alcohol.
Cimetidine (and antacids or ranitidine)	NR	Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by	Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.	Administration of multiple daily doses of cimetidine (400 mg three times daily for four days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg three times daily). Dosage adjustment for	Coadministration of cimetidine (800 mg twice daily for 8 days) with asenapine (5 mg single dose) resulted in 13% decrease in C_{max} and 1% increase in $AUC_{0-\infty}$ on asenapine pharmacokinetics. No asenapine dose

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
		37% the C_{max} of aripiprazole, and by 13% the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.		quetiapine is not required when it is given with cimetidine.	adjustment is required.
CYP2D6 inhibitors	Lurasidone is not a substrate of CYP2D6 enzymes. This suggests that an interaction of lurasidone with drugs that are inhibitors or inducers of these enzymes is unlikely.	Inhibitors of CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and increase blood levels. Coadministration of a 10 mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when quinidine is given concomitantly with aripiprazole. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and should lead to similar dose	Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. Olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.	Coadministration of fluoxetine (60 mg once daily) did not alter the steady-state pharmacokinetics of quetiapine.	Coadministration of paroxetine (20 mg once daily for 9 days) with asenapine (5 mg single dose) resulted in 13% decrease in C_{max} and 9% decrease in $AUC_{0-\infty}$ on asenapine pharmacokinetics. No asenapine dose adjustment is required when coadministered with CYP2D6 inhibitors (e.g., paroxetine, cimetidine). Asenapine should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
		reductions. When the CYP2D6 inhibitor is withdrawn from combination therapy, the aripiprazole dose should be increased.			
CYP1A2 inhibitor (e.g., fluvoxamine)	Lurasidone is not a substrate of CYP1A2 enzymes. This suggests that an interaction of lurasidone with drugs that are inhibitors or inducers of these enzymes is unlikely.	Aripiprazole is not a substrate of CYP1A2 enzymes. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors like smoking, is unlikely.	Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.	NR	Coadministration of fluvoxamine (25 mg twice daily for 8 days) with asenapine (5 mg single dose) resulted in 13% increase in C_{max} and 29% increase in $AUC_{0-\infty}$ on asenapine pharmacokinetics. Fluvoxamine should be coadministered with caution.
CYP3A4 inhibitors (e.g., ketoconazole, ditiazem, etc.)	Lurasidone is predominantly metabolized by CYP3A4; interaction of lurasidone with strong and moderate inhibitors of this enzyme has been observed. When coadministration of lurasidone with a moderate CYP3A4	Inhibitors of CYP3A4 (e.g., ketoconazole) can inhibit aripiprazole elimination and cause increased blood levels. When ketoconazole is given concomitantly with aripiprazole, the aripiprazole dose should be reduced to one-half of its normal dose. Other strong	In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.	Coadministration of ketoconazole (200 mg once daily for four days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution	When coadministration of asenapine with CYP3A4 inhibitor such as cimetidine is considered, no asenapine dose adjustment is required.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	inhibitor such as diltiazem is considered, the dose should not exceed 40 mg/day. Lurasidone should not be used in combination with a strong CYP3A4 inhibitor such as ketoconazole.	inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.		(reduced dosage) is indicated when quetiapine is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, protease inhibitors).	
CYP3A4 inducers (e.g., rifampin, carbamazepine)	Lurasidone is predominantly metabolized by CYP3A4; interaction of lurasidone with strong and moderate inducers of this enzyme has been observed. Lurasidone should not be used in combination with strong CYP3A4 inducer, such as rifampin.	Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.		Coadministration of quetiapine (250 mg three times per day) and phenytoin (100 mg three times per day) increased the mean oral clearance of quetiapine by five-fold. Increased doses of quetiapine may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate).	When coadministration of asenapine with CYP3A4 inducer such as carbamazepine is considered, no asenapine dose adjustment is required.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
Digoxin (P-gp substrate)	Coadministration of lurasidone (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin approximately 9%, and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with lurasidone.	NR	NR	NR	NR
Drugs with hypotensive effects/ antihypertensive agents	NR	NR	Due to its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.	Because of its potential for inducing hypotension, quetiapine may enhance the effects of certain antihypertensive agents.	Because of its α1-adrenergic antagonism with potential for inducing hypotension, asenapine may enhance the effects of certain antihypertensive agents.
Imipramine	NR	NR	Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite, desipramine.	Coadministration of imipramine (75 mg twice daily) did not alter the steady state pharmacokinetics of quetiapine.	When coadministration of asenapine with imipramine is considered, no asenapine dose adjustment is required.
Levodopa and dopamine agonists	NR	NR	Olanzapine may antagonize the effects of levodopa and dopamine agonists.	Quetiapine may antagonize the effects of levodopa and dopamine agonists.	NR
Lithium	Coadministration of lithium (600 mg twice daily for 8 days) with	Coadministration of therapeutic doses of lithium	Multiple doses of olanzapine (10 mg for eight days) did not	Concomitant administration of quetiapine (250 mg	A population pharmacokinetics analysis indicated that

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	lurasidone (120 mg once daily for 8 days) resulted in 0.9-times C_{max} and 1.1-times AUC on lurasidone pharmacokinetics. No dose adjustment of lurasidone is required when coadministered with lithium.	(1200-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole.No dosage adjustment of aripiprazole is required when administered concomitantly with lithium. Coadministration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.	influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.	three times daily) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.	the concomitant administration of lithium had no effect on the pharmacokinetics of asenapine. Lithium pre-dose serum concentrations collected from an adjunctive therapy study were comparable between asenapine treated patients and placebo treated patients indicating a lack of effect of asenapine on lithium plasma levels.
Lorazepam	NR	Coadministration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy patients (N = 40: 35 males and 5 females; ages 19−45 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of aripiprazole is required when administered	Administration of intramuscular lorazepam (2 mg) one hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this coadministration of intramuscular	The mean oral clearance of lorazepam (2 mg, single-dose) was reduced by 20% in the presence of quetiapine administered as 250 mg at three-times-daily dosing.	NR

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
		concomitantly with lorazepam.	lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone.		
Midazolam (CYP34A substrate)	Coadministration of lurasidone (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively, relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with lurasidone.	NR	NR	NR	NR
Oral contraceptive (OC) (estrogen/ progesterone)	Coadministration of lurasidone (40 mg/day) at steady state with an OC containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not	NR	NR	NR	NR

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	affected by coadministration of lurasidone and OC. Dose adjustment of OC dose is not required when coadministered with lurasidone.				
Valproate	NR	When valproate (500 mg/day-1500 mg/day) and aripiprazole (30 mg/day) were coadministered, at steady state the C_{max} and AUC of aripiprazole were decreased by 25%. When aripiprazole (30 mg/day) and valproate (1000 mg/day) were coadministered, at steady state there were no clinically significant changes in the C_{max} or AUC of valproate. Therefore, no dosage adjustment of valproate is required when administered concomitantly with aripiprazole.	Olanzapine (10 mg daily for two weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.	NR	No asenapine dose adjustment is required when coadministered with valproate. Valproic acid pre-dose serum concentrations collected from an adjunctive therapy study were comparable between asenapine-treated patients and placebo-treated patients indicating a lack of effect of asenapine on valproic acid plasma levels.
Use in Specific Populations					
Pregnant women	Teratogenic Effects: Pregnancy Category B: Lurasidone was not teratogenic in rats and rabbits. There are no	Teratogenic Effects: Pregnancy Category C: In animal studies, aripiprazole demonstrated developmental toxicity,	Teratogenic Effects: Pregnancy Category C: In oral reproduction studies in rats at doses up to 18 mg/kg/day and	Teratogenic Effects: Pregnancy Category C: In animal studies, embryo-fetal toxicity occurred. There are no	Teratogenic Effects: Pregnancy Category C: In animal studies, asenapine increased post-implantation loss

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	adequate and well-controlled studies of lurasidone in pregnant women. Nonteratogenic effects: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. Lurasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	including possible teratogenic effects in rats and rabbits. Nonteratogenic effects: There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. Aripiprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m2 basis, respectively), no evidence of teratogenicity was observed. There are no adequate and well-controlled trials with olanzapine in pregnant females. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nonteratogenic effects: Neonates exposed to antipsychotic drugs (including olanzapine) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor,	adequate and well-controlled studies of quetiapine XR use in pregnant women. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nonteratogenic effects: Neonates exposed to antipsychotic drugs (including quetiapine) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	and decreased pup weight and survival at doses similar to or less than recommended clinical doses. In these studies, there was no increase in the incidence of structural abnormalities caused by asenapine. There are no adequate and well-controlled studies of asenapine in pregnant women. Nonteratogenic effects: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. Asenapine should be used during pregnancy only if the potential benefit justifies the

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
			somnolence, respiratory distress and feeding disorder in these neonates. Olanzapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.		potential risk to the fetus.
Nursing mothers	Lurasidone was excreted in milk of rats during lactation. It is not known if lurasidone or its metabolites are excreted in human milk. Breast feeding in women receiving lurasidone should be considered only if the potential benefit justifies the potential risk to the child.	Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.	In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.	Quetiapine was excreted into human milk. It is recommended that women receiving these treatments should not breast-feed. In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 µg/L. The estimated infant dose ranged from 0.09% to 0.43% of the weight-adjusted maternal dose. Based on a limited number (N=8) of mother/infant pairs, calculated infant daily doses range from less than 0.01 mg/kg (at a maternal daily dose up to 100 mg quetiapine) to 0.1 mg/kg (at a maternal	Asenapine is excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Caution should be exercised when asenapine is administered to a nursing woman. It is recommended that women receiving asenapine should not breast-feed.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
				daily dose of 400 mg).	
Labor and delivery	The effect of these treatments on labor and delivery in humans is unknown				
Pediatric use	Safety and effectiveness of lurasidone in pediatric and adolescent patients have not been established.	Safety and effectiveness in pediatric patients with schizophrenia were established in a six-week, placebo-controlled clinical trial in 202 pediatric patients aged 13–17 years. The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients 10-17 years of age were similar to those in adults after correcting for the differences in body weights.	Safety and effectiveness in children <13 years of age have not been established.	Safety and effectiveness of quetiapine have not been established in pediatric patients, and quetiapine is not approved for patients under the age of 18 years.	Safety and effectiveness in pediatric patients have not been established.
Geriatric use	Clinical studies of lurasidone in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently than younger patients. In elderly patients with psychosis (65 to 85), lurasidone concentrations (20 mg/day) were similar in elderly and young patients. No dose adjustment is necessary	No age effect was detected in single-dose pharmacokinetic studies. After multiple doses, the pharmacokinetics of aripiprazole in elderly patients appeared similar to that observed in young, healthy patients. No dosage adjustment is recommended for elderly patients. In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years)	In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to	In general, there was no indication of any different tolerability of quetiapine in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring	Multiple factors that might increase the pharmacodynamic response to asenapine, causing poorer tolerance or orthostasis, could be present in elderly patients, and these patients should be monitored carefully. Elderly patients with dementia-related psychosis treated with asenapine are at an increased risk of death compared to placebo. Asenapine is not approved for the

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	in elderly patients. Elderly patients with dementia-related psychosis treated with lurasidone are at an increased risk of death compared to placebo. Lurasidone is not approved for the treatment of patients with dementia-related psychosis.	patients compared to younger adult patients (18-64 years).	patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patients. In a study involving healthy patients, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years).	during the initial dosing period in the elderly. The mean plasma clearance of quetiapine was reduced by 30%-50% in elderly patients when compared to younger patients.	treatment of patients with dementia-related psychosis.
Renal impairment	It is recommended that lurasidone dose should not exceed 40 mg/day in patients with moderate and severe renal impairment (Clcr ≥10 mL/min to <50 mL/min. After administration of a single dose of 40 mg lurasidone to patients with mild, moderate, and severe renal impairment mean C_{max}	In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydroaripiprazole is less	Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and	Clinical experience with quetiapine in patients with renal impairment is limited. Patients with severe renal impairment had a 25% lower mean oral clearance than normal patients, but plasma quetiapine concentrations in the patients with renal insufficiency were within the range of concentrations seen in normal patients	The exposure of asenapine following a single dose of 5 mg was similar among patients with varying degrees of renal impairment and patients with normal renal function.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	increased by 40%, 92%, and 54%, respectively, and mean $AUC_{(0-\infty)}$ increased by 53%, 91%, and 2-times, respectively, compared to healthy matched patients.	than 1% of the dose. No dosage adjustment is required in patients with renal impairment.	normal patients, indicating that dosage adjustment based upon the degree of renal impairment is not required.	receiving the same dose. Dosage adjustment is therefore not needed.	
Hepatic impairment	It is recommended that lurasidone dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of lurasidone 20 mg, lurasidone $AUC_{0\text{-last}}$ increased 1.5 times higher in patients with mild hepatic impairment (Child-Pugh Class A), 1.7 times higher in patients with moderate hepatic impairment (Child-Pugh Class B), and three-fold in patients with severe hepatic impairment (Child-Pugh Class C) compared to healthy matched patients. Mean C_{max} was 1.3, 1.2, and 1.3 times higher for mild, moderate, and severe hepatically impaired patients,	In a single-dose study (15 mg of aripiprazole) in patients with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy patients, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. No dosage adjustment is required in patients with hepatic impairment.	Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in patients with clinically significant (Child-Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.	As quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed. Hepatically impaired patients had a 30% lower mean oral clearance of quetiapine than normal patients. In two of eight hepatically impaired patients, AUC and C_{max} were three times higher than those observed typically in healthy patients. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed.	In patients with severe hepatic impairment who were treated with a single dose of asenapine 5 mg, asenapine exposures (on average), were seven-fold higher than the exposures observed in patients with normal hepatic function. Thus, asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	respectively, compared to the values for healthy matched patients.				
Gender	Population pharmacokinetic evaluation indicated that the mean AUC of lurasidone was 18% higher in women than in men, and correspondingly, the apparent oral clearance of lurasidone was lower in women. Mean C_{max} of lurasidone was similar between women and men. No dosage adjustment of lurasidone is recommended based on gender.	C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30-40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.	Clearance of olanzapine is approximately 30% lower in women than in men. There were no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.	There is no gender effect on the pharmacokinetics of quetiapine.	The potential difference in asenapine pharmacokinetics between males and females was not studied in a dedicated trial. In a population pharmacokinetic analysis, no significant differences between genders were observed.
Race	Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of lurasidone, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of lurasidone. No dosage adjustment is recommended based on	Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.	In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.	There is no race effect on the pharmacokinetics of quetiapine.	In a population pharmacokinetic analysis, no effect of race on asenapine concentrations was observed. In a dedicated study, the pharmacokinetics of asenapine was similar in Caucasian and Japanese patients.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	race.				
Smoking status	Based on in vitro studies utilizing human liver enzymes, lurasidone is not a substrate for CYP1A2; smoking is therefore not expected to have an effect on the pharmacokinetics of lurasidone.	No dosage adjustment is recommended based on smoking status.	Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.	Smoking has no effect on the oral clearance of quetiapine.	A population pharmacokinetic analysis indicated that smoking had no effect on the clearance of asenapine in smokers.
Adverse Reactions					
Most common AEs Dystonia	In six-week placebo-controlled premarketing studies, the most common AEs (≥5% and at least twice the rate of placebo) were somnolence, akathisia, nausea, parkinsonism, and agitation. See Table 6 of the Package Insert for list of AEs ≥2% of lurasidone-treated patients and that occurred at greater incidence than in the placebo-treated patients.	The only commonly observed AE reported in clinical trials in patients (≥5% and at least twice that for placebo) was akathisia (aripiprazole [2−30 mg/day] 8%; placebo 4%).	The most common AEs (≥5% and at least twice that for placebo) were postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia.	The most common AEs (≥5% and at least twice that for placebo) were dry mouth, dyspepsia, somnolence, and dizziness.	The most common adverse reactions (≥5% and at least twice the rate on placebo) in schizophrenia were akathisia, oral hypoesthesia, and somnolence. The safety profile of asenapine in the maintenance treatment of schizophrenia was similar to that seen with acute treatment.
	Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.				
	In the six-week, placebo-controlled clinical trials, dystonia	NR	Events of dystonia have been reported infrequently (<1%) with	NR	NR

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	occurred in 4.7% of lurasidone-treated patients compared to 0.7% of patients receiving placebo. Seven patients (0.7%) discontinued clinical trials due to dystonic events.		olanzapine use.		
Extrapyramidal symptoms (EPS)	In the six-week, placebo-controlled schizophrenia studies, for lurasidone-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% vs. 5.1% for placebo-treated patients; and the incidence of akathisia for lurasidone-treated patients was 15.0% vs. 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of lurasidone (120 mg/day). See Table 8 of the Package Insert. In the six-week, placebo-controlled	In six-week, placebo-controlled trials in schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult schizophrenia trials, the objectively	In a fixed-dosage-range, placebo-controlled 6-week clinical trial of oral olanzapine in schizophrenia, Parkinsonism was seen in 15% of placebo patients, compared to 12–14% of olanzapine patients. Akathisia was seen in 23% of placebo patients, compared to 16–27% of olanzapine patients.	In placebo-controlled clinical trials with quetiapine, utilizing doses up to 800 mg per day, the incidence of any adverse reactions potentially related to EPS ranged from 8% to 11% for quetiapine and 4% to 11% for placebo. In three-arm placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of quetiapine XR, the incidence of any adverse reactions potentially related to EPS was 8% for quetiapine XR and 8% for quetiapine (without evidence of being dose related), and 5% in the placebo group. In these studies, the incidence of	In the six-week, placebo-controlled schizophrenia trials, the incidence of reported EPS-related events, excluding events related to akathisia, for asenapine-treated patients was 10% vs. 7% for placebo; and the incidence of akathisia-related events for asenapine-treated patients was 6% vs. 3% for placebo. The mean change from baseline for the all-asenapine 5 mg or 10 mg twice daily treated group was comparable to placebo in each of the rating scale scores (SAS for EPS, BAS for akathisia, and the AIMS for dyskinesias).

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	schizophrenia studies, data was objectively collected on Simpson Angus Rating Scale for EPS, the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for lurasidone-treated patients was comparable to placebo-treated patients, with the exception of the BAS global score (lurasidone, 0.2; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in lurasidone-treated patients vs. placebo for the BAS (lurasidone, 16.0%; placebo, 7.6%) and the SAS (lurasidone, 5.3%; placebo, 2.5%).	collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.		the individual adverse reactions (akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) was generally low and did not exceed 3% for any treatment group. At the end of treatment, the mean change from baseline in SAS total score and BAS global score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups. The incidence of extrapyramidal symptoms was consistent with that seen with the profile of quetiapine in schizophrenia patients.	
Laboratory test abnormalities	In a between-group comparison of the pooled data from six-week, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements,	Between-group comparison revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in	An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database	In three-arm quetiapine placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil	The effects on fasting serum glucose levels, total cholesterol, and fasting triglycerides in the six-week schizophrenia trials revealed no clinically relevant mean changes. In a 52-week,

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	triglycerides, and glucose from baseline to endpoint. There were also no clinically important differences between lurasidone and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. Creatinine: In the six-week, placebo-controlled trials, the mean change from baseline in creatinine was 0.06 mg/dL for lurasidone-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% of lurasidone-treated patients and 1.4% on placebo. The threshold for high creatinine value varied from ≥1.1 to ≥1.3 mg/dL based on the centralized laboratory definition for each study. Transaminases: The mean change in AST and ALT for	routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis in adult or pediatric patients. In a long-term (26-week), placebo-controlled trial in schizophrenia, there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, or total cholesterol measurements.	of about 2,400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevations to >200 IU/L was 2% (50/2381). None of these patients experienced jaundice or other symptoms attributable to liver impairment, and most had transient changes that tended to normalize while olanzapine treatment was continued. In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 2% (29/1438) of olanzapine-treated patients, compared to	count <1.5 x 10^9/L was 1.5% in patients treated with quetiapine XR and 1.5% for quetiapine, compared to 0.8% in placebo-treated patients. In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine and 1515 on placebo, the incidence of at least one occurrence of neutrophil count <1.0 x 10^9/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine, compared to 0.1% (2/1349) in patients treated with placebo. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should	double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of fasting glucose was 2.4 mg/dL. The effects on total cholesterol and fasting triglycerides in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes. In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean decrease from baseline of total cholesterol was 6 mg/dL, and the mean decrease from baseline of fasting triglycerides was 9.8 mg/dL. Transient elevations in serum transaminases (primarily ALT) in the six-week schizophrenia trials were more

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	lurasidone- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥3 times ULN was similar for all lurasidone-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).		0.3% (4/1196) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.	discontinue quetiapine at the first sign of a decline in WBC in absence of other causative factors. In short-term placebo-controlled trials, decreases in hemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 8.3% (594/7155) of quetiapine-treated patients compared to 6.2% (219/3536) of patients treated with placebo. In a database of controlled and uncontrolled clinical trials, decreases in hemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 11% (2277/20729) of quetiapine-treated patients.	common in treated patients but mean changes were not clinically relevant. In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of ALT was 1.6 units/L. The effects on prolactin levels in the six-week schizophrenia trials revealed no clinically relevant changes in mean change in baseline. In a long-term (52-week), double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean decrease in prolactin from baseline for asenapine-treated patients was 26.9 ng/mL. The proportion of patients with creatine kinase elevations >3 times ULN at any time were 6.4% and 11.1% for patients

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
					treated with asenapine 5 mg BID and 10 mg BID, respectively, as compared to 6.7% for placebo-treated patients in short-term, fixeddose trials in schizophrenia.
ECG changes	ECG measurements were taken at various time points during the lurasidone clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with lurasidone. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program. The effects of lurasidone on the QT/QC interval were evaluated in a dedicated QT study involving 87 clinically stable patients	Between-group comparisons for a pooled analysis of placebo-controlled trials revealed no significant differences between oral aripiprazole and placebo in the proportion of patients with potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients.	In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs. no change with placebo). This increase in heart rate may be related to olanzapine's potential to induce orthostatic changes.	2.5% of quetiapine patients, and 2.3% of placebo patients, had tachycardia (>120 bpm) at any time during the trials. Quetiapine was associated with a mean increase in heart rate, assessed by ECG, of 6.3 bpm compared to a mean increase of 0.5 bpm for placebo. The incidence of adverse reactions of tachycardia was 1.9% for quetiapine compared to 0.5% for placebo. Quetiapine use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients.	NR

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
	with schizophrenia or schizoaffective disorder, who were treated with lurasidone doses of 120 mg/day or 600 mg/day, or ziprasidone 160 mg/day. Holter monitor-derived ECG assessments were obtained over an eight-hour period at baseline and steady state. No patients treated with lurasidone experienced QTc increases >60 msec from baseline, nor did any patient experience a QTc of >500 msec				
Weight gain	See above in listed Warnings and Precautions.	In four-week to six-week trials in adults with schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight (aripiprazole [8%] compared to placebo [3%]).	See above in listed Warnings and Precautions.	See above in listed Warnings and Precautions.	See above in listed Warnings and Precautions.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
Overdosage					
	In premarketing clinical studies involving more than 2,096 patients and/or healthy patients, accidental or intentional overdosage of lurasidone was identified in one patient who ingested an estimated 560 mg of lurasidone. This patient recovered without sequelae.	Seventy-six cases of deliberate or accidental overdosage with oral aripiprazole have been reported worldwide. These include overdoses with oral aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 cases recovered without sequelae, and one case recovered with sequelae (mydriasis and feeling abnormal). The largest known case of acute ingestion with a known outcome involved 1080 mg of oral aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdosage in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities. Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral	In premarketing trials involving more than 3,100 patients and/or normal patients, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analyses or ECG. Vital signs were usually within normal limits following overdoses. In post-marketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included	In clinical trials, survival has been reported in acute overdoses of up to 30 g of quetiapine. Most patients who overdosed experienced no AEs or recovered fully from the reported events. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.	In premarketing clinical studies involving more than 3350 patients and/or healthy patients, accidental or intentional acute overdosage of asenapine was identified in three patients. Among these few reported cases of overdose, the highest estimated ingestion of asenapine was 400 mg. Reported adverse reactions at the highest dosage included agitation and confusion.

Generic Name	Lurasidone	Aripiprazole	Olanzapine	Quetiapine XR	Asenapine
		aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor.	agitation/ aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.		

*Warnings and precautions not appearing in the lurasidone label and only appearing in one other label are as follows:

- Quetiapine XR: cataracts, hypothyroidism, transaminase elevations, priapism

**Drug interactions not appearing in the lurasidone label and only appearing in one other comparator label are as follows:

- Olanzapine: charcoal
- Olanzapine: CYP1A2 inducers, carbamazepine
- Quetiapine XR: thioridazine

†Drugs having no clinically important interactions with the comparators of interest are as follows:

- Lurasidone: Not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes; interaction of lurasidone with drugs that are inhibitors or inducers of these enzymes is unlikely.
- Aripiprazole: famotidine, valproate, lithium, lamotrigine, dextromethorphan, warfarin, omeprazole, lorazepam, escitalopram, venlafaxine, fluoxetine, paroxetine, and sertraline
- Quetiapine XR: antiyprine, divalproex, haloperidol, risperidone
- Olanzapine: biperiden, CYP2C9, CYP2C19, CYP3A inhibitors, diazepan, theophylline, warfarin

Abbreviations: AE = adverse event, AIMS = Assessments of Involuntary Movement Scales, ALT = alanine transaminase, AST = aspartate transaminase, AUC = area under the concentration curve, BAS = Barnes Akathisia Scale, BID = two times a day, BPM = beats per minute, CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, CBC = complete blood count, C_{max} = maximum plasma concentration, CNS = central nervous system, ECG = electrocardiogram, EPS = extrapyramidal symptom, g = gram, GGT = gamma-glutamyltransferase, h = hour, HDL = high-density lipoprotein, HI = hepatic impairment, kg = kilogram, L = liter, lb = pound, LDL = low-density lipoprotein, msec = millisecond, N = number of patients, NMS = neuroleptic malignant syndrome, NR = not reported, OC = oral contraceptive, PR interval = time from the onset of the P wave to the beginning of the QRS complex, QD = once a day, QRS = Q, R, and S waves in an ECG, QT = QT interval, QTc = corrected QT interval, SAS = Simpson Angus Rating Scale, $t_{1/2}$ = terminal half-life, ULN = upper limit of normal, WBC = white blood cell, XR = Extended release.

2.2. Place of Product in Therapy

2.2.1. Disease Description

2.2.1.1. Epidemiology and Risk Factors

Schizophrenia is a chronic and disabling neurodegenerative disorder. Although there is no cure for schizophrenia, it is treatable. Schizophrenia has an estimated population prevalence of approximately 1% (estimated 2.4 million adults), with a diagnosed prevalence of 0.51% in the United States (US).[15,16] It affects both genders equally.[17]

Schizophrenia typically first manifests in young adults, with the peak ages of onset in the early to mid-20s in men and late 20s in women.[18] It is believed to be caused by a combination of genetic and environmental factors.[19] Twin studies in schizophrenia have found an approximate 50% correspondence rate for monozygotic twins[19], leaving room for the influence of environmental factors, such as exposure to viruses prenatally and pregnancy/birth complications,[20,21] family environment, stress, or substance abuse.[22] Recent research has identified certain genes that appear to increase the risk for developing schizophrenia.[19]

2.2.1.2. Pathophysiology

- Schizophrenia has been characterized as a "genetic disorder of the synapse."[23] It is likely that multiple genes are involved, each exerting a modest effect on the development (synaptogeneses), adaptation (plasticity), and function (neurotransmission) of synapses in the brain.[19, 23]
- The symptoms of schizophrenia are mediated by a dysfunction in neurotransmission at specific receptors localized in specific regions of the brain:[24, 25, 26]
    - D_2 dopaminergic receptors mediate the positive and negative symptoms of psychosis. Blocking these receptors in certain areas of the brain (e.g., mesolimibic dopamine pathway) with treatment mitigates psychotic symptoms but blockade in other areas (e.g., mesocortical dopamine pathway, nigrostriatal pathway, etc.) can also lead to unwanted hypoactivity resulting in unwanted effects, such as EPS.[24]
    - D_3 dopaminergic receptors are believed to play a possible role in the mediation of symptoms of psychosis.[27]
    - Serotonergic receptors are also believed to play a role in schizophrenia:[24, 25]
        - $5\text{-}HT_{2A}$ is believed to cause excitation of cortical pyramidal neurons, excitation of glutamate release, and inhibition of dopamine release and to play a possible role in sleep and hallucinations
        - $5\text{-}HT_{1a}$ is believed to cause inhibition of cortical pyramidal neurons and regulation of hormones and to play a possible role in depression, anxiety, and cognition
        - $5HT_{2c}$ is believed to play a possible role in appetite control and weight regulation
        - $5HT_6$ is believed to play a possible role in enhancing cognitive functioning and in motor function

        - $5HT_7$ is believed to play a possible role in circadian rhythms, sleep, mood, thermoregulation, learning and memory, endocrine regulation, and motor function
    - Glutamatergic receptors (mGluR2 and mGluR3) are responsible for presynaptic autoregulation of excitatory neurotransmission triggered by glutamate and are believed to play a possible role in neuroprotection and mood stabilization.[19, 24]
    - N-methyl d-aspartate (NMDA) receptors are responsible for modulation of excitatory postsynaptic neurotransmission triggered by glutamate.[24]
    - Side effects of antipsychotic treatment are thought to be associated with multiple receptors, including:[24,28]
        - Muscarinic receptors (M_1), which are believed to play a possible role in constipation, blurred vision, dry mouth, and drowsiness
        - Histaminic receptors (H_1), which are believed to play a possible role in weight gain, drowsiness, and sedation
        - Alpha1-adrenergic receptors (α_1), which are believed to play a possible role in dizziness, drowsiness, and sexual dysfunction
        - Alpha2-adrenergic receptors (α_2), which are believed to play a possible role in cognition and sexual dysfunction

Abnormalities in brain morphology, including lateral and third ventricular enlargement, medial temporal lobe volume reductions, and superior temporal gyrus volume reductions, particularly on the left side of the brain, and cingulate and cingulum bundle irregularities are also believed to play a role in the development of schizophrenia.[29, 30, 31] Given the number of brain areas implicated in the disease, it is hypothesized that a network of afflicted brain regions mediates the abnormal functioning in schizophrenia.[31]

2.2.1.3. Clinical Presentation

Schizophrenia is characterized by a mixture of positive symptoms (e.g., hallucinations, delusions, and thought and movement disorders), negative symptoms (e.g., flat affect, anhedonia, alogia, and avolition), and cognitive deficits (e.g., impaired memory, attention, and planning/organizing). Mood symptoms such as depression, anxiety, hostility, and excitement can also be present in patients with schizophrenia.[17, 32]

The course of schizophrenia is variable and often cyclical in nature, with some patients experiencing acute relapses followed by periods of stability. Others remain chronically ill or slowly worsen over time. Complete remission is rare.[18]

The DSM-IV has been widely used for the diagnosis of schizophrenia (to be replaced in 2013 by DSM-V, which is currently in development). DSM-IV diagnosis of schizophrenia requires two (or more) of the following, each present for a significant portion of time during a one-month period (or less if successfully treated): delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms (e.g., affective flattening, alogia, or avolition). Furthermore, for a significant portion of the time, since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement). These signs and symptoms must persist for more than six months. Schizoaffective and mood disorders with psychotic features must be ruled out.[18] There are no reliable laboratory tests

used in the diagnosis of schizophrenia, and disease confirmation rests solely on a review of the patient's medical and family history and a thorough mental status examination conducted by a qualified mental health professional.[19]

2.2.1.4. Societal, Humanistic, and Economic Burden

CV and metabolic disorders, such as diabetes, hypertension, metabolic syndrome, and obesity, are more prevalent in persons with schizophrenia than in the general population.[33] The prevalence of metabolic syndrome and diabetes is approximately double that of the general population (40.9% vs. 23.7% and 10.3% vs. 5.6%, respectively).[34, 35] The prevalence of CV risk factors is high in patients with schizophrenia: 58% of patients have dyslipidemia, 45% have hypertension, 15% have abnormal fasting glucose, and 68% are obese.[36] Individuals with schizophrenia have a higher risk of CV disease mortality than the general population.[37]

The increased prevalence of modifiable CV risk factors may be attributable to schizophrenia itself. In addition, a number of atypical antipsychotics have been associated with weight gain and other metabolic abnormalities.[38, 39, 40]

The life expectancy of individuals with schizophrenia is reduced by approximately 15 years compared with the general population.[41] The risk of death in individuals with schizophrenia is elevated for both natural and unnatural causes (approximately two and eight times that of the general population, respectively).[42] The risk of death from suicide is approximately 12 times that of the general population.[42]

The total annual excess (compared with matched controls) cost of schizophrenia in the US was estimated at $62.7 billion in 2002, with indirect costs of $32.4 billion (of which $21.6 billion was due to unemployment), direct non-healthcare costs of $7.6 billion (including living costs offset), and direct healthcare costs of $22.7 ($6.9 billion outpatient, $5.0 billion drugs, $2.8 billion inpatient, $8.0 million long-term care).[43]

Although schizophrenia accounts for a lower number of hospital stays compared to other mental illnesses, 2004 data from the Healthcare Cost and Utilization Project show that patients admitted for schizophrenia have the longest average length of stay (11.1 days) and the highest average total cost per stay ($8,000) compared with other mental health and substance abuse disorders.[44]

Recently diagnosed patients (<1 year from index event) incur significantly higher annual health care costs compared to chronic schizophrenia patients (≥3 years from index event) ($20,654 vs. $15,489), largely due to higher rates of hospitalization.[45]

Analyses of 2001−2002 data from the Medical Expenditures Panel Survey found an average cost per year of $3,726 per individual with schizophrenia living in the community. Public insurance paid almost three-quarters of the total expenditures (49.3% Medicaid and 17.7% Medicare). Overall health costs increased 20% to 90% for individuals with schizophrenia and comorbidities such as diabetes, dyslipidemia, or hypertension.[46]

Data from a recently published, prospective, observational study (1997−2003) show that the 12-month direct mental health costs for patients with prior relapse (within six months prior to the one-year study) were three times higher than costs for patients without a relapse ($33,187 vs. $11,771), underscoring the economic importance of relapse prevention as a treatment goal for schizophrenia patients.[47]

A study based on California Medicaid claims data (2001−2003) reported that approximately one-third (36.6%) of inpatient admissions for schizophrenia occur during gaps in the antipsychotic prescription record (based on a 15-day gap). The study estimated that improving treatment adherence

could decrease the number of hospital admissions by 12.3%, lower the number of inpatient treatment days by 13.1%, and save the national Medicaid system approximately $106 million annually.[48]

Appropriate early intervention and treatment have been associated with better outcomes in schizophrenia.[18,49, 50]

It is well established that the onset of schizophrenia dramatically alters the lives of patients and their families, often with devastating consequences, including broken relationships, isolation, disability and dependence, unemployment, and sometimes prison or homelessness, which significantly adds to non-healthcare-related costs of schizophrenia.[51]

A recent study comparing middle-aged and older community-dwelling schizophrenia patients to normal controls showed that persons with schizophrenia score significantly lower on the physical and mental component summary scores of the Short Form (36) Health Survey (SF-36), indicating that health-related quality of life is poorer in patients with schizophrenia than the general population.[52]

The closure of mental hospitals combined with shortened length of inpatient stays for acute episodes have shifted the care of schizophrenia patients to their families. According to a 2008 survey conducted by the National Alliance on Mental Illness, 63% of persons with schizophrenia have accepted financial support or money from family members, 56% have relied on them for transportation, and 50% have relied on them for housing.[52] Caregivers report that they struggle to find time for themselves; approximately 41% of those surveyed have provided more than 10 years of care and 19% for more than 40 hours per week.[53]

Two recently published literature reviews on the caregiver burden in schizophrenia have highlighted the tendency for caregivers to withdraw from social interactions with family and friends. Limited access to emotional and tangible social support represents one causal pathway that increases caregivers' risk of stress, anxiety, and depression.[53, 54]

2.2.2. Approaches to Treatment

- Despite scientific advances, schizophrenia remains one of the most challenging diseases to treat due to its variable nature, the heterogeneity of clinical response, the side effects of treatment, and its association with high morbidity and mortality.[50, 55]

2.2.2.1. Overview of Treatment Options

- The current standard of care for the treatment of schizophrenia is the use of atypical antipsychotics,[50, 56] which include oral asenapine, aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, quetiapine XR, risperidone, and ziprasidone, as well as a number of long-acting injectable formulations of risperidone and, more recently, paliperidone palmitate and olanzapine pamoate.[57, 58] These medications are perceived to have an improved side effect profile with regards to EPS and are believed to remediate the negative symptoms of schizophrenia better (not confirmed for all atypicals)[59] than their precursors, typical antipsychotics (e.g., haloperidol).[60]
- Psychosocial therapy is recommended as an adjunctive treatment for patients with schizophrenia. An important aspect of treatment of patients with schizophrenia is to have a multidimensional treatment plan in place that includes a psychiatrist, a case manager, and family involvement to reduce hospitalizations and homelessness.[61] Psychosocial treatment approaches include family interventions, supported employment, assertive community treatment, social skills training, and cognitive/behavioral psychotherapy.[50, 56]

2.2.2.1.1. Studies Comparing Other Available Antipsychotics

- Prior to lurasidone's approval, results from two large non-industry-sponsored studies (CATIE and CUtLASS) have raised questions regarding the clinical superiority of atypical vs. typical antipsychotics; and demonstrated that certain atypicals, particularly clozapine and olanzapine, may be associated with metabolic problems, including serious weight gain, diabetes, and hyperlipidemia.[62, 63, 64]
- It has been reported that clozapine and olanzapine are associated with an increased risk of diabetes and dyslipidemia, while ziprasidone and aripiprazole are not.[32] Among the atypical antipsychotics, the relative tendency to cause weight gain is as follows: clozapine > olanzapine > risperidone = quetiapine > ziprasidone = aripiprazole.[65] The atypical antipsychotic agents that are perceived to be more efficacious (i.e., olanzapine, clozapine) and carry the burden of increased side effects; however agents with milder side effect profile (i.e., aripiprazole, ziprasidone) are often perceived not to be as effective.[62 ,66,67] A comparison of the risk of adverse events among currently available atypical antipsychotic agents is shown in Table 4, below.

Table 4: Comparative Risk of Adverse Effects of Atypical Antipsychotics[68]

Adverse Effect	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anticholinergic effects	0	+++	+	+	0	0
Dyslipidemia	0	+++	+++	++	+	0
EPS	+	0	+	0	++	+
Type 2 diabetes	+	++	++	+	+	+
Weight gain	0	+++	+++	++	++	0

Note: 0 = rare, + = lower risk, ++ = medium risk, +++ = higher risk
Abbreviations: EPS = extrapyramidal symptoms

- Discontinuation rates for antipsychotic treatment are high; in CATIE, 74% of participants stopped study medication before 18 months (olanzapine: 64%, risperidone: 74%, perphenazine: 75%, ziprasidone: 79%, quetiapine: 82%) across treatment groups.[63] Poor adherence to antipsychotic treatment has been shown to increase the risk of relapse and subsequent hospitalization.[69] Similarly, switching antipsychotics for non-clinical reasons has been shown to worsen clinical outcomes.[70]

2.2.2.2. Place and Anticipated Use of Lurasidone

- Lurasidone is expected to be used as a first-line therapy in adult patients with a DSM-IV diagnosis of schizophrenia in accordance with clinical guidelines.

2.2.2.3. Proposed Ancillary Disease or Care Management Intervention Strategies

- There are no planed ancillary disease or care management intervention strategies.

2.2.2.4. Expected Outcomes of Therapy

- Treatment with lurasidone is expected to improve the symptoms of schizophrenia. An increased incidence of cardio metabolic risks factors (increases in dyslipidemia, glucose, weight, or BMI) is expected to occur infrequently with lurasidone treatment. The most

common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with lurasidone were somnolence, akathisia, nausea, parkinsonism, and agitation, based on the pooled data from five six-week, double-blind, placebo-controlled studies. The apparent dose-related adverse reactions were akathisia and somnolence.[2] The differences in cardiometabolic changes and safety and tolerability of lurasidone are described in detail in Section 3.

2.2.2.4.1. Atypical Antipsychotics Clinical Pharmacology

- The mechanism of action of atypical antipsychotics is unknown. However, it is believed that their efficacy for the treatment of schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2a}$) receptor antagonism. Atypical antipsychotics' effectiveness and tolerability are believed to be related to each product's binding affinity to D_2 and $5HT_{2a}$ receptors, as well as to other dopamine and serotonin receptors, alpha adrenergic receptors, histaminic receptors, and muscarinic receptors. Each atypical antipsychotic has a distinct receptor binding profile that differentiates it from the others. (Table 5 below).

Table 5: Receptor Binding Affinities for Atypical Antipsychotics[71]

Binding Affinities (Ki;nM)	Lurasidone	Haloperidol	Risperidone	Aripiprazole	Clozapine	Olanzapine
Dopamine						
D_1	262[a]	83	60.6	387	189	58
D_2	0.994	2.0	4.9	0.95	431	72
D_3	15.7	12	12.2	4.5	646	63
D_4	29.7	5.0	7.5	> 1000	22.3	21
Serotonin						
$5\text{-}HT_{1A}$	6.38	1202	427	5.6	105	2063
$5\text{-}HT_{2A}$	0.47	53	0.17	8.7	5.4	2.0
$5\text{-}HT_{2C}$	415[b]	3085	12	75	10.7	6.4
$5\text{-}HT_6$	-	3666	2241	574	17	6.0
$5\text{-}HT_7$	0.495	378	6.6	10	18	105
Norepinephrine						
α_1	47.9[a]	12	5.0	25	1.6	109
$\alpha 2_A$	40.7	1113	151	74	142	314
$\alpha 2_C$	10.8	550	1.3	38	34	29
Histamine						
H_1	> 1000[c]	3002	5.184	29	2.0	4.9
Acetylcholine						
M_1	> 1000	> 10000	> 10000	6776	14	24

Cloned cells expressing human receptors unless otherwise noted: [a]at; [b]orcine; [c]uinea pig

- The correlation between receptor binding profile and clinical efficacy and safety is not well established. It has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. In vitro and in vivo receptor binding studies revealed that lurasidone is an antagonist with a high affinity at dopamine D_2, serotonin $5\text{-}HT_{2A}$, and $5\text{-}HT_7$ receptors; is an antagonist with moderate affinity at human α_{2C} adrenoceptors; is a partial agonist at serotonin $5\text{-}HT_{1A}$ receptors; and is an antagonist at α_{2A} adrenoceptors. Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors.[1]

2.2.2.5. Additional Drug Development or Post-marketing Obligations

- A pediatric study for the treatment of schizophrenia in pediatric patients aged 13 to 17 years to obtain pharmacokinetic data and provide information pertinent to the dosing of lurasidone tablets in the population[72]
- A pediatric study for the treatment of schizophrenia in pediatric patients aged 13 to 17 years to evaluate the efficacy and safety of lurasidone tablets in the population[72]
- A longer-term maintenance study to evaluate the efficacy of lurasidone tablets in the treatment of adults with schizophrenia[72]
- A study to evaluate the minimum effective dose of lurasidone tablets in the treatment of adults with schizophrenia[72]

2.2.3. Relevant Treatment Guidelines and Consensus Statements

The primary goals of schizophrenia treatment are to minimize or eliminate symptoms, improve quality of life, encourage and maintain recovery from the disease to the greatest extent possible, and prevent relapse.[50] Practice guidelines on the management of schizophrenia and use of medications are available from the American Psychiatric Association (APA), Schizophrenia Patient Outcomes Research Team (PORT), Texas Medication Algorithm Project (TMAP), and American Society of Health System Pharmacists (ASHP).[50,62,73, 74] All of these guidelines are based on evidence sourced from a combination of well conducted randomized trials, meta-analyses, and cohort studies, as well as expert opinion. The APA and PORT guidelines are described in more detail here.

Both working groups classify schizophrenia management into treatment for the acute and maintenance phase. Although second-generation antipsychotics are generally recommended over their precursors, the majority of atypicals are given equivalent status in these practice guidelines, with stress placed on choosing the appropriate medication to match the individual patient's treatment history and characteristics, including prior treatment response and side effect profile, and the patient's preferences (e.g., oral vs. injectable formulations).[50, 56] The APA also recommends that treatment practices should evolve over time to accommodate the fluctuations in a given patient's illness.[50]

<u>Acute phase:</u> For patients who are experiencing an acute exacerbation of their illness, atypical antipsychotics (other than clozapine) should be used as first-line treatment to mitigate psychotic symptoms. The choice of medication should be based on the patient's preferences and clinical history.[50,56] Clozapine is recommended for treatment-resistant patients whose symptoms are not controlled after trying two other atypical antipsychotic agents.[56] A treatment algorithm for managing the acute phase of schizophrenia is detailed in Table 6 below.

Table 6: Choice of Medication in the Acute Phase of Schizophrenia Based on Patient Profiles[50]

Patient Profile	Risperidone, Olanzapine, Quetiapine, Ziprasidone, or Aripiprazole	Clozapine	Long-acting Injectable Antipsychotics
First episode	Yes		
Persistent suicidal ideation or behavior		Yes	
Persistent hostility and aggressive behavior		Yes	
Tardive dyskinesia	Yes; all these drugs may not be equal in their lower/no tardive dyskinesia liability	Yes	
History of sensitivity to extrapyramidal side effects	Yes, except higher doses of risperidone		
History of sensitivity to prolactin elevation	Yes, except risperidone		
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia	Ziprasidone or aripiprazole		
Repeated nonadherence to pharmacological treatment			Yes

Note: This algorithm does not include paliperidone or iloperidone, which were approved after the 2004 APA guidelines were released.

Maintenance phase: It is recommended that patients continue their acute antipsychotic medication to sustain symptom control and lower the risk of relapse. In addition to oral medication, long-acting injectable medications are recommended as a treatment option in the stabilization period.[56] As schizophrenia is a chronic disease, it is important that the effectiveness of treatments be considered in light of their long-term tolerability profiles. Clinicians should seek to establish the minimum effective dose to prevent relapse for a given patient.[50] Psychosocial support, including family interventions, supported employment, assertive community treatment, social skills training, and cognitive/behavioral psychotherapy are recommended. Furthermore, mitigation of comorbidities, such as substance abuse and obesity, are also recommended.[50,56]

2.2.4. Evidence for Pharmacogenomic Tests and Drugs

Not applicable.

3. SUPPORTING CLINICAL EVIDENCE

3.1 Overview of Key Clinical Efficacy and Safety Studies **Page 73**

3.2 Clinical Evidence Table Spreadsheets **Page 138**

3.1. Overview of Key Clinical Efficacy and Safety Studies

Pre-FDA Approval

Registration Trials

- At the time of FDA approval, the efficacy and safety of lurasidone was established at a dose range of 40 mg to 120 mg in five, six week, randomized, double blind, placebo controlled trials (studies D1050006, D1050049, D1050196, D1050229, and D1050231) in the treatment of adult patients with schizophrenia. Study D1050231 included olanzapine 15 mg/day an active-control to confirm assay sensitivity. Study D1050049 was a failed study as neither the active-control (haloperidol) nor any of the lurasidone doses separated from placebo on the primary endpoint. Therefore, no efficacy conclusions can be drawn from study D1050049; however it was included in pooled safety assessments. Pooled safety data from these studies are presented below and in the Package Insert.[1, 2] Individual study results are presented in Section 3.1.1.
    - Efficacy:
        - Results from four studies (D1050006, D1050196, D1050229, and D1050231) showed the superiority of lurasidone compared with placebo in clinical assessments of psychopathology and schizophrenia symptoms as measured by the primary endpoint, the change from baseline to study endpoint (week 6) in PANSS total score (D1050229, and D1050231) and BPRSd score (D1050006, D1050196) compared to placebo.[3, 4,75]
        - Improvements were initially observed within the first week of treatment, with efficacy persisting through six weeks.[3, 4,75]
        - Repeated efficacy was observed at each dose of lurasidone (40 mg, D1050006 and D1050231; 80 mg, D1050196, D1050229; 120 mg, D1050006 and D1050231).[3,4,75]
    - Safety (Pooled Results):
        - The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with lurasidone were somnolence, akathisia, nausea, parkinsonism, and agitation. Among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with lurasidone, the apparent dose-related adverse reactions were akathisia and somnolence A total of 9.4% (94/1004) lurasidone-treated patients and 5.9% (27/455) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in patients treated with lurasidone that were at least 2% and at least twice the placebo rate.[1]
        - In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically relevant effects on total cholesterol, triglycerides, glucose, and parameters in hematology, urinalysis, or serum chemistry.[1]
        - The mean increase in weight was 0.75 kg for lurasidone patients vs. 0.26 kg for placebo patients. The mean change in glucose and HbA1c for lurasidone vs. placebo patients was 1.3 mg/dL vs. -0.7 mg/dL and 0.02%

vs. 0.02%, respectively. The mean change in lipids for lurasidone vs. placebo patients were -8.2 mg/dL vs. -8.5 mg/dL for total cholesterol, -4.4 mg/dL vs. -2.8 mg/dL for low-density lipoprotein (LDL) cholesterol, and -9.3 mg/dL vs. -15.7 mg/dL for triglycerides. The median change from baseline to endpoint in prolactin levels for lurasidone treated patients was an increase of 1.1 ng/mL compared to a decrease of 0.6 ng/mL in the placebo-treated patients. The increase in prolactin was dose-related and was greater in female patients.[1]

Uncontrolled Longer-term Studies

- In addition to the six-week placebo controlled studies, a number of longer-term studies (primarily open-label extension studies) were also conducted. In these studies, lurasidone was associated with a:
  - Mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236), and +1.2 mg/dL at week 52 (n=244);
  - Mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n=238) and -3.5 (n=238) mg/dL at week 36, and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively;
  - Mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303), and -0.71 kg at week 52 (n=244); and
  - Median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189), and -3.3 ng/mL at week 52 (n=243).[1]
- Among the uncontrolled longer-term studies, a 1 year, open-label, flexible dose (40-120 mg/day) study (D1001048) in Japanese patients demonstrated that lurasidone was associated with a gradual and sustained improvement in total PANSS and BPRS scores.
  - The most frequently reported AEs were: schizophrenia (34%), nasopharyngitis (33%), serum prolactin increase (19%), and insomnia (18%). AEs occurred in 27% of patients. The majority of AEs (68%) occurred within the first 4 weeks of treatment; 4.3% were reported as severe.[76]

<u>Post-FDA Approval</u>

Following FDA approval, additional short-term and longer term controlled and uncontrolled studies have been completed. More detailed results from these studies are presented in Section 3.1.3.

Short-term Controlled Studies

- A six week, randomized, double blind, placebo controlled trials (D1050233) demonstrated the efficacy and safety of lurasidone at daily doses of 80 and 160 mg/day in patients with an acute exacerbation of schizophrenia. Quetiapine XR 600 mg/day was included as an active control to confirm assay sensitivity. The primary endpoint in this study was the change from baseline to study endpoint (week 6) in PANSS total score compared to placebo.
  - The least square mean change from baseline in the PANSS total score was -22.2 for lurasidone 80 mg (p-value vs. placebo: <0.001), -26.5 for lurasidone 160 mg (p-value vs. placebo: <0.001), and -10.3 for placebo.

- The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with either lurasidone doses were akathisia, nausea, parkinsonism, dizziness, somnolence.[5]

Longer-term Comparator Controlled Studies

- Study D1050234, a 12 month, double-blind, parallel group study comparing lurasidone (flexibly dosed 40-160 mg/day) to quetiapine XR (flexibly dosed 200-800 mg/day) for relapse prevention in adult patients with schizophrenia demonstrated that lurasidone was non-inferior to quetiapine XR in preventing relapse.
  - The time to relapse of psychotic symptoms, primary endpoint, showed a hazard ratio (HR) of 0.728 [95%CI: 0.410,1.295], indicating a 27% lower risk of relapse for lurasidone vs. quetiapine XR.
  - The probability of relapse at Month 12 endpoint (based on Kaplan-Meier survival analysis) was 23.7% for lurasidone and 33.6% for quetiapine XR.
  - Commonly observed adverse events (incidence ≥5%) for lurasidone vs. quetiapine XR, respectively: akathisia (12.6% vs. 2.4%), headache (10.6% vs. 9.4%), insomnia (7.9% vs. 9.4%), anxiety (6.0% vs. 3.5%), weight increased (6.0% vs. 8.2%), parkinsonism (6.0% vs. 0.0%); schizophrenia (4.6% vs. 15.3%), psychotic disorder (4.0% vs. 8.2%), and agitation (4.0% vs. 5.9%).[6]
- Study D1050237 was a 1-year, double blind trial that evaluated the long term safety and tolerability of lurasidone (flexibly dosed between 40 to 120 mg/day) in the treatment of schizophrenia or schizoaffective disorder and included risperidone (flexibly dosed between 2 to 6 mg/day) as an active comparator. The primary safety and tolerability measures were primary objectives in this study.
  - The most common adverse events (incidence ≥10%) in lurasidone treatment group were nausea, insomnia, sedation, akathisia, somnolence, headache, and vomiting. The most common adverse events in the risperidone treatment group were weight increased, somnolence, headache, sedation, insomnia, and nausea.
  - Among the patients who completed 12 months of treatment, mean weight change was -0.9 kg for lurasidone and +2.6 kg for risperidone; median changes in total cholesterol, triglycerides, glucose, and prolactin were -1.5 mg/dL, -8.5 mg/dL, 0.0 mg/dL, and -0.4 ng/mL, respectively for lurasidone and -8.0 mg/dL, 0.0 mg/dL, +3.0 mg/dL, 14.8 ng/mL, respectively for risperidone.[7]

Longer-Term Uncontrolled Studies (Open-label Extension Studies)

- Patients who successfully completed Study D1050231, a six week, multicenter, randomized, double-blind, placebo- and active controlled study with lurasidone 40 mg/day, lurasidone 120 mg/day and olanzapine 15 mg/day (to confirm assay sensitivity), had the option to enter a 6 month, open-label extension study (D1050231E) with flexibly dosed lurasidone (40 to 120 mg/day).
  - The two adverse events that occurred with an incidence >10% in lurasidone treated patients were akathisia (13.0%) and insomnia (11.0%).

  - Except for patients who received olanzapine 15 mg in the initial double-blind phase, patients who were in the 6 months open label treatment with lurasidone did not result in meaningful changes in body weight and body mass index. Patients who were switched from olanzapine 15 mg/day to lurasidone and completed open-label treatment (n=31) experienced a mean (SD) reduction of -1.9 (5.7) kg in weight. Laboratory findings for patients who continued on lurasidone (and were on lurasidone in the preceding study) and completed open-label treatment (n=55) included mean changes from open label baseline to endpoint in cholesterol (-4.9 mg/dL), triglycerides (-11.6 mg/dL), insulin (-3.2 mU/L), and glucose (+6.7 mg/dL). Patients switched from olanzapine to lurasidone showed sustained decreases in lipids. Prolactin, which had increased during the double-blind phase of the study (median changes of +2.2 ng/mL in the lurasidone arms (combined) and +3.8 ng/mL on olanzapine arms at LOCF endpoint), showed a median decrease of -1.3 ng/mL (LOCF) during the OL extension.[9]

- Patients who successfully completed study D1050229, a six-week, double-blind treatment phase of the study had the option to continue into the 22-month, open-label extension phase designed to evaluate the safety and tolerability of flexibly dosed lurasidone (40, 80, and 120 mg/day) in the treatment of patients with schizophrenia (study D1050229E).
  - The majority of discontinuations were due to withdrawal of consent (n=60, 24.0%), insufficient clinical response or worsening of condition (n=57, 23%), and AEs (n=37, 15.0%). The five most frequently reported TEAEs were schizophrenia (12.4% of all patients), akathisia (10.8% of all patients), somnolence (10.8% of all patients), vomiting (8.8% of all patients), and nausea (8.4% of all patients). The majority of TEAEs reported were classified as either mild or moderate.
  - Over the entire course of the study (double-blind phase and OL extension), there were overall mean changes in total cholesterol (-3.8 mg/dL), HDL (-2.4 mg/dL), LDL (-2.7 mg/dL), triglycerides (-2.0 mg/dL), and glucose (+1.6 mg/dL). During the OL extension phase, median prolactin decreased overall from OL baseline to study end by -1.20 ng/mL.[8]

Swtich Study

- A recently completed 6-week, open-label study assessed the results of switching outpatients with schizophrenia from other antipsychotic agents to lurasidone (40 mg, 80 mg, or 40 mg then 80 mg) for two weeks, during which patients were tapered off their prior antipsychotic agents. Patients were then continued on flexibly dosed lurasidone 40-120 mg for the following 4 weeks. Doses were administered once-daily in the evening with food or within 30 minutes after eating. The following are top-line results from the study; the study data is currently being analyzed:
  - At the end of week 6, the cumulative probability of treatment failure for all patients switched from other antipsychotics to lurasidone was 7.9%. Treatment failure was defined a priori as discontinuation due to insufficient clinical response, exacerbation of underlying disease, or due to adverse event.
  - Improvements from baseline to LOCF endpoint in PANSS total score, CGI-S score, and CDSS score were all statistically significant ($p<0.0001$).
  - Most common adverse events (incidence ≥5%) were nausea (13.8%), insomnia (12.9%), akathisia (12.5%), headache (9.6%), vomiting (7.1%), somnolence

(6.7%), and dry mouth (5.8%). Sixteen of 240 patients (6.7%) discontinued treatment due to adverse events.[77]

Ongoing Studies

- Studies in patients with schizophrenia that are currently ongoing include: a double-blind, placebo-controlled study withdrawal study of lurasidone for the maintenance treatment of patients with schizophrenia; a long-term, open-label, flexible-dose continuation study in patients who have completed a prior lurasidone study; a randomized, single blind study to assess cognitive remediation in patients stabilized on lurasidone; and a double-blind, parallel-group study of lurasidone in patients with schizophrenia. These studies are noted in Section 3.1.4.

3.1.1. Methodological Overview of D1050006, D1050049, D1050196, D1050229, D1050231, D10502333 [4,5,78,79,80,81,82]

In these trials, adult patients (≥18 years of age) with a primary diagnosis of schizophrenia, hospitalized with an acute exacerbation of psychotic symptoms and duration of illness ≥1 year were treated with once-daily (QD) fixed doses of lurasidone 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg, placebo or active control (haloperidol/olanzapine/quetiapine XR). The studies included a screening period (up to 14 days), a three-to-seven-day single-blind placebo washout period, a baseline assessment, and a six-week double-blind treatment period.[5,7] Studies D1050006, D1050049, and D1050196 were conducted in the United States between February 2001 and December 2004. Studies D1050229 and D1050231 were multicontinental trials conducted between October 2007 and June 2009. Study D1050233 was a multicontinental trial conducted between October 2008 and June 2010. As shown in

Table 7, three trials included active controls to confirm assay sensitivity.

Table 8 presents the inclusion and exclusion criteria of the trials.

Table 7: Treatment Arms in D1050006, D1050049, D1050196, D1050229, D1050231, D1050233

Study Number	Placebo	Lurasidone QD					Haloperidol QD 10 mg	Olanzapine QD 15 mg	Quetiapine XR QD 600 mg
		20 mg	40 mg	80 mg	120 mg	160 mg			
D1050006[a]	X	-	X	-	X	-	-	-	-
D1050049[b]	X	X	X	X	-	-	X	-	-
D1050196	X	-	-	X	-	-	-	-	-
D1050229[c]	X	-	X	X	X	-	-	-	-
D1050231[d]	X	-	X	-	X	-	-	X	-
D1050233[e]	X	-	-	X	-	X	-	-	X

Abbreviations: QD = once daily
[a] Patients received 80 mg for 5 days and began 120 mg on Day 6.
[b] Patients received a fixed dose of haloperidol 10 mg QD.
[c] Patients received 80 mg for 3 days and began 120 mg on Day 4.
[d] Patients received olanzapine 10 mg for 7 days and began 15 mg on Day 8, consistent with the manufacturer's labeling and dosing recommendations.
[e] Patients randomized to the lurasidone 160 mg dose group received lurasidone 120 mg for Days 1 and 2, then the assigned 160 mg QD thereafter. Patients randomized to the quetiapine XR 600 mg dose group received quetiapine XR 300 mg for Days 1 and 2, then the assigned 600 mg QD thereafter.

Table 8: Summary of Inclusion and Exclusion Criteria* (D1050006, D1050049, D1050196, D1050229, D1050231, D1050233)

D1050006, D1050049, D1050196	D1050229, D1050231, D1050233
Inclusion Criteria	
18–64 years of age, inclusive.	18–75 years of age, inclusive
Satisfied DSM-IV criteria (including disorganized, paranoid and undifferentiated subtypes); patient had to have an acute exacerbation of symptoms.	Satisfied DSM-IV criteria for a primary diagnosis of schizophrenia (including disorganized, paranoid, and undifferentiated subtypes). Experienced acute exacerbation of psychotic symptoms <2 months and marked deterioration of function from baseline (by history) or patient had been hospitalized for treatment of an acute psychotic exacerbation for <2 weeks before screening.
Minimum duration of illness of at least 1 year	Minimum duration of illness of at least 1 year
Demonstrated sufficient pathology at baseline (BPRS total score of ≥42) and a score of ≥4 on ≥2 items of the Positive Symptom Subscale of PANSS	PANSS total score of ≥80 at screening and baseline, with a score of ≥4 (moderate) on ≥2 on the following PANSS items: delusions, conceptual, disorganization, hallucinations, unusual thought content, and suspiciousness
Score of ≥4 on the CGI-S at baseline	Score of ≥4 on the CGI-S at screening and baseline
Exclusion Criteria	
Resistance to antipsychotic drug treatment, defined as failure to respond to > 2 antipsychotic agents from 2 chemical classes or clozapine, given at an adequate dose for sufficient time.	Resistance to neuroleptic treatment, defined as failure to respond to >2 or more marketed antipsychotic agents from 2 different classes, given at an adequate dose for a sufficient period of time over the last year

Note: Table does not include a complete list of inclusion and exclusion criteria.

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, CNS = central nervous system, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, HIV = human immunodeficiency virus, PANSS = Positive and Negative Syndrome Scale

A summary of primary and secondary efficacy endpoints for the six, 6-week, placebo-controlled trials is illustrated in Table 9. Primary endpoints for D1050006, D1050049, and D1050196 were assessed at the Day 42 last observation carried forward (LOCF) endpoint using analysis of covariance (ANCOVA).[72,73,81,82] Primary endpoints in D1050229, D1050231, and D1050233 were evaluated using a mixed model for repeated measures (MMRM) model based on the intent-to-treat (ITT) population.

Table 9: Summary of Efficacy Endpoints in D1050006, D1050049, D1050196, D1050229, D1050231, D1050233

Efficacy Endpoint	D1050006	D1050049	D1050196	D1050229	D1050231	D1050233
Primary Endpoint						
Change from baseline to week 6 in BPRSd[a]	X	X	X	-	-	-
Change from baseline to week 6 in PANSS total score	-	-	-	X	X	X
Secondary Endpoints						
Change from baseline to week 6 in PANSS total score	X	X	X	X	X	X
Change from baseline to week 6 in CGI-S	X	X	X	X	X	X
Change from baseline to week 6 in CGI-I	X	-	-	-	-	-
Responder rates at week 6[b]	X	X	X	-	-	-
Change from baseline to week 6 in MADRS	-	X	X	X	X	X
Change from baseline to day 4 in PANSS total score	-	-	-	X	X	X
PANSS responder rates at week 6[c]	-	-	-	X	X	X
Change from baseline to week 6 in PANSS positive subscale	X	X	X	X	X	X
Change from baseline to week 6 in PANSS negative subscale	X	X	X	X	X	X
Change from baseline to week 6 in PANSS psychopathology subscale	X	X	X	X	X	X
Change from baseline to week 6 in PANSS cognitive subscale	-	-	X	-	-	-

[a] The BPRSd is the Brief Psychiatric Rating Scale, as derived from the PANSS.
[b] BPRSd decrease from baseline ≥20% and/or CGI ≤2.
[c] Responders are defined as those who achieved a 20% or greater improvement in PANSS total score from baseline over the study period.

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impression scale – Improvement, CGI-S = Clinical Global Impressions scale – Severity of Illness, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, PANSS = Positive and Negative Syndrome Scale.

Safety parameters included EPS evaluated using the Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS), and abnormal involuntary movement scale (AIMS) assessments, clinical laboratory tests, physical examination, ECGs, and AEs.

3.1.2. Results of Completed Short-term Lurasidone Safety and Efficacy Trials

3.1.2.1. Study D1050233

Phase III, randomized, double-blind, placebo- and active comparator (quetiapine XR) controlled clinical trial to study the efficacy and safety of two doses of lurasidone in acutely psychotic patients with schizophrenia.[5]

Study Patients

A total of 488 patients met entry criteria and were randomized to once-daily treatment with 80 mg or 160 mg/day lurasidone, 600 mg/day quetiapine XR as the active control, or placebo in a 1:1:1:1 ratio. A total of 353 patients (72%) completed the double-blind study phase. The majority of discontinuations were due to insufficient clinical response or a worsening of existing condition (n=65, 13%), withdrawal of consent (n=48, 10%), or an AE not associated with worsening of an existing condition (n=15, 3%). Patients who completed the double-blind treatment were eligible for entry into a 12-month, double-blind extension study (results included in Section 3.1.3). A total of 482 patients were included in the ITT population, and 486 were analyzed for safety. Baseline characteristics were generally balanced across treatment groups (Table 10).

Table 10: Baseline Characteristics, Study D1050233, Safety Population

Baseline Characteristic	Lurasidone 80 mg N=125	Lurasidone 160 mg N=121	Quetiapine XR 600 mg N=119	Placebo N=121
Sex, n (%) Male	96 (77)	82 (68)	77 (65)	77 (64)
Age, years, Mean (Range)	36.2 (18-61)	37.9 (18-63)	37.4 (18-58)	37.4 (19-65)
Race, n (%), White	75 (60)	63 (52)	69 (58)	68 (56)
DSM-IV subtype, n (%), paranoid*	116 (93)	108 (89)	110 (95)	111 (93)
PANSS total Score, mean ± SD*	97.7 ± 9.7	97.5 ± 11.8	97.7 ± 10.2	96.6 ± 10.2
CGI-S, mean ± SD*	5.0 ± 0.5	5.0 ± 0.6	4.9 ± 0.6	4.9 ± 0.5
MADRS, mean ± SD*	11.6 ± 7.6	11.2 ± 7.8	12.3 ± 8.1	11.3 ± 6.7

*ITT population: Lurasidone 80 mg (N = 125), Lurasidone 160 mg (N = 121), Quetiapine XR 160 mg (N = 116), placebo (N=120)

Abbreviations: CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, SD = standard deviation

Efficacy Results

The difference from placebo in the mean change in the PANSS total score from baseline to week 6 was significant in the lurasidone 80 mg group (-11.9, p<0.001) and the lurasidone 160 mg group (-16.2, p<0.001) (primary endpoint). A summary of primary and secondary endpoint results are shown in Table 11.

Table 11: Summary of Primary and Secondary Endpoints, Repeated Measures Model or ANCOVA Model, Study D1050233, ITT Population

Endpoint	Lurasidone 80 mg	Lurasidone 160 mg	Quetiapine XR 600 mg	Placebo
Primary Endpoint				
PANSS Total[a]	**N=125**	**N=121**	**N=116**	**N=120**
Change from baseline to week 6 (SE)	-22.2 (1.8)	-26.5 (1.8)	-27.8 (1.8)	-10.3 (1.8)
Difference from placebo at week 6 (SE)[b]	-11.9 (2.6)	-16.2 (2.5)	-17.5 (2.6)	-
p-value vs. placebo	<0.001[c]	<0.001[c]	<0.001[a]	-
Secondary Endpoints				
CGI-S[a]	**N=125**	**N=121**	**N=116**	**N=120**
Change from baseline to week 6 (SE)	-1.5 (0.1)	-1.7 (0.1)	-1.7 (0.1)	-0.9 (0.1)
Difference from placebo at week 6 (SE)[b]	-0.6 (0.1)	-0.8 (0.1)	-0.8 (0.1)	-
p-value vs. placebo	<0.001[c]	<0.001[c]	<0.001[a]	-
PANSS Total[a]	**N=125**	**N=121**	**N=116**	**N=120**
Change from baseline to day 4 (SE)	-4.1 (0.5)	-4.8 (0.5)	-4.0 (0.5)	-2.4 (0.5)
Difference from placebo at day 4 (SE)[b]	-1.7 (0.7)	-2.5 (0.7)	-1.6 (0.7)	-
p-value vs. placebo	0.014	<0.001	0.028	-
PANSS positive subscore[a]	**N=125**	**N=121**	**N=116**	**N=120**
Difference from placebo at week 6 (SE)[b]	-3.8 (0.9)	-5.4 (0.9)	-5.8 (0.9)	-
p-value vs. placebo	<0.001[a]	<0.001[a]	<0.001[a]	-
PANSS negative subscore[a]	**N=125**	**N=121**	**N=116**	**N=120**
Difference from placebo at week 6 (SE)[b]	-2.8 (0.6)	-3.3 (0.6)	-3.2 (0.6)	-

Endpoint	Lurasidone 80 mg	Lurasidone 160 mg	Quetiapine XR 600 mg	Placebo
p-value vs. placebo	<0.001[a]	<0.001[a]	<0.001[a]	-
PANSS general psychopathology subscore[a]	**N=125**	**N=121**	**N=116**	**N=120**
Difference from placebo at week 6 (SE)[b]	-5.0 (1.2)	-7.2 (1.2)	-7.9 (1.2)	-
p-value vs. placebo	<0.001[a]	<0.001[a]	<0.001[a]	-
MADRS[d]	**N=116**	**N=112**	**N=110**	**N=116**
LS mean change from baseline to week 6 LOCF endpoint (SE)	-4.0 (0.5)	-4.4 (0.5)	-4.3 (0.5)	-1.0 (0.5)
Difference from placebo week 6 LOCF endpoint (SE)	-2.9 (0.7)	-3.3 (0.7)	-3.3 (0.8)	-
p-value vs. placebo	<0.001[d]	<0.001[d]	<0.001[d]	-
Responders[e]	**N=125**	**N=121**	**N=116**	**N=120**
n (%)	81 (65)	95 (79)	92 (79)	49 (41)
p-value vs. placebo	<0.001	<0.001	<0.001	-

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts are from differences of change from baseline treatment estimates for each lurasidone dose group and quetiapine XR vs. placebo.
[c] Adjusted p-values were adjusted with Hommel-based tree-gate keeping procedures.
[d] LS means and p-values were from an ANCOVA with treatment and pooled center as fixed factors and Baseline value as a covariate.
[e] Responders are defined as those who achieved a 20% or greater improvement in PANSS total score from baseline over the study period.
Responder analysis of PANSS total score at LOCF Week 6 Endpoint was based on a logistic regression of response, with effects for treatment group and baseline score.

Abbreviations: CGI-S = Clinical Global Impression scale – Severity of Illness, ITT = intent-to-treat, LOCF = last observation carried forward MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SE = standard error, LS = least squares, N = number of patients.

Safety Results

The proportion of patients in the combined lurasidone treatment groups (60.2%) reporting ≥1 TEAE was similar to the placebo group (62.0%). The five most frequently reported TEAEs in patients treated with lurasidone were headache, insomnia, akathisia, nausea, and vomiting. Change in EPS as measured by the SAS, BAS, and AIMS scores was generally absent to mild in lurasidone-treated patients. No ECG abnormalities were associated with lurasidone treatment. The most common TEAEs (occurring in ≥5%, any treatment group) are listed in Table 12.

Table 12: Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050233, Safety Population

Treatment-emergent Adverse Events, n (%)	Lurasidone 80 mg N=125	Lurasidone 160 mg N=121	Quetiapine XR 600 mg N=119	Placebo N=121
Patients with >1 TEAE	**72 (57.6)**	**76 (62.8)**	**71 (59.7)**	**75 (62.0)**
Agitation	4 (3.2)	6 (5.0)	3 (2.5)	10 (8.3)
Akathisia	10 (8.0)	9 (7.4)	2 (1.7)	1 (0.8)
Anxiety	9 (7.2)	4 (3.3)	1 (0.8)	10 (8.3)
Arthralgia	2 (1.6)	1 (0.8)	7 (5.9)	1 (0.8)
Constipation	3 (2.4)	1 (0.8)	8 (6.7)	3 (2.5)
Dizziness	6 (4.8)	7 (5.8)	16 (13.4)	2 (1.7)
Dry mouth	2 (1.6)	2 (1.7)	9 (7.6)	1 (0.8)
Dyspepsia	3 (2.4)	7 (5.8)	3 (2.5)	4 (3.3)
Headache	12 (9.6)	12 (9.9)	13 (10.9)	13 (10.7)
Insomnia	14 (11.2)	8 (6.6)	5 (4.2)	11 (9.1)
Nausea	10 (8.0)	8 (6.6)	4 (3.4)	4 (3.3)
Parkinsonism	7 (5.6)	8 (6.6)	4 (3.4)	0
Psychotic disorder	0	0	0	7 (5.8)
Somnolence	5 (4.0)	8 (6.6)	16 (13.4)	1 (0.8)
Stomach discomfort	4 (3.2)	3 (2.5)	2 (1.7)	6 (5.0)
Upper respiratory tract infection	2 (1.6)	1 (0.8)	6 (5.0)	1 (0.8)
Vomiting	8 (6.4)	9 (7.4)	6 (5.0)	6 (5.0)
Weight increased	1 (0.8)	2 (1.7)	8 (6.7)	1 (0.8)

Abbreviations: N = number of patients, TEAE = treatment-emergency adverse event

There were 15 serious adverse events (SAE) reported by 12 patients during the six-week study period (2.0% in the combined lurasidone treatment group, 2.5% of quetiapine XR patients, and 3.3% of placebo patients). Six SAEs (in 4 patients) were considered to be at least possibly related to study medication. Of these six SAEs, two were suicidal ideation, one was suicidal behavior, and two were psychotic disorder, all in the placebo group.

Laboratory data showed an association between lurasidone treatment with a small increase from baseline to LOCF endpoint in prolactin (median increase of 1.7 ng/mL in lurasidone-combined treatment groups vs. median decrease of -0.80 ng/mL in the placebo group, p=0.004). Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 13.

Table 13: Summary of Prolactin Levels, Study D1050233, Safety Population

Endpoint	Lurasidone 80 mg	Lurasidone 160 mg	Quetiapine XR 600 mg	Placebo
Prolactin (ng/mL; male), LOCF	**N=85**	**N=78**	**N=68**	**N=71**
Median change from baseline	0.20	2.35	-0.90	0.00
Rank ANCOVA mean score test vs. placebo	0.963	0.006	0.369	-
Prolactin (ng/mL; female), LOCF	**N=26**	**N=36**	**N=39**	**N=40**
Median change from baseline	5.60	7.00	0.60	-1.65
Rank ANCOVA mean score test vs. placebo	0.013	0.004	0.671	-

LOCF is defined as the last post-baseline measurement collected through either the week 6 visit day (for patients entering into extension phase) or within seven days after the 6-week phase study medication discontinuation (for discontinued patients not entering into the extension phase).

Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, N = number of patients

The percentage of patients with a ≥7% increase in body weight at LOCF endpoint was 4% of patients in the lurasidone 80 mg group, 4% of patients in the lurasidone 160 mg group, and 3% of patients in the placebo group. In the quetiapine XR group, 15% of patients had a ≥7% increase in body weight at LOCF endpoint. Mean changes from baseline for metabolic endpoints are listed in Table 14. Glucose, triglycerides, LDL, HDL, total cholesterol, and insulin were intended to be collected at fasting.

Table 14: Summary of Metabolic Endpoints, Study D1050233, Safety Population

Endpoint	Lurasidone 80 mg	Lurasidone 160 mg	Quetiapine XR 600 mg	Placebo
Total Cholesterol (mg/dL), LOCF	**N=111**	**N=114**	**N=107**	**N=111**
Mean change from baseline (SD)	-4.3 (30.3)	-6.8 (29.5)	10.0 (33.6)	-9.0 (29.5)
Rank ANCOVA mean score test vs. placebo	0.435	0.627	<0.001	-
HDL (mg/dL), LOCF	**N=111**	**N=114**	**N=107**	**N=111**
Mean change from baseline (SD)	-0.1 (7.9)	-0.9 (11.8)	0.6 (9.9)	-2.2 (7.8)
Rank ANCOVA mean score test vs. placebo	0.026	0.063	0.017	-
LDL (mg/dL), LOCF	**N=111**	**N=114**	**N=107**	**N=111**
Mean change from baseline (SD)	-2.4 (25.3)	-2.9 (24.8)	6.3 (29.4)	-4.5 (22.9)
Rank ANCOVA mean score test vs. placebo	0.959	0.509	0.002	-

Endpoint	Lurasidone 80 mg	Lurasidone 160 mg	Quetiapine XR 600 mg	Placebo
Triglycerides (mg/dL), LOCF	**N=111**	**N=114**	**N=106**	**N=111**
Mean change from baseline (SD)	-11.1 (74.2)	-10.1 (53.3)	20.9 (113.6)	-9.4 (75.9)
Rank ANCOVA mean score test vs. placebo	0.707	0.860	0.023	-
Glucose (mg/dL), LOCF	**N=111**	**N=112**	**N=107**	**N=110**
Mean change from baseline (SD)	-2.4 (20.6)	2.3 (19.9)	6.5 (24.4)	1.3 (20.3)
Rank ANCOVA mean score test vs. placebo	0.627	0.992	0.101	-
HbA1c (%), LOCF	**N=109**	**N=111**	**N=104**	**N=108**
Mean change from baseline (SD)	0.09 (0.42)	0.01 (0.28)	0.03 (0.31)	0.01 (0.30)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-
C-reactive Protein (mg/dL), LOCF	**N=106**	**N=114**	**N=105**	**N=109**
Mean change from baseline (SD)	0.065 (0.462)	0.345 (2.295)	0.193 (1.541)	0.144 (0.974)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-
Insulin (mU/L), LOCF	**N=106**	**N=114**	**N=104**	**N=109**
Mean change from baseline (SD)	-1.69 (28.97)	5.13 (36.38)	5.16 (48.23)	1.11 (30.86)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-
Weight (kg), LOCF	**N=116**	**N=113**	**N=111**	**N=115**
Mean change from baseline (SD)	0.62 (2.58)	0.60 (3.08)	2.09 (3.34)	0.13 (2.50)
Rank ANCOVA mean score test vs. placebo	0.046	0.299	<0.001	-
BMI (kg/m^2), LOCF	**N=116**	**N=113**	**N=111**	**N=115**
Mean change from baseline (SD)	0.21 (0.85)	0.20 (1.01)	0.72 (1.13)	0.03 (0.84)
Rank ANCOVA mean score test vs. placebo	0.034	0.266	<0.001	-

LOCF is defined as the last post-baseline measurement collected through either the week 6 visit day (for patients entering into the extension phase) or within seven days after the 6-week phase study medication discontinuation (for discontinued patients not entering into the extension phase).

Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward, N = number of patients, NR = not reported, SD = standard deviation

3.1.2.2. Study D1050231

Phase III, randomized, placebo- and active comparator- (olanzapine) controlled trial to study the safety and efficacy of two doses of lurasidone HCl in acutely psychotic patients with schizophrenia.[4,79]

Study Patients

A total of 478 patients met entry criteria and were randomized to once-daily treatment with 40 mg or 120 mg lurasidone, 15 mg olanzapine as the active control, or placebo in a 1:1:1:1 ratio. Olanzapine was dosed according to manufacturer recommendations. A total of 298 patients (62%) completed the double-blind study phase. The majority of discontinuations were due to withdrawal of consent (n=75, 16%), insufficient clinical response or a worsening of existing condition (n=61, 13%), or an AE not associated with worsening of an existing condition (n=30, 6%). Patients who completed the double-blind treatment were eligible for entry into a six-month, open-label extension study. A total of 473 patients were included in the ITT population, and 475 were analyzed for safety. Baseline characteristics were generally balanced across treatment groups (

Table 15).

Table 15: Baseline Characteristics, Study D1050231, Safety Population

Baseline Characteristic	Lurasidone 40 mg N=119	Lurasidone 120 mg N=118	Olanzapine 15 mg N=122	Placebo N=116
Sex, n (%) Male	93 (78)	93 (79)	95 (78)	90 (78)
Age, years, Mean (Range)	37.7 (18-63)	37.9 (18-68)	38.3 (19-62)	36.9 (18-64)
Race, n (%), White	44 (37)	48 (41)	41 (34)	37 (32)
DSM-IV subtype, n (%), paranoid*	106 (89)	105 (89)	100 (82)	98 (86)
PANSS total Score, mean ± SD*	96.6 ± 10.7	97.9 ± 11.3	96.3 ± 12.2	95.8 ± 10.8
CGI-S, mean ± SD*	5.0 ± 0.7	5.0 ± 0.6	4.9 ± 0.7	4.9 ± 0.7
MADRS, mean ± SD*	10.8 ± 7.0	11.4 ± 7.2	10.8 ± 6.2	10.6 ± 6.1

*ITT population: Lurasidone 40 mg (N = 119), Lurasidone 120 mg (N = 118), Olanzapine 15 mg (N = 122), placebo (N = 114)

Abbreviations: CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, SD = standard deviation

Efficacy Results

The difference from placebo in the mean change in the PANSS total score from baseline to week 6 was significant in the lurasidone 40 mg group (-9.7, p=0.002) and the lurasidone 120 mg group (-7.5,

p=0.022) (primary endpoint). A summary of primary and secondary endpoint results are shown in Table 16.

Table 16: Summary of Primary and Secondary Endpoints, Repeated Measures Model, Study D1050231, ITT Population

Endpoint[a]	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Primary Endpoint				
PANSS Total	**N=119**	**N=118**	**N=122**	**N=114**
Change from baseline to week 6 (SE)	-25.7 (2.0)	-23.6 (2.1)	-28.7 (1.9)	-16.0 (2.1)
Difference from placebo at week 6 (SE)[b]	-9.7 (2.9)	-7.5 (30)	-12.6 (2.8)	-
p-value vs. placebo	0.002[c]	0.022[c]	<0.001[a]	-
Secondary Endpoints				
CGI-S	**N=119**	**N=118**	**N=122**	**N=114**
Change from baseline to week 6 (SE)	-1.5 (0.1)	-1.4 (0.1)	-1.5 (0.1)	-1.1 (0.1)
Difference from placebo at week 6 (SE)b	-0.4 (0.1)	-0.3 (0.1)	-0.5 (0.1)	-
p-value vs. placebo	0.011[c]	0.040[c]	<0.001[a]	-
PANSS Total	**N=119**	**N=118**	**N=122**	**N=114**
Change from baseline to day 4 (SE)	-5.1 (0.7)	-5.4 (0.7)	-6.1 (0.7)	-4.8 (0.7)
Difference from placebo at day 4 (SE)b	-0.2 (1.0)	-0.6 (1.0)	-1.3 (0.9)	-
p-value vs. placebo	0.798	0.559	0.166	-
PANSS positive subscore	**N=118**	**N=118**	**N=121**	**N=114**
Change from baseline to week 6 (SE)	-7.7 (0.7)	-7.5 (0.7)	-9.3 (0.7)	-5.4 (0.7)
p-value vs. placebo	0.035c	0.035c	<0.001a	-
PANSS negative subscore	**N=118**	**N=118**	**N=121**	**N=114**
Change from baseline to week 6 (SE)	-6.0 (0.5)	-5.2 (0.6)	-6.2 (0.5)	-3.6 (0.5)
p-value vs. placebo	0.004[c]	0.045[c]	<0.001[a]	-

Endpoint[a]	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
PANSS general psychopathology subscore	**N=118**	**N=118**	**N=121**	**N=114**
Change from baseline to week 6 (SE)	-12.4 (1.0)	-11.1 (1.0)	-13.3 (0.9)	-7.8 (1.0)
p-value vs. placebo	0.002[c]	0.022[c]	<0.001[a]	-
MADRS	**N=116**	**N=109**	**N=119**	**N=111**
Change from baseline to week 6 (SE)	-3.5 (0.5)	-3.2 (0.6)	-5.0 (0.5)	-2.8 (0.6)
Difference from placebo week 6 (SE)b	-0.8 (0.8)	-0.5 (0.8)	-2.3 (0.8)	-
p-value vs. placebo	0.571[c]	0.571[c]	0.003[a]	-
Responders[d]	**N=118**	**N=118**	**N=121**	**N=114**
n (%)	73 (62)	71 (60)	89 (74)	56 (49)
p-value vs. placebo	0.108[c]	0.108[c]	<0.001	-

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts are from differences of change from baseline treatment estimates for each lurasidone dose group vs. placebo.
[c] Adjusted p-values were adjusted with Hommel-based tree-gate keeping procedures.
[d] Responders are defined as those who achieved a 20% or greater improvement in PANSS total score from baseline over the study period.
Responder analysis of PANSS total score at LOCF Week 6 Endpoint was based on a logistic regression of response, with effects for treatment group and baseline score.

Abbreviations: CGI-S = Clinical Global Impression scale – Severity of Illness, ITT = intent-to-treat, LOCF = last observation carried forward MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, PANSS = Positive and Negative Syndrome Scale, SE = standard error

Safety Results

The proportion of patients in the combined lurasidone treatment groups (78.9%) reporting ≥1 TEAE was similar to the placebo group (72.4%). The five most frequently reported TEAEs in patients treated with lurasidone were headache, akathisia, somnolence, insomnia, and sedation. Change in EPS as measured by the SAS, BAS, and AIMS scores was generally absent to mild in lurasidone-treated patients. No ECG abnormalities were associated with lurasidone treatment. The most common TEAEs (occurring in ≥5%, any treatment group) are listed in Table 17.

Table 17: Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050231, Safety Population

Treatment-emergent Adverse Events, n (%)	Lurasidone 40 mg N=119	Lurasidone 120 mg N=118	Olanzapine 15 mg N=122	Placebo N=116
Patients with >1 TEAE	**90 (75.6)**	**97 (82.2)**	**100 (82.0)**	**84 (72.4)**
Agitation	14 (11.8)	7 (5.9)	8 (6.6)	6 (5.2)
Akathisia	14 (11.8)	27 (22.9)	9 (7.4)	1 (0.9)
Anxiety	12 (10.1)	12 (10.2)	7 (5.7)	8 (6.9)
Back pain	6 (5.0)	6 (5.1)	7 (5.7)	5 (4.3)
Constipation	6 (5.0)	9 (7.6)	8 (6.6)	6 (5.2)
Decreased appetite	6 (5.0)	1 (0.8)	2 (1.6)	2 (1.7)
Dizziness	5 (4.2)	6 (5.1)	3 (2.5)	2 (1.7)
Dry mouth	2 (1.7)	3 (2.5)	12 (9.8)	1 (0.9)
Dyspepsia	9 (7.6)	9 (7.6)	6 (4.9)	7 (6.0)
Dystonia	4 (3.4)	9 (7.6)	1 (0.8)	1 (0.9)
Headache	26 (21.8)	21 (17.8)	17 (13.9)	25 (21.6)
Increased appetite	1 (0.8)	3 (2.5)	7 (5.7)	4 (3.4)
Insomnia	15 (12.6)	14 (11.9)	13 (10.7)	13 (11.2)
Musculoskeletal stiffness	3 (2.5)	6 (5.1)	3 (2.5)	2 (1.7)
Nausea	13 (10.9)	9 (7.6)	6 (4.9)	5 (4.3)
Parkinsonism	11 (9.2)	13 (11.0)	6 (4.9)	2 (1.7)
Psychotic disorder	2 (1.7)	4 (3.4)	4 (3.3)	8 (6.9)
Restlessness	7 (5.9)	4 (3.4)	4 (3.3)	3 (2.6)
Salivary hypersecretion	2 (1.7)	8 (6.8)	1 (0.8)	0 (0)
Sedation	11 (9.2)	16 (13.6)	18 (14.8)	4 (3.4)
Somnolence	12 (10.1)	18 (15.3)	11 (9.0)	5 (4.3)
Toothache	4 (3.4)	3 (2.5)	12 (9.8)	6 (5.2)
Tremor	2 (1.7)	9 (7.6)	7 (5.7)	5 (4.3)
Vomiting	5 (4.2)	10 (8.5)	3 (2.5)	8 (6.9)
Weight increased	2 (1.7)	2 (1.7)	25 (20.5)	6 (5.2)

Abbreviations: N = number of patients, TEAE = treatment-emergency adverse event

There were 23 serious adverse events (SAE) reported by 18 patients during the six-week study period (3.4% in the combined lurasidone treatment group, 4.1% of olanzapine patients, and 4.3% of placebo patients). The most common SAEs were related to worsening of the underlying condition of schizophrenia.

Laboratory data indicate an association between lurasidone treatment and a modest increase in prolactin (median increase of 2.15 ng/mL in lurasidone-combined treatment groups vs. -0.65 ng/mL in the placebo group, p<0.001). Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 18.

Table 18: Summary of Prolactin Levels, Study D1050231, Safety Population

Endpoint	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine15 mg	Placebo
Prolactin (ng/mL; male), LOCF	**N=93**	**N=90**	**N=94**	**N=89**
Median change from baseline	0.50	3.45	3.20	-0.70
Rank ANCOVA mean score test vs. placebo	0.085	<0.001	<0.001	-
Prolactin (ng/mL; female), LOCF	**N=26**	**N=25**	**N=27**	**N=25**
Median change from baseline	1.85	8.40	9.10	-0.30
Rank ANCOVA mean score test vs. placebo	0.493	0.003	<0.001	-

LOCF is defined as the last post-baseline measurement collected through either the week 6 visit day (for patients entering into the open-label phase) or within seven days after the double-blind phase study medication discontinuation (for discontinued patients not entering into the open-label phase).

Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, N = number of patients

The percent of patients with a ≥7% increase in weight at any time point was similar with lurasidone 40 mg (10.1%), lurasidone 120 mg (4.2%), and placebo (8.7%); 40.2% of patients had a ≥7% increase in body weight with olanzapine. Mean changes from baseline for metabolic endpoints are listed in Table 19. Glucose, triglycerides, LDL, HDL, total cholesterol, and insulin were intended to be collected at fasting.

Table 19: Summary of Metabolic Endpoints, Study D1050231, Safety Population

Endpoint	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Total Cholesterol (mg/dL), LOCF	**N=115**	**N=102**	**N=115**	**N=107**
Mean change from baseline (SD)	-8.6 (29.8)	-7.3 (25.3)	9.6 (31.2)	-6.8 (28.7)
Rank ANCOVA mean score test vs. placebo	0.598	0.604	<0.001	-
HDL (mg/dL), LOCF	**N=115**	**N=102**	**N=115**	**N=107**
Mean change from baseline (SD)	-0.9 (9.3)	-0.4 (8.5)	-2.1 (9.3)	-1.2 (8.1)

Endpoint	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Rank ANCOVA mean score test vs. placebo	0.790	0.848	0.170	-
LDL (mg/dL), LOCF	**N=115**	**N=102**	**N=115**	**N=107**
Mean change from baseline (SD)	-4.9 (23.3)	-4.6 (20.9)	4.3 (25.9)	-1.8 (24.8)
Rank ANCOVA mean score test vs. placebo	0.653	0.358	0.010	-
Triglycerides (mg/dL), LOCF	**N=115**	**N=102**	**N=115**	**N=107**
Mean change from baseline (SD)	-8.3 (76.2)	-5.0 (85.5)	50.0 (115.0)	0.1 (64.8)
Rank ANCOVA mean score test vs. placebo	0.314	0.540	<0.001	-
Glucose (mg/dL), LOCF	**N=118**	**N=114**	**N=121**	**N=113**
Mean change from baseline (SD)	0.0 (19.2)	0.5 (20.9)	10.3 (34.8)	0.4 (24.6)
Rank ANCOVA mean score test vs. placebo	0.718	0.396	0.036	-
HbA1c (%), LOCF	**N=113**	**N=101**	**N=112**	**N=107**
Mean change from baseline (SD)	-0.04 (0.24)	0.06 (0.29)	0.18 (0.57)	-0.05 (0.25)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-
C-reactive Protein (mg/dL), LOCF	**N=119**	**N=115**	**N=121**	**N=114**
Mean change from baseline (SD)	0.048 (0.627)	-0.028 (0.404)	0.192 (0.662)	0.076 (0.527)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	NR
Insulin (mU/L), LOCF	**N=119**	**N=115**	**N=121**	**N=114**
Mean change from baseline (SD)	-3.15 (31.48)	-1.30 (24.29)	5.92 (30.81)	-2.39 (46.28)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-
HOMA-IR (U), LOCF	**N=119**	**N=115**	**N=121**	**N=114**
Mean change from baseline (SD)	-1.30 (11.57)	-0.28 (7.72)	2.61 (11.97)	-1.32 (18.25)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-

Endpoint	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
Weight (kg), LOCF	**N=119**	**N=118**	**N=122**	**N=115**
Mean change from baseline (SD)	0.98 (2.85)	1.05 (2.19)	4.15 (4.26)	0.62 (2.74)
Rank ANCOVA mean score test vs. placebo	0.117	0.068	<0.001	-
BMI (kg/m^2), LOCF	**N=119**	**N=118**	**N=122**	**N=115**
Mean change from baseline (SD)	0.34 (0.97)	0.35 (0.73)	1.39 (1.37)	0.21 (0.94)
Rank ANCOVA mean score test vs. placebo	0.123	0.058	<0.001	-

LOCF is defined as the last post-baseline measurement collected through either the week 6 visit day (for patients entering into the open-label phase) or within seven days after the double-blind phase study medication discontinuation (for discontinued patients not entering into the open-label phase).

Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance (analyzed post-hoc), LDL = low-density lipoprotein, LOCF = last observation carried forward, N = number of patients, NR = not reported, SD = standard deviation

3.1.2.3. Study D1050229

Phase III, randomized, placebo-controlled clinical trial to study the safety and efficacy of three doses of lurasidone HCl in acutely psychotic patients with schizophrenia.[82]

Study Patients

A total of 500 patients met entry criteria and were randomized to once-daily treatment with 40 mg, 80 mg, or 120 mg lurasidone or placebo in a 1:1:1:1 ratio. A total of 328 (66%) patients completed the double-blind phase. The majority of discontinuations were due to withdrawal of consent (n=52, 10%), insufficient clinical response or a worsening of existing condition (n=81, 16%), or an AE not associated with worsening of an existing condition (n=19, 4%). Patients who completed the double-blind treatment were eligible for entry into a 22-month OL extension study. A total of 489 patients were included in the efficacy analysis (ITT) and 496 in the safety population. Baseline characteristics were generally balanced across treatment groups (Table 20).

Table 20: Baseline Characteristics, Study D1050229, Safety Population

Baseline Characteristic	Lurasidone 40 mg N=124	Lurasidone 80 mg N=121	Lurasidone 120 mg N=124	Placebo N=127
Sex, n (%) Male	83 (67)	78 (64)	92 (74)	93 (73)
Age, years, Mean (range)	40.7 (18-72)	38.7 (19-62)	37.7 (18-65)	38.1 (20-64)
Race, n (%), White	57 (46)	61 (50)	60 (48)	66 (52)
DSM-IV subtype, n (%), Paranoid*	109 (89)	104 (87)	108 (87)	109 (88)
PANSS Total score, mean ± SD*	96.5 ± 11.5	96.0 ± 10.8	96.0 ± 9.7	96.8 ± 11.1
CGI-S Score, mean ± SD*	5.0 ± 0.7	4.9 ± 0.6	4.9 ± 0.6	4.9 ± 0.6
MADRS, mean ± SD*	11.2 ± 6.4	11.1 ± 7.1	11.3 ± 7.3	11.9 ± 6.8

*ITT population: Lurasidone 40 mg (N = 122), Lurasidone 80 mg (N = 119), Lurasidone 120 mg (N = 124), placebo (N = 124)

Abbreviations: CGI-S = Clinical Global Impression scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

Efficacy Results

The difference from placebo in the mean change in the PANSS total score from baseline to week 6 was significant in the lurasidone 80 mg group (-6.4, p=0.034) but not in the lurasidone 40 mg (-2.1) or lurasidone 120 mg (-3.5) groups (primary endpoint). A summary of primary and secondary endpoint results are shown in the table below (Table 21).

Table 21: Summary of Primary and Secondary Endpoints, Repeated Measures Model, Study D1050229, ITT Population

Endpoint[a]	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
Primary Endpoint				
PANSS Total	**N=121**	**N=118**	**N=123**	**N=124**
Change from baseline to week 6 (SE)	-19.2 (1.7)	-23.4 (1.8)	-20.5 (1.8)	-17.0 (1.8)
Difference from placebo at week 6 (SE)[b]	-2.1 (2.5)	-6.4 (2.5)	-3.5 (2.5)	-
p-value vs. placebo	0.591[c]	0.034[c]	0.391[c]	-
Secondary Endpoints				
CGI-S	**N=122**	**N=119**	**N=124**	**N=124**
Change from baseline to week 6 (SE)	-1.1 (0.1)	-1.4 (0.1)	-1.2 (0.1)	-1.0 (0.1)
Difference from placebo at week 6 (SE)[b]	-0.1 (0.1)	-0.4 (0.1)	-0.2 (0.1)	-
p-value vs. placebo	0.591[c]	0.034[c]	0.543[c]	-

Endpoint[a]	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
PANSS Total	**N=121**	**N=118**	**N=123**	**N=124**
Change from baseline to day 4 (SE)	-4.3 (0.7)	-4.2 (0.7)	-4.3 (0.7)	-3.2 (0.7)
Difference from placebo at day 4 (SE)[b]	-1.1 (0.9)	-1.0 (0.9)	-1.0 (0.9)	-
p-value vs. placebo	0.241	0.296	0.263	-
PANSS positive subscore	**N=121**	**N=118**	**N=123**	**N=124**
Change from baseline to week 6 (SE)	-6.5 (0.6)	-8.6 (0.6)	-7.5 (0.6)	-5.3 (0.6)
p-value vs. placebo	0.153[c]	<0.001[c]	0.018[c]	-
PANSS negative subscore	**N=121**	**N=118**	**N=123**	**N=124**
Change from baseline to week 6 (SE)	-4.5 (0.4)	-4.8 (0.4)	-4.4 (0.4)	-4.2 (0.4)
p-value vs. placebo	0.788[c]	0.788[c]	0.788[c]	-
PANSS general psychopathology subscore	**N=121**	**N=118**	**N=123**	**N=124**
Change from baseline to week 6 (SE)	-8.6 (0.9)	-10.3 (0.9)	-9.3 (0.9)	-8.4 (0.9)
p-value vs. placebo	0.842[c]	0.347[c]	0.842[c]	-
MADRS	**N=120**	**N=116**	**N=123**	**N=122**
Change from baseline to week 6 (SE)	-3.3 (0.5)	-4.3 (0.5)	-2.9 (0.5)	-3.4 (0.5)
Difference from placebo at week 6 (SE)[b]	0.1 (0.7)	-0.9 (0.7)	0.5 (0.7)	-
p-value vs. placebo	0.876[c]	0.612[c]	0.876[c]	-
Responders[d]	**N=121**	**N=118**	**N=123**	**N=124**
n (%)	70 (58)	79 (67)	80 (65)	67 (54)
p-value vs. placebo	0.545[c]	0.114[c]	0.152[c]	-

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts are from differences of change from baseline treatment estimates for each lurasidone dose group vs. placebo.
[c] Adjusted p-values were adjusted with Hommel-based tree-gate keeping procedures.
[d] Responders are defined as those who achieved a 20% or greater improvement in PANSS total score from baseline over the study period. Responder analysis of PANSS total score at LOCF Week 6 Endpoint is based on a logistic regression of response, with effects for treatment group and baseline score.

Abbreviations: PANSS = Positive and Negative Syndrome Scale, CGI-S = Clinical Global Impression scale – Severity of Illness, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, NR = not reported, SE = standard error

Safety Results

A larger proportion of patients in the combined lurasidone treatment groups (79.1%) reported ≥1 TEAE compared with the placebo group (66.9%). The most frequently reported TEAEs in patients treated with lurasidone were akathisia, headache, somnolence, and nausea. Analyses of the BAS, AIMS, and SAS assessments showed a relatively low potential for moderate to severe EPS and akathisia in lurasidone-treated patients. No ECG abnormalities were associated with lurasidone treatment. The most common TEAEs (occurring in ≥5%, in any treatment group) are listed in Table 22.

Table 22: Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050229, Safety Population

Treatment-emergent Adverse Events, n (%)	Lurasidone 40 mg N=124	Lurasidone 80 mg N=121	Lurasidone 120 mg N=124	Placebo N=127
Patients with >1 TEAE	**96 (77.4)**	**90 (74.4)**	**106 (85.5)**	**85 (66.9)**
Agitation	7 (5.6)	3 (2.5)	7 (5.6)	2 (1.6)
Akathisia	14 (11.3)	21 (17.4)	30 (24.2)	4 (3.1)
Back pain	3 (2.4)	7 (5.8)	2 (1.6)	2 (1.6)
Dyspepsia	6 (4.8)	7 (5.8)	12 (9.7)	6 (4.7)
Dystonia	6 (4.8)	9 (7.4)	3 (2.4)	1 (0.8)
Headache	23 (18.5)	16 (13.2)	21 (16.9)	20 (15.7)
Insomnia	8 (6.5)	9 (7.4)	6 (4.8)	10 (7.9)
Musculoskeletal stiffness	1 (0.8)	6 (5.0)	3 (2.4)	5 (3.9)
Nausea	14 (11.3)	8 (6.6)	15 (12.1)	9 (7.1)
Parkinsonism	8 (6.5)	5 (4.1)	12 (9.7)	0
Psychotic disorder	2 (1.6)	3 (2.5)	6 (4.8)	8 (6.3)
Sedation	7 (5.6)	13 (10.7)	13 (10.5)	6 (4.7)
Somnolence	13 (10.5)	12 (9.9)	18 (14.5)	7 (5.5)
Vomiting	5 (4.0)	7 (5.8)	12 (9.7)	5 (3.9)
Weight increased	6 (4.8)	4 (3.3)	9 (7.3)	3 (2.4)

Abbreviations: TEAE = treatment-emergent adverse event

The proportion of patients with SAEs was similar between the combined lurasidone-treated patients (3.0%) and the placebo patients (3.9%). Most SAEs (76.5%, 13/17) were an exacerbation of the underlying condition of schizophrenia.

In the combined lurasidone treatment groups, the median change from baseline in prolactin was 0.70 ng/mL vs. 0.35 ng/mL for placebo (rank ANCOVA mean score test vs. placebo 0.054). Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 23.

Table 23: Summary of Prolactin Levels, Study D1050229, Safety Population

Endpoint	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
Prolactin (ng/mL; male), LOCF	**N=81**	**N=75**	**N=90**	**N=88**
Median change from baseline	0.30	0.40	1.40	0.25
Rank ANCOVA mean score test vs. placebo	0.694	0.249	0.013	-
Prolactin (ng/mL; female), LOCF	**N=40**	**N=43**	**N=32**	**N=34**
Median change from baseline	-2.20	2.00	6.40	0.85
Rank ANCOVA mean score test vs. placebo	0.072	0.027	0.005	-

LOCF is defined as the last post-baseline measurement collected through either the week 6 visit day (for patients entering into the open-label phase) or within seven days after the double-blind phase study medication discontinuation (for discontinued patients not entering into the open-label phase).

Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward

No clinically relevant treatment group differences were observed for cardio-metabolic outcomes throughout the study period. Minor increases in weight and BMI were observed in patients treated with lurasidone. Mean changes from baseline for metabolic endpoints are listed in Table 24. Glucose, triglycerides, LDL, HDL, and total cholesterol were intended to be collected at fasting.

Table 24: Summary of Metabolic Endpoints, Study D1050229, Safety Population

Endpoint	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
Total Cholesterol (mg/dL), LOCF	**N=113**	**N=111**	**N=119**	**N=108**
Mean change from baseline (SD)	-3.5 (26.9)	-9.4 (29.0)	-2.7 (27.2)	-10.8 (29.3)
Rank ANCOVA mean score test vs. placebo	0.026	0.242	0.019	-
HDL (mg/dL), LOCF	**N=113**	**N=111**	**N=119**	**N=108**
Mean change from baseline (SD)	-0.8 (8.5)	-1.5 (8.7)	-1.0 (8.9)	-3.2 (7.0)
Rank ANCOVA mean score test vs. placebo	0.004	0.023	0.002	-
LDL (mg/dL), LOCF	**N=113**	**N=111**	**N=119**	**N=108**
Mean change from baseline (SD)	-3.3 (21.8)	-6.1 (22.8)	-2.3 (21.3)	-5.2 (23.5)

Endpoint	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
Rank ANCOVA mean score test vs. placebo	0.291	0.514	0.167	-
Triglycerides (mg/dL), LOCF	**N=113**	**N=111**	**N=119**	**N=108**
Mean change from baseline (SD)	-0.5 (86.0)	-2.9 (72.1)	-0.5 (62.8)	-14.7 (68.9)
Rank ANCOVA mean score test vs. placebo	0.230	0.333	0.362	-
HbA1c (%), LOCF	**N=111**	**N=110**	**N=118**	**N=105**
Mean change from baseline (SD)	0.04 (0.37)	0.01 (0.34)	0.04 (0.33)	-0.01 (0.24)
Rank ANCOVA mean score test vs. placebo	NR	NR	NR	-
Glucose (mg/dL), LOCF	**N=121**	**N=118**	**N=122**	**N=122**
Mean change from baseline (SD)	6.1 (29.2)	-1.9 (26.1)	5.7 (21.5)	-1.7 (30.5)
Rank ANCOVA mean score test vs. placebo	0.410	0.090	0.877	-
Weight (kg), LOCF	**N=121**	**N=118**	**N=124**	**N=124**
Mean change from baseline (SD)	0.92 (2.84)	1.26 (3.07)	0.59 (2.90)	0.30 (2.67)
Rank ANCOVA mean score test vs. placebo	0.049	0.023	0.391	-
BMI (kg/m^2), LOCF	**N=122**	**N=118**	**N=124**	**N=124**
Mean change from baseline (SD)	0.31 (0.96)	0.42 (1.04)	0.19 (0.97)	0.07 (0.86)
Rank ANCOVA mean score test vs. placebo	0.035	0.015	0.351	-

LOCF is defined as the last post-baseline measurement collected through either the week 6 visit day (for patients entering into the open-label phase) or within seven days after the double-blind phase study medication discontinuation (for discontinued patients not entering into the open-label phase).

Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, kg = kilograms, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward, NR = not reported

3.1.2.4. Study D1050006

Phase II double-blind, randomized, fixed dose, placebo-controlled, parallel-group, 6-week, efficacy, safety, and tolerability study of two dose levels of lurasidone in patients with schizophrenia by DSM IV criteria who are experiencing acute exacerbation of symptoms.[79]

Study Patients

A total of 149 patients met entry criteria and were randomly assigned to once-daily treatment with 40 mg or 120 mg lurasidone or placebo in a 1:1:1 ratio. A total of 51 (34.2%) patients completed the study. The majority of discontinuations were due to withdrawal of consent (n=37, 24.8%), lack of efficacy (n=33, 22.1%), or AEs (n=14, 9.4%). A total of 145 patients were included in the ITT population, and 149 were analyzed for safety. Baseline characteristics were balanced across the treatment groups (Table 25).

Table 25: Baseline Characteristics, Study D1050006, Safety Population

Baseline Characteristic	Lurasidone 40 mg N=50	Lurasidone 120 mg N=49	Placebo N= 50
Sex, n (%) Male	36 (72.0)	36 (73.5)	42 (84.0)
Age, years, Mean (Range)	39.8 (21-61)	41.0 (24-59)	38.1 (18-56)
Race, n (%) White	20 (40.0)	22 (44.9)	20 (40.0)
DSM-IV subtype, N (%), Paranoid	45 (90.0)	44 (89.8)	45 (90.0)
BPRS score, mean ± SD	54.6 ± 9.1	52.5 ± 7.6	54.4 ± 8.3
PANSS score, mean ± SD	92.8 ± 16.1	89.6 ± 13.4	93.3 ± 16.4
CGI-S score, mean ± SD	4.8 ± 0.7	4.7 ± 0.6	4.6 ± 0.7

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression Scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

Efficacy Results

The mean change in the BPRS total score from baseline to week 6 was significant in the lurasidone 40 mg group (-9.4, p=0.018) and lurasidone 120 mg group (-1.1, p=0.004) as compared to placebo. A summary of primary and secondary endpoints are shown in Table 26, below.

Table 26: Summary of Primary and Secondary Endpoints, Study D1050006, ITT LOCF-3 Population

Endpoint[a]	Lurasidone 40 mg N=49	Lurasidone 120 mg N=47	Placebo N=49
Primary Endpoint			
BPRS, LS mean change (SE)	**-9.4 (1.58)**	**-11.0 (1.58)**	**-3.8 (1.57)**
p-value vs. placebo	0.018	0.004	-
Secondary Endpoints			
PANSS Total, LS mean change (SE)	**-14 (2.74)**	**-17 (2.73)**	**-6.2 (2.74)**
p-value vs. placebo	0.076	0.009	-
PANSS positive symptoms, LS mean change (SE)	**-4.6 (0.78)**	**-5.1 (0.79)**	**-1.8 (0.78)**
p-value vs. placebo	0.018	0.005	-
PANSS negative symptoms, LS mean change (SE)	**-2.7 (0.77)**	**-4.0 (0.77)**	**-1.0 (0.77)**
p-value vs. placebo	0.177	0.011	-
PANSS general psychopathology symptoms, LS mean (SE)	**-5.8 (1.52)**	**-7.8 (1.51)**	**-2.5 (1.51)**
p-value vs. placebo	0.185	0.023	-
CGI-S , LS mean change (SE)	**-0.8 (0.15)**	**-0.8 (0.14)**	**-0.1 (0.14)**
p-value vs. placebo	0.002	0.001	-
CGI-I , LS mean change (SE)	**3.3 (0.19)**	**3.2 (0.20)**	**4.1 (0.19)**
p-value vs. placebo	0.006	0.002	-
Responders, %			
BPRS decrease ≥20%	**51.1**	**44.7**	**18.3**
p-value vs. placebo	0.000	0.003	-
CGI ≤2	**36.7**	**30.4**	**12.2**
p-value vs. placebo	0.005	0.031	-
BPRS decrease ≥20% and CGI ≤2	**34.7**	**28.3**	**10.2**
p-value vs. placebo	0.129	0.454	-

[a] Each dose group of lurasidone compared to placebo with a 2-sided Dunnett's t-test. The analysis of variance model used was center, treatment, and the baseline efficacy parameter as the covariate. The p-value presented is the Dunnett's adjusted p-value.

Abbreviations: CGI-I = Clinical Global Impression Improvement scale; CGI-S = Clinical Global Impression Scale – Severity of Illness, ITT = intent to treat, LOCF-3 = last observation carried forward from day 3, LS = least squares, PANSS = Positive and Negative Syndrome Scale, SE = standard error

Safety Results

Lurasidone 40 mg and 120 mg were well-tolerated. No ECG abnormalities were associated with lurasidone treatment. The most common adverse events (occurring in ≥5% in any treatment group) are listed in Table 27. A dose response relationship was suggested for nausea and akathisia.

Table 27: Number (%) of Patients Reporting the Most Common Adverse Events (Incidence ≥5%), Study D1050006, Safety Population

Adverse Events, n (%)	Lurasidone 40 mg N=50	Lurasidone 120 mg N=49	Placebo N=50
Patients with ≥1 AE	**40 (80)**	**38 (78)**	**36 (72)**
Abdominal Pain NOS	0 (0.0)	0 (0.0)	4 (8.0)
Akathisia	4 (8.0)	7 (14.3)	0 (0.0)
Back Pain	2 (4.0)	3 (6.1)	1 (2.0)
Constipation	4 (8.0)	0 (0.0)	3 (6.0)
Diarrhea NOS	3 (6.0)	0 (0.0)	4 (8.0)
Dizziness (excluding vertigo)	6 (12.0)	5 (10.2)	3 (6.0)
Dyspepsia	4 (8.0)	2 (4.1)	6 (12.0)
Extrapyramidal Disorder	2 (4.0)	3 (6.1)	0 (0.0)
Fatigue	4 (8.0)	1 (2.0)	4 (8.0)
Headache NOS	8 (16.0)	3 (6.1)	5 (10.0)
Insomnia	3 (6.0)	4 (8.2)	0 (0.0)
Nausea	5 (10.0)	11 (22.4)	2 (4.0)
Muscle Cramps	1 (2.0)	3 (6.1)	0 (0.0)
Pain in Limb	3 (6.0)	1 (2.0)	1 (2.0)
Schizophrenia NOS Aggravated	2 (4.0)	1 (2.0)	5 (10.0)
Sedation	9 (18.0)	7 (14.3)	5 (10.0)
Somnolence	4 (8.0)	5 (10.2)	2 (4.0)
Tremor	3 (6.0)	4 (8.2)	0 (0.0)
Vomiting NOS	4 (8.0)	4 (8.2)	3 (6.0)

Abbreviations: NOS = not otherwise specified

SAEs were reported by 8.0%, 8.0%, and 4.1% of placebo, lurasidone 40 mg, and lurasidone 120 mg patients, respectively. All SAEs were related to the worsening of schizophrenia symptomatology, and their relationship to treatment was deemed unlikely.

Increased prolactin levels were observed with lurasidone 40 mg and 120 mg (median change from baseline: 3.5 ng/mL and 7.7 ng/mL, respectively) vs. placebo (-1.3 ng/mL); however, no prolactin-related clinical symptoms were reported. Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 28.

Table 28: Summary of Prolactin Levels, Study D1050006, Safety Population

Endpoint	Lurasidone 40 mg	Lurasidone 120 mg	Placebo
Prolactin (ng/mL; male), LOCF	**N=34**	**N=34**	**N=40**
Median change from baseline	3.4	4.7	-1.4
Prolactin (ng/mL; female), LOCF	**N=13**	**N=13**	**N=7**
Median change from baseline	2.8	7.5	0.0

Day 42 LOCF

Abbreviations: LOCF = last observation carried forward

No statistically significant differences between lurasidone and placebo were observed for the AIMS, SAS, or BAS by week 6, and no statistically significant differences were observed for the AIMS and the SAS at any time point during the study. Mean changes from baseline for metabolic and endpoints are listed in Table 29. When possible, laboratory specimens were taken with patients in the fasting state.

Table 29: Summary of Metabolic Endpoints, Study D1050006, Safety Population

Endpoint*	Lurasidone 40 mg	Lurasidone 120 mg	Placebo
Total Cholesterol (mg/dL), LOCF	**N=48**	**N=47**	**N=48**
Mean change from baseline (SD)	-12.9 (32.7)	-4.3 (22.9)	-8.9 (36.6)
Triglycerides (mg/dL), LOCF	**N=48**	**N=47**	**N=48**
Mean change from baseline (SD)	-6.2 (114.0)	-2.5 (121.0)	-21.2 (120.0)
Glucose (mg/dL), LOCF	**N=47**	**N=45**	**N=46**
Mean change from baseline (SD)	-0.1 (19.1)	-2.7 (33.5)	-4.8 (35.8)
Weight (kg), LOCF	**N=48**	**N=49**	**N=49**
Mean change from baseline (SD)	0.3 (2.17)	0.2 (2.55)	0.0 (2.92)

Day 42 LOCF

*Changes in LDL and HDL not available. P-values not available.

Abbreviations: LOCF = last observation carried forward, SD = standard deviation

3.1.2.5. Study D1050196

Phase II, double-blind fixed dose study of lurasidone HCl and placebo in the treatment of schizophrenia.[3,78]

Study Patients

A total of 180 patients met entry criteria and were randomly assigned to once-daily treatment with 80 mg lurasidone or placebo in a 1:1 ratio. A total of 99 (55%) patients completed the study. The majority of discontinuations were due to lack of efficacy (n=38, 21.1%), withdrawal of consent (n=27, 15.0%), or AEs (n=7, 3.8%). A total of 180 patients were included in the ITT population, and 180 were analyzed for safety. Baseline characteristics were generally balanced across the treatment groups (Table 30).

Table 30: Baseline Characteristics, Study D1050196, Safety Population

Baseline Characteristic	Lurasidone 80 mg N=90	Placebo N=90
Sex, n (%), Male	68 (75.6)	70 (77.8)
Age, years, Mean (Range)	39.7 (22-62)	41.9 (21-63)
Race, n (%), White	35 (38.9)	26 (28.9)
DSM-IV subtype, n (%), Paranoid	73 (81.1)	72 (80.0)
BPRS score, mean ± SD	55.1 ± 6.0	56.1 ± 6.8
PANSS total score, mean ± SD	94.4 ± 10.9	96.0 ± 11.6
CGI-S score, mean ± SD	4.8 ± 0.7	4.8 ± 0.7
MADRS score, mean ± SD	14.2 ± 8.0	14.5 ± 8.3

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression Scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

Efficacy Results

The mean change in the BPRS score from baseline to week 6 was significantly greater in the lurasidone 80 mg group (-8.9) than in the placebo group, (-4.2; p = 0.0118). A summary of the primary and secondary endpoint results are shown in Table 31 below.

Table 31: Summary of Primary and Secondary Endpoints, Study D1050196, Day 42 LOCF

Endpoint[a]	Lurasidone 80 mg N=90	Placebo N=90
Primary Endpoint		
BPRS, LS mean change (SE)	**-8.9 (1.3)**	**-4.2 (1.4)**
p-value vs. placebo	0.0118	-
Secondary Endpoints		
PANSS Total, LS mean change (SE)	**-14.1 (2.1)**	**-5.5 (2.2)**
p-value vs. placebo	0.0040	-
PANSS positive subscore, LS mean change (SE)	**-4.3 (0.7)**	**-1.7 (0.7)**
p-value vs. placebo	0.0060	-
PANSS negative subscore, LS mean change (SE)	**-2.9 (0.5)**	**-1.3 (0.5)**
p-value vs. placebo	0.0250	-
PANSS general psychopathology subscore, LS mean change (SE)	**-7.0 (1.1)**	**-2.7 (1.2)**
p-value vs. placebo	0.0061	-
PANSS cognitive subscore, LS mean change (SE)	**-2.1 (0.4)**	**-0.5 (0.4)**
p-value vs. placebo	0.0015	-
CGI-S, LS mean change (SE)	**-0.6 (0.1)**	**-0.2 (0.1)**
p-value vs. placebo	0.0072	-
MADRS, LS mean change (SE)	**-2.9 (0.8)***	**-0.1 (0.9)****
p-value vs. placebo	0.0187	-
Respondersb, %	48.9	35.6
p-value vs. placebo	0.072	-

*n=86, **n=83

[a]Lurasidone compared to placebo using analysis of covariance model including treatment, investigator, and baseline terms.

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression – Severity Scale, LS = least squares, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SE = standard error

Safety Results

The proportion of patients experiencing ≥1 AE was not significantly higher in the lurasidone group (76.7%) than in the placebo group (68.9%). No clinically significant differences were seen for the AIMS or the SAS; however, a modest but significant difference was observed for the BAS score (+0.2 and -0.1 for lurasidone and placebo, respectively, p=0.03). No ECG abnormalities were associated with lurasidone treatment. The most common treatment-emergent adverse events (occurring in ≥5%, either treatment group) are listed in Table 32.

Table 32: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050196, Safety Population

Treatment-Emergent Adverse Events, n(%)	Lurasidone 80 mg N=90	Placebo N=90
Patients with >1 TEAE	**69 (76.7)**	**62 (68.9)**
Akathisia	8 (8.9)	3 (3.3)
Anxiety	6 (6.7)	1 (1.1)
Back pain	3 (3.3)	5 (5.6)
Constipation	10 (11.1)	5 (5.6)
Dyspepsia	10 (11.1)	3 (3.3)
Headache	10 (11.1)	9 (10.0)
Insomnia	9 (10.0)	3 (3.3)
Nausea	15 (16.7)	3 (3.3)
Sedation	9 (10.0)	4 (4.4)
Somnolence	10 (11.1)	3 (3.3)
Toothache	5 (5.6)	3 (3.3)
Upper respiratory tract infection NOS	3 (3.3)	6 (6.7)
Vomiting NOS	10 (11.1)	5 (5.6)

Abbreviations: NOS = not otherwise specified; TEAE = treatment-emergent adverse event

The rate of SAEs was low in each group (lurasidone = 3.3%, placebo = 4.4%); all SAEs in the lurasidone group were due to an exacerbation of preexisting schizophrenia, and none were judged by the investigator to be due to lurasidone.

Lurasidone was associated with a small but significant increase in prolactin compared to placebo at endpoint (median change 2.4 vs. -0.3 ng/mL, respectively, p=0.0129). Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 33.

Table 33: Summary of Prolactin Levels, Study D1050196, Safety Population

Endpoint[a]	Lurasidone 80 mg	Placebo
Prolactin (ng/mL; male), LOCF	**N=57**	**N=58**
Median change from baseline	1.4	-0.3
p-value compared to placebo	0.3154	-
Prolactin (ng/mL; female), LOCF	**N=19**	**N=19**
Median change from baseline	9.2	-1.8

Endpoint[a]	Lurasidone 80 mg	Placebo
p-value compared to placebo	0.0055	-

[a] Lurasidone compared to placebo using analysis of variance model with treatment as a main effect.

Abbreviations: LOCF = last observation carried forward

Lurasidone was associated with a small increase in weight relative to placebo. Mean change from baseline in hemoglobin A1c (HbA1c) was slightly greater in the lurasidone-treated patients, but the difference was only marginally significant (p = 0.049). No clinically significant differences were seen in metabolic laboratory tests. Mean changes from baseline for metabolic and endpoints are listed in Table 34. Laboratory specimens were taken with the subject in the fasting state before breakfast.

Table 34: Summary of Metabolic Endpoints, Study D1050196, Safety Population

Endpoint[a]	Lurasidone 80 mg	Placebo
Total Cholesterol (mg/dL), LOCF	**N=81**	**N=82**
Mean change from baseline (SD)	-10.1 (33.37)	-7.1 (29.62)
p-value compared to placebo	NR	-
LDL (mg/dL), LOCF	**N=70**	**N=72**
Mean change from baseline (SD)	-5.2 (27.30)	-0.7 (23.96)
p-value compared to placebo	NR	-
HDL (mg/dL), LOCF	**N=76**	**N=78**
Mean change from baseline (SD)	-1.2 (8.13)	-3.0 (9.03)
p-value compared to placebo	NR	-
Triglycerides (mg/dL), LOCF	**N=81**	**N=82**
Mean change from baseline (SD)	-24.4 (76.36)	-31.7 (95.24)
p-value compared to placebo	NR	-
Glucose (fasting), mg/dL, LOCF	**N=71**	**N=73**
Mean change from baseline (SD)	2.9 (19.84)	3.4 (24.70)
p-value compared to placebo	NR	-
HbA1c (%), LOCF	**N=79**	**N=79**
Mean change from baseline (SD)	0.1 (0.36)	0.0 (0.55)
p-value compared to placebo	0.049	-
Weight (kg), LOCF	**N=89**	**N=90**
Mean change from baseline (SD)	1.2 (3.01)	0.3 (3.13)
p-value compared to placebo	0.050	-

[a] Lurasidone compared to placebo using analysis of variance model with treatment as a main effect.

Abbreviations: HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward, NR = not resported, SD = standard deviation

3.1.2.6. Study D1050049

Phase II, 6-week, double-blind, randomized, fixed dose, parallel-group study of the efficacy and safety of three dose levels of lurasidone HCl compared to placebo and haloperidol in patients with schizophrenia who are experiencing an acute exacerbation of symptoms.[81]

Study Patients

A total of 356 patients met entry criteria and were randomly assigned to once-daily treatment with 20 mg, 40 mg, or 80 mg of lurasidone, placebo, or 10 mg haloperidol in a 1:1:1:1:1 ratio. A total of 151 (42.4%) patients completed the study. The majority of discontinuations were due to lack of efficacy (n=76, 21.3%), withdrawal of consent (n=74, 20.8%), or AEs (n=31, 8.7%). A total of 349 patients were included in the ITT population, and 353 were analyzed for safety. Baseline characteristics were generally balanced across treatment groups (Table 35).

Table 35: Baseline Characteristics, Study D1050049, Safety Population

Baseline Characteristic	Lurasidone 20 mg N=71	Lurasidone 40 mg N=67	Lurasidone 80 mg N=71	Haloperidol 10 mg N=72	Placebo N=72
Sex, n (%) Male	51 (71.8)	46 (68.7)	52 (73.2)	58 (80.6)	55 (76.4)
Age, years, Mean (Range)	40.7 (19-64)	42.0 (20-63)	42.2 (18-59)	40.0 (19-60)	41.0 (21-60)
Race, n(%) White	32 (45.1)	30 (44.8)	24 (33.8)	29 (40.3)	38 (52.8)
DSM-IV subtype, n (%),Paranoid	56 (78.9)	60 (89.6)	63 (88.7)	62 (86.1)	66 (91.7)
BPRS score, Mean ± SD	55.4 ± 7.2	55.0 ± 7.4	54.5 ± 7.3	56.1 ± 7.9	56.8 ± 8.3
PANSS score, Mean ± SD	94.7 ± 13.3	93.4 ± 15.0	93.1 ± 13.6	94.3 ± 13.6	96.5 ± 15.2
CGI-S score, Mean ± SD	4.7 ± 0.8	4.8 ± 0.8	4.7 ± 0.8	4.8 ± 0.7	4.8 ± 0.7
MADRS score, Mean ± SD	13.5 ± 7.3	13.0 ± 7.4	13.7 ± 8.1	15.6 ± 9.6	14.6 ± 8.7

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

Efficacy Results

The mean BPRS total score improved from baseline to week 6 (primary endpoint) for all treatment groups for the ITT LOCF population; however, no statistically significant differences were seen between any of the active treatment groups (including haloperidol) and placebo. Haloperidol was used as an

internal standard to assess the clinical sensitivity of the trial. Because the trial was unable to discern treatment effects between haloperidol and placebo for the primary and secondary endpoints, no clinical inferences or conclusions can be made regarding the efficacy of lurasidone (Table 36).

Table 36: Summary of Primary and Secondary Endpoints to Week 6 LOCF, Study D1050049, ITT-LOCF Population

Endpoint[a]	Lurasidone 20 mg N=71	Lurasidone 40 mg N=65	Lurasidone 80 mg N=70	Haloperidol 10 mg N=72	Placebo N=71
Primary Endpoint					
BPRS, LS Mean change (SE)	**-5.0 (1.38)**	**-5.2 (1.44)**	**-8.0 (1.40)**	**-9.8 (1.37)**	**-7.9 (1.38)**
p-value vs. placebo	0.357	0.437	1.000	0.747	-
Secondary Endpoints					
PANSS Total, LS Mean change (SE)	**-7.1 (2.31)**	**-7.2 (2.42)**	**-13.6 (2.34)**	**-16.0 (2.29)**	**-12.3 (2.32)**
p-value vs. placebo	0.109	0.126	0.694	0.252	-
PANSS positive subscore, LS mean change (SE)	**-2.1 (0.73)**	**-2.6 (0.76)**	**-4.2 (0.74)**	**-5.7 (0.72)**	**-3.4 (0.73)**
p-value vs. placebo	0.211	0.459	0.460	0.025	-
PANSS negative subscore, LS Mean change (SE)	**-1.8 (0.67)**	**-1.9 (0.70)**	**-3.1 (0.67)**	**-3.1 (0.66)**	**-2.6 (0.67)**
p-value vs. placebo	0.386	0.494	0.581	0.536	-
PANSS general psychopathology subscore, LS Mean change (SE)	**-3.1 (1.18)**	**-2.8 (1.23)**	**-6.4 (1.19)**	**-7.0 (1.17)**	**-5.9 (1.18)**
p-value vs. placebo	0.091	0.062	0.773	0.505	-
CGI-S , LS Mean change (SE)	**-0.5 (0.11)**	**-0.4 (0.12)**	**-0.8 (0.12)**	**-0.8 (0.12)**	**-0.7 (0.11)**
p-value vs. placebo	0.179	0.128	0.595	0.463	-
MADRS, LS Mean change (SE)	**-1.3 (0.97)**	**-1.1 (1.02)***	**-2.5 (0.98)**	**-2.7 (0.96)**	**-1.9 (0.97)**
p-value vs. placebo	0.620	0.565	0.668	0.562	-
Responders[b], %					
BPRS decrease ≥20%	**33.8**	**33.8**	**41.4**	**41.7**	**38.0**
p-value vs. placebo	0.723	0.641	0.483	0.464	-
CGI ≤2	**4.2**	**3.1**	**5.7**	**4.2**	**7.0**

Endpoint[a]	Lurasidone 20 mg N=71	Lurasidone 40 mg N=65	Lurasidone 80 mg N=70	Haloperidol 10 mg N=72	Placebo N=71
p-value vs. placebo	0.263	0.221	0.620	0.389	-

*n=64

[a] P-values from ANCOVA model with baseline as a continuous covariate and treatment and center as class variables.

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression scale – Severity of Illness, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SE = standard error

Safety Results

The AEs that occurred most frequently with lurasidone compared to placebo were nausea, vomiting, akathisia, somnolence, sedation, fatigue, and agitation, with all but agitation showing a dose response. Mean changes from baseline were generally comparable across treatment groups for the AIMS, SAS, and BAS; no significant differences between lurasidone and placebo were observed. No ECG abnormalities were associated with lurasidone treatment. The most common adverse events (occurring in ≥5% in any treatment group) are listed in Table 37.

Table 37: Number (%) of Patients Reporting the Most Common Adverse Events (Incidence ≥5%), Study D1050049, Safety Population

Adverse Event, n (%)	Lurasidone 20 mg N=71	Lurasidone 40 mg N=67	Lurasidone 80 mg N=71	Haloperidol 10 mg N=72	Placebo N=72
Patients with ≥1 AE	**53 (74.6)**	**57 (85.1)**	**56 (78.9)**	**63 (87.5)**	**57 (79.2)**
Agitation	6 (8.5)	7 (10.4)	2 (2.8)	2 (2.8)	3 (4.2)
Akathisia	4 (5.6)	9 (13.4)	13 (18.3)	14 (19.4)	7 (9.7)
Anxiety	2 (2.8)	5 (7.5)	1 (1.4)	4 (5.6)	4 (5.6)
Anxiety aggravated	0 (0.0)	4 (6.0)	2 (2.8)	5 (6.9)	0 (0.0)
Arthralgia	0 (0.0)	3 (4.5)	2 (2.8)	4 (5.6)	3 (4.2)
Back pain	0 (0.0)	4 (6.0)	2 (2.8)	4 (5.6)	1 (1.4)
Constipation	2 (2.8)	1 (1.5)	6 (8.5)	3 (4.2)	9 (12.5)
Cough	3 (4.2)	4 (6.0)	1 (1.4)	1 (1.4)	5 (6.9)
Diarrhea NOS	3 (4.2)	2 (3.0)	2 (2.8)	2 (2.8)	4 (5.6)
Dizziness	4 (5.6)	3 (4.5)	4 (5.6)	3 (4.2)	3 (4.2)
Dyspepsia	10 (14.1)	8 (11.9)	10 (14.1)	7 (9.7)	9 (12.5)
Dystonia	0 (0.0)	2 (3.0)	2 (2.8)	11 (15.3)	1 (1.4)
Extrapyramidal disorder	2 (2.8)	4 (6.0)	4 (5.6)	15 (20.8)	3 (4.2)
Fatigue	5 (7.0)	2 (3.0)	9 (12.7)	6 (8.3)	3 (4.2)
Gastrointestinal upset	1 (1.4)	0 (0.0)	0 (0.0)	4 (5.6)	1 (1.4)

Adverse Event, n (%)	Lurasidone 20 mg N=71	Lurasidone 40 mg N=67	Lurasidone 80 mg N=71	Haloperidol 10 mg N=72	Placebo N=72
Headache	16 (22.5)	15 (22.4)	16 (22.5)	14 (19.4)	23 (31.9)
Insomnia	5 (7.0)	5 (7.5)	4 (5.6)	10 (13.9)	4 (5.6)
Nasopharyngitis	3 (4.2)	2 (3.0)	1 (1.4)	4 (5.6)	2 (2.8)
Nausea	8 (11.3)	7 (10.4)	13 (18.3)	4 (5.6)	8 (11.1)
Pain NOS	1 (1.4)	4 (6.0)	2 (2.8)	1 (1.4)	5 (6.9)
Pharyngitis	4 (5.6)	4 (6.0)	2 (2.8)	2 (2.8)	4 (5.6)
Psychosis aggravated	1 (1.4)	4 (6.0)	3 (4.2)	2 (2.8)	3 (4.2)
Rash NOS	1 (1.4)	4 (6.0)	2 (2.8)	3 (4.2)	3 (4.2)
Sedation	7 (9.9)	11 (16.4)	14 (19.7)	14 (19.4)	6 (8.3)
Somnolence	4 (5.6)	4 (6.0)	8 (11.3)	9 (12.5)	4 (5.6)
Toothache	2 (2.8)	1 (1.5)	0 (0.0)	1 (1.4)	4 (5.6)
Tremor	1 (1.4)	1 (1.5)	0 (0.0)	4 (5.6)	1 (1.4)
Vomiting NOS	5 (7.0)	5 (7.5)	12 (16.9)	4 (5.6)	5 (6.9)

Abbreviations: N = number of patients, NOS = not otherwise specified

The occurrence of SAEs was comparable among all five treatment groups: 11.1% (placebo), 7.0% (lurasidone 20 mg), 14.9% (lurasidone 40 mg), 5.6% (lurasidone 80 mg), and 8.3% (haloperidol 10 mg) of patients. The majority involved worsening of psychosis and other attendant symptomatology.

All lurasidone groups demonstrated slight increases in mean prolactin compared with placebo, but increases were less than those seen with haloperidol. The differences were generally comparable at week 6, except for females in the haloperidol group (median increase from baseline of 27.6 ng/mL). Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 38.

Table 38: Summary of Prolactin Levels, Study D1050049, Safety Population

Endpoint	Lurasidone 20 mg	Lurasidone 40 mg	Lurasidone 80mg	Haloperidol 10 mg	Placebo
Prolactin (ng/mL; male), LOCF	**N=48**	**N=44**	**N=49**	**N=49**	**N=52**
Median change from baseline	-1.1	0.1	1.1	8.4	-2.1
Prolactin (ng/mL; female), LOCF	**N=17**	**N=16**	**N=16**	**N=11**	**N=17**
Median change from baseline	-0.7	-1.3	-1.0	27.6	-7.9

Abbreviations: LOCF = last observation carried forward

No important differences were found among groups in changes from baseline to week 6 in laboratory examinations, ECGs, EPS, or vital signs. Mean changes (SD) from baseline for metabolic endpoints are listed in Table 39. Laboratory specimens were taken with the subject in the fasting state before breakfast.

Table 39: Summary of Metabolic Endpoints, Study D1050049, Safety Population

Endpoint*	Lurasidone 20 mg	Lurasidone 40 mg	Lurasidone 80 mg	Haloperidol 10 mg	Placebo
Total Cholesterol (mg/dL), LOCF	**N=68**	**N=64**	**N=71**	**N=68**	**N=70**
Mean change from baseline (SD)	-12.2 (38.22)	-17.8 (30.46)	-10.6 (26.63)	-12.5 (45.70)	-10.4 (31.29)
Triglycerides (mg/dL), LOCF	**N=68**	**N=64**	**N=71**	**N=68**	**N=70**
Mean change from baseline (SD)	-27.6 (134.4)	-14.7 (107.0)	-16.9 (93.19)	-36.4 (138.9)	-28.9 (118.0)
Glucose (mg/dL), LOCF	**N=68**	**N=64**	**N=71**	**N=67**	**N=70**
Mean change from baseline (SD)	-1.4 (22.07)	1.9 (19.47)	0.3 (33.14)	1.7 (23.15)	-1.8 (27.72)
Weight[a] (kg), LOCF	**N=69**	**N=66**	**N=71**	**N=71**	**N=69**
Mean change from baseline (SD)	-0.2 (2.57)	0.0 (3.55)	0.9 (4.21)	0.1 (3.09)	0.1 (2.95)
p-value vs. placebo	0.602	0.946	0.144	0.942	-

*Changes in LDL and HDL not available. P-values not available.

Abbreviations: LOCF = last observation carried forward; SD = standard deviation

3.1.3. Results of Longer-term Studies

3.1.3.1. Study D1050234

Phase III, randomized, double-blind, active comparator (quetiapine XR)-controlled clinical trial to study the safety and efficacy of lurasidone in patients with schizophrenia[6]

Study Design

Study D1050234 was a double-blind, parallel group study that compared the efficacy and safety of lurasidone (LUR) (flexibly dosed 40-160 mg/day) and quetiapine XR (QXR) (flexibly dosed 200-800 mg/day) in adult patients with schizophrenia. Patients who entered Study D1050234 had all demonstrated a clinical response in the preceding study D1050233, which was a 6-week, double-blind, placebo-controlled study involing fixed doses of LUR (80 mg/day or 160 mg/day) and QXR (600 mg/day) in patients with acute schizophrenia.

Clinical response was defined as patients, who were treated with either LUR (80 mg/day or 160 mg/day) or QXR (600 mg/day), with ≥20% improvement in PANSS total score and CGI S score ≤4 at completion of the acute treatment in study D1050233 (Day 42). The primary endpoint for study D1050234 was time to relapse, comparing LUR to QXR in a non-inferiority analysis utilizing a COX proportional hazards model. Relapse was defined as: either a worsening of ≥30% PANSS total score from D1050233 Day 42 and CGI S ≥3; or re hospitalization for worsening of psychosis; or emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others.

Patients who were randomized to placebo in study D1050233 and entered into study D1050234 were excluded from the primary efficacy analysis.

The mean modal LUR dose in this flexible dose study was 120 mg/day (all patients started the extension phase at 120 mg/day fixed dose for 7 days). The mean modal QXR dose was 600 mg/day (all patients started the extension phase at 600 mg/day fixed dose for 7 days).

Study Patients

A total of 292 out of 353 patients completed study D1050233 and elected to participate in the double-blind extension phase. Assigned treatment groups were as follows:

- n = 151 LUR to LUR (LUR 80 mg or 160 mg in the acute treatment phase followed by flexibly dosed LUR 40-160 mg in the extension phase);
- n = 56 in the PBO to LUR (placebo in the acute treatment phase to flexibly dosed LUR 40-160 mg in the extension phase) (this arm was not included in the non-inferiority analysis due to the time difference in exposure to active treatment); and
- n = 85 in the QXR to QXR (QXR 600 mg in the acute treatment phase followed by flexibly dosed QXR 200-800 mg in the extension phase).

Pre-specified efficacy and safety analyses were based on the LUR→LUR and QXR→QXR treatment groups.

The overall discontinuation rate in the LUR to LUR treatment group was 48% compared to 61% in the QXR to QXR treatment group. Patient discontinuation reasons reported included (LUR vs. QXR,

respectively): insufficient clinical response (LUR 9% vs. QXR 21%); adverse event (LUR 7% vs. QXR 5%); withdrawal of consent (LUR 19% vs. QXR 22%); lost to follow-up (LUR 7% vs. QXR 11%); protocol violation (LUR 5% vs. QXR 1%); administrative (LUR 3% vs. QXR 1%).

Baseline characteristics for patients entering Study D1050234 are provided in Table 40.

Table 40: Baseline Characteristics, Study D1050234, Safety Population

Baseline Characteristic	LUR to LUR N=151	QXR to QXR N=85
Sex, n (%) Male	108 (72)	52 (61)
Age, years, Mean (Range)	37.1 (18-63)	38.5 (18-58)
Race, n (%), White	87 (58)	56 (66)
DSM-IV subtype, n (%), paranoid	140 (93)	82 (96)
PANSS total Score, core baseline (acute phase), mean ± SD*	97.7 ± 10.3	97.9 ± 10.6
CGI-S, core baseline (acute phase), mean ± SD*	4.9 ± 0.5	4.9 ± 0.6

*Intent to treat population (LUR to LUR: N=132; QXR to QXR: N=72)

Abbreviations: CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, LUR to LUR = lurasidone 80 mg or 160 mg in the acute treatment phase followed by flexibly dosed lurasidone 40-160 mg in the extension phase, QXR to QXR = quetiapine XR 600 mg in the acute treatment phase followed by flexibly dosed quetiapine XR 200-800 mg in the extension phase, N = number of patients, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation.

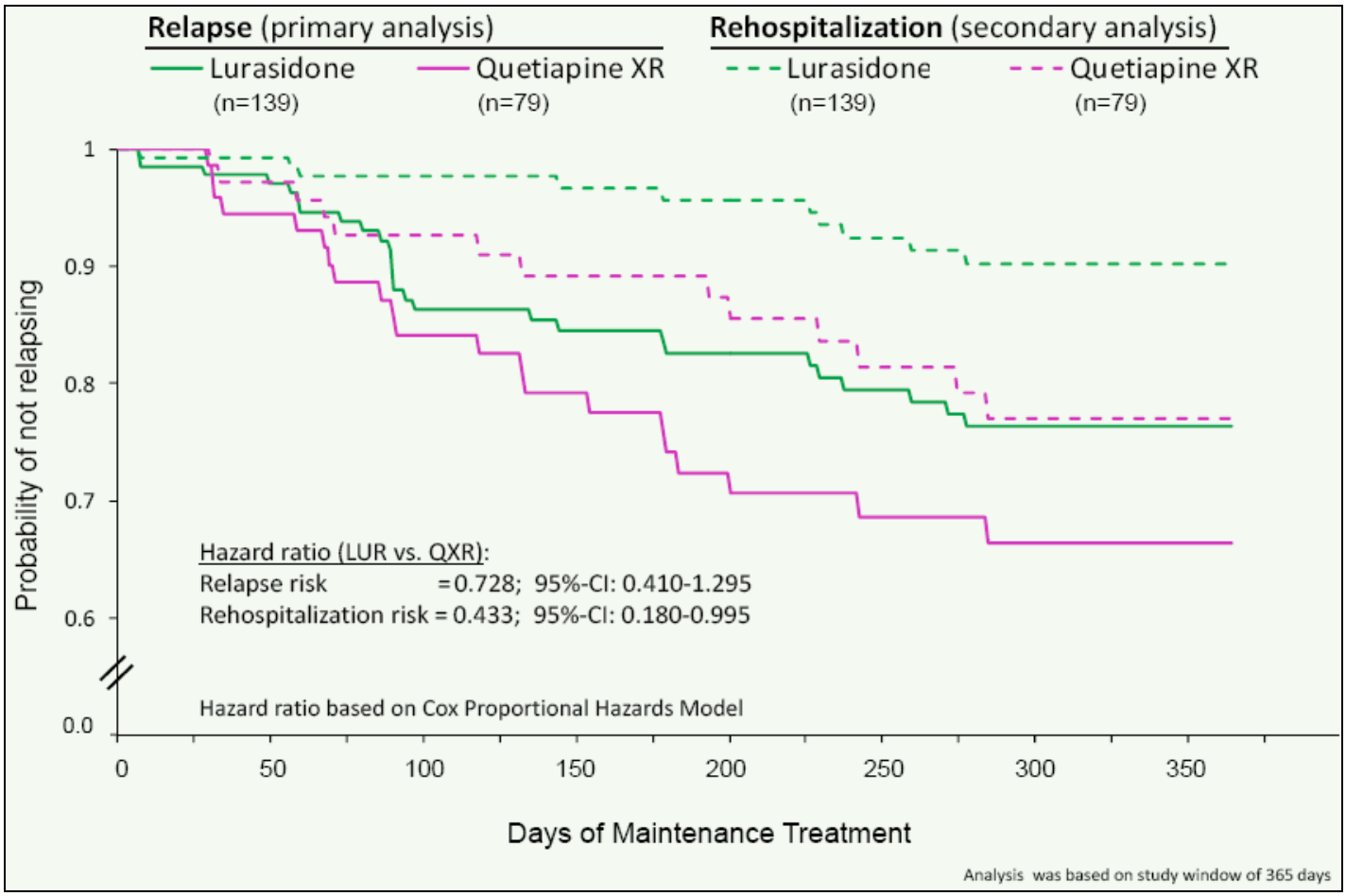
Efficacy Results

The analysis of the primary endpoint, time to relapse, showed a hazard ratio (HR) of 0.728 with a 95% confidence interval (CI): [0.410,1.295] (

Figure 1). The protocol pre specified non-inferiority (NI) margin was 1.93. Since the upper limit of the 95% CI, 1.295, was below the pre specified NI margin of 1.93, non-inferiority of LUR compared to QXR was demonstrated. The pre specified non-inferiority margin of 1.93 was selected based on the results of a meta analysis from a landmark comparative analysis of second generation antipsychotics by Leucht et al., 2003.[83]

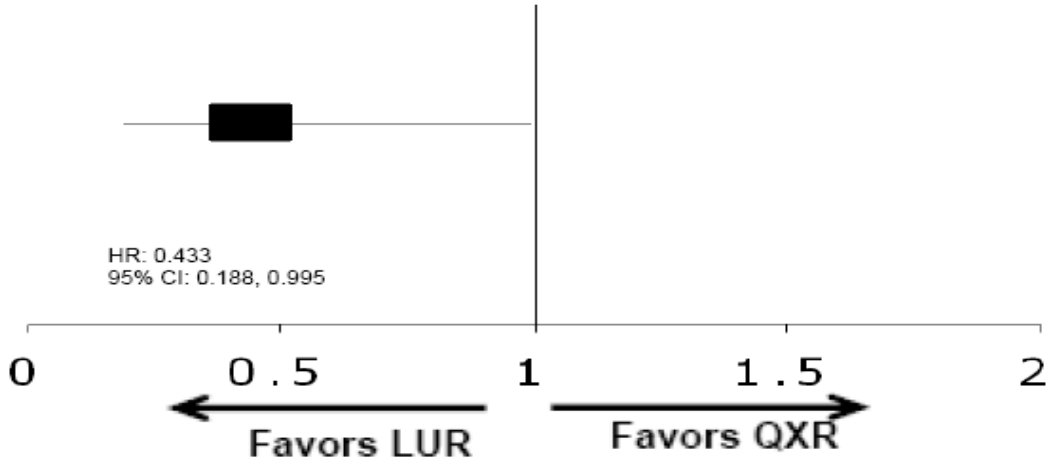
The observed relapse rate for LUR was 20.9% (29/139) versus 26.6% (21/79) for QXR.

Figure 1: Time to Relapse for Lurasidone vs. Quetiapine XR



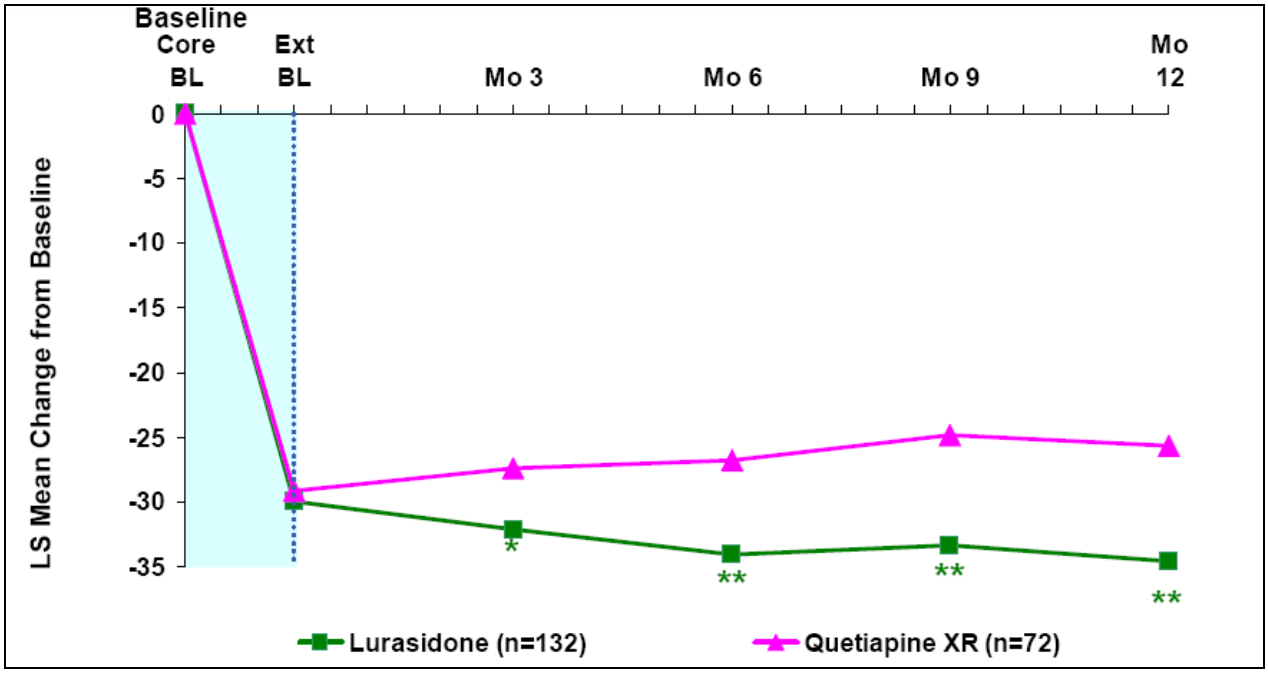
Time to rehospitalization for all patients in the trial was evaluated post hoc (Figure 2).

Figure 2: Time to Rehospitalization, Study D1050234



The least square mean changes in PANSS score from the baseline of the preceding 6 week, placebo controlled study (core baseline) to Month 12 endpoint for patients continuing treatment on LUR vs. patients continuing treatment on QXR were -34.6 and -25.7, respectively (p=0.006) (Figure 3).

Figure 3: Least Square Mean Change in PANSS Total Score (MMRM) from Core Baseline to Month 12 (ITT Population)



*p<0.05; **p<0.01

Abbreviations: Intent to treat population (LUR to LUR: N=132; QXR to QXR: N=72); LS = least square; MMRM = Mixed Model for Repeated Measures; n = number of patients; PANSS = Positive and Negative Syndrome Scale.

On the CGI-S, the least square mean changes from the baseline of the preceding 6-week, placebo controlled study to Month 12 endpoint for patients continuing treatment on LUR compared to patients continuing on QXR were -1.9 vs. -1.6, respectively (p=0.069; ITT population, MMRM).

Safety Results

The proportion of patients experiencing ≥1 AE in the extension phase was 97 (64.2%) and 61 (71.8%) for the LUR to LUR and QXR to QXR treatment groups, respectively. Serious TEAE occurred in 15 (9.9%) and 17 (20.0%) of patients in the LUR to LUR and QXR to QXR treatment groups, respectively.

The most common treatment-emergent adverse events (occurring in ≥5%) are listed in Table 41.

Table 41: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050234, Safety Population

Treatment-Emergent Adverse Events, n (%)	LUR to LUR N=151	QXR to QXR N=85
Patients with ≥1 TEAE	**97 (64.2)**	**61 (71.8)**
Agitation	6 (4.0)	5 (5.9)
Akathisia	19 (12.6)	2 (2.4)
Anxiety	9 (6.0)	3 (3.5)
Headache	16 (10.6)	8 (9.4)
Insomnia	12 (7.9)	8 (9.4)
Parkinsonism	9 (6.0)	0
Psychotic disorder	6 (4.0)	7 (8.2)
Schizophrenia	7 (4.6)	13 (15.3)
Weight increased	9 (6.0)	7 (8.2)

Abbreviations: LUR to LUR = lurasidone 80 mg or 160 mg in the acute treatment phase followed by flexibly dosed lurasidone 40-160 mg in the extension phase, QXR to QXR = quetiapine XR 600 mg in the acute treatment phase followed by flexibly dosed quetiapine XR 200-800 mg in the extension phase, N = number of patients, TEAE = treatment emergent adverse event.

Median observed change in prolactin from core baseline to 12 months was +0.6 ng/mL in the LUR-LUR group vs. -0.7 ng/mL in the QXR QXR group. Median observed change in prolactin from core baseline to LOCF endpoint was +0.6 ng/mL for LUR treated patients and -0.9 ng/mL for QXR treated patients.

Prolactin median change from core baseline to endpoint by gender is presented in Table 42.

Table 42: Change from Core Baseline to Month 12 and LOCF Endpoint in Prolactin Levels, Study D1050234, Safety Population

Endpoint	LUR to LUR N=151	QXR to QXR N=85
Prolactin (ng/mL; male), Month 12 / LOCF	n=58 / n=93	n=21 / n=43
Median change from core baseline to Month 12	-0.20	-0.30
Median change from core baseline to LOCF	0.10	-0.90
Prolactin (ng/mL; female), Month 12 / LOCF	n=19 / n=36	n=12 / n=28
Median change from core baseline to Month 12	1.30	-1.15
Median change from core baseline to LOCF	1.05	-1.10

Abbreviations: LUR to LUR = lurasidone 80 mg or 160 mg in the acute treatment phase followed by flexibly dosed lurasidone 40-160 mg in the extension phase, QXR to QXR = quetiapine XR 600 mg in the acute treatment phase followed by flexibly dosed quetiapine XR 200-800 mg in the extension phase, N = number of patients, LOCF = last observation carried forward.

A summary of metabolic endpoints measured are presented in Table 43.

Table 43: Change from Core Baseline to Month 12 and LOCF Endpoint in Metabolic Endpoints, Study D1050234, Safety Population (LUR N= 151; QXR N = 85)

Endpoint	LUR to LUR N=151	QXR to QXR N=85
Total Cholesterol (mg/dL), Month 12 / LOCF	**n=77 / n=129**	**n=33 / n=71**
Median change from core baseline to Month 12	0.0	4.0
Median change from core baseline to LOCF	-2.0	4.0
HDL (mg/dL), Month 12 / LOCF	**n=77 / n=129**	**n=33 / n=71**
Median change from core baseline to Month 12	0.0	4.0
Median change from core baseline to LOCF	0.0	4.0
LDL (mg/dL), Month 12 / LOCF	**n=77 / n=129**	**n=33 / n=71**
Median change from core baseline to Month 12	-3.0	0.0
Median change from core baseline to LOCF	-4.0	-3.0
Triglycerides (mg/dL), Month 12 / LOCF	**n=77 / n=129**	**n=33 / n=71**
Median change from core baseline to Month 12	-18.0	-7.0
Median change from core baseline to LOCF	-7.0	-7.0
Glucose (mg/dL), Month 12 / LOCF	**n=76 / n=130**	**n=33 / n=71**
Median change from core baseline to Month 12	1.0	1.0
Median change from core baseline to LOCF	1.0	2.0
HbA1c (%), Month 12 / LOCF	**n=76 / n=128**	**n=33 / n=71**

Endpoint	LUR to LUR N=151	QXR to QXR N=85
Median change from core baseline to Month 12	0.10	0.10
Median change from core baseline to LOCF	0.10	0.0
Weight (kg), Month 12 / LOCF	**n=78 / n=131**	**n=33 / n=73**
Mean change from core baseline to Month 12	0.73	1.23
≥7% increase, n (%)	9.0	5.0
≥7% decrease, n (%)	4.0	3.0
Mean change from core baseline to LOCF	0.82	2.18
≥7% increase, n (%)	16.0	16.0
≥7% decrease, n (%)	5 .0	6.0
BMI (kg/m^2), Month 12 / LOCF	**n=78 / n=131**	**n=33 / n=73**
Mean change from core baseline to Month 12	0.28	0.45
Mean change from core baseline to LOCF	0.31	0.77

Abbreviations: BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LUR to LUR = lurasidone 80 mg or 160 mg in the acute treatment phase followed by flexibly dosed lurasidone 40-160 mg in the extension phase, QXR to QXR = quetiapine XR 600 mg in the acute treatment phase followed by flexibly dosed quetiapine XR 200-800 mg in the extension phase, LDL = low-density lipoprotein, N = Safety Population, n = observed cases; SD = standard deviation, LOCF = last observation carried forward.

3.1.3.2. Study D1050237

Long-term safety, tolerability, and effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder: a randomized, active comparator (risperidone)-controlled trial.[7]

Study Design

Study D1050237, a 12 month, randomized, double-blind, multicenter, parallel-group study, evaluated the long-term safety, tolerability, and effectiveness of lurasidone compared with risperidone in clinically stable adult patients (≥18 years of age) with a primary diagnosis of schizophrenia or schizoaffective disorder, and duration of illness ≥1 year. Patients were treated with lurasidone (dosed at 80 mg/day on Days 1-7; flexibly dosed between 40 to 120 mg/day from Day 8), or risperidone (dosed at 2 mg/day on Days 1-2; 4 mg/day on Day 3; flexibly dosed between 2-6 mg/day from Day 8), for 12 months. The mean (SD) daily dose of lurasidone was 84.7 (21.8) mg. The mean (SD) daily dose of risperidone was 4.3 (1.0) mg. The median doses of lurasidone and risperidone were 80.0 mg and 4.0 mg, respectively.[2]

The study included a 14-day screening period, seven-day single-blind placebo washout period, a baseline assessment, and a 12-month double-blind treatment period. Table 44 presents the inclusion and exclusion criteria of the trial.

Table 44: Summary of Inclusion and Exclusion Criteria (D1050237)[7]*

Inclusion Criteria	Exclusion Criteria
18–75 years of age, inclusive	Resistance to antipsychotic treatment, defined as failure to respond to 2 or more antipsychotic agents administered at an adequate dose for ≥6 weeks or history of intolerance to 3 or more agents.
Satisfied DSM-IV criteria (including disorganized, paranoid and undifferentiated subtypes)	BMI <18.5 or >40 kg/m^2
Minimum duration of illness of at least 1 year	Type 1 diabetes
Clinically stable: CGI-S ≤4; no change in antipsychotic medications ≥6 weeks prior to Screening; no hospitalizations at ≥8 weeks prior to Screening; and a score of ≤4 (moderate or less) on PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content)	Patients with abnormal lab parameters as determined by the Investigator

*Table does not include a complete list of inclusion and exclusion criteria.

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions scale – Severity of Illness, CNS = central nervous system, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale.

Study Patients

A total of 629 patients met entry criteria and were randomly assigned in a 2:1 ratio to once daily treatment with either lurasidone or risperidone. A total of 608 patients were included in the ITT population, and 621 patients were analyzed for safety. Baseline characteristics were generally balanced across the treatment groups (Table 45).

Table 45: Baseline Characteristics, Study D1050237, Safety Population

Baseline Characteristic	Lurasidone 40-120 mg N=419	Risperidone 2-6 mg N=202
Sex, n (%), Male	302 (72.0)	126 (62.0)
Age, years, Mean (Range)	41.7 (18-73)	41.6 (18-65)
Race, n (%), White	151 (36.0)	88 (44.0)
DSM-IV subtype, n (%), Paranoid	301 (72.0)	146 (72.0)
PANSS total score, mean ± SD*	65.0 ± 12.3	65.3 ± 12.3
CGI-S score, mean ± SD*	3.4 ± 0.6	3.5 ± 0.6
MADRS score, mean ± SD*	7.5 ± 6.9	8.1 ± 7.4

*ITT population: Lurasidone 40-120 mg (N = 410), Risperidone 2-6 mg (N = 198)

Abbreviations: CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, SD = standard deviation.

Safety Results

A total of 236 (38%) patients completed the study. The overall discontinuation rate in lurasidone treatment group was 65% compared to 52% in the risperidone treatment group. Discontinuations due to insufficient clinical response or worsening of existing condition were 10% in the lurasidone and 8% risperidone treatment groups. The discontinuations due to adverse events were 21.5% in the lurasidone and 14.4% in the risperidone treatment groups.

The proportion of patients experiencing ≥1 adverse event in the lurasidone treatment group (84.5%) was similar compared to the risperidone group (84.7%). Change in movement disorder signs or symptoms as measured by change in SAS, BAS, and AIMS scores, were generally absent to mild in patients treated with either lurasidone or risperidone. No ECG abnormalities were associated with lurasidone treatment. The most common treatment-emergent adverse events (occurring in ≥5%, either treatment group) are listed in Table 46.

Table 46: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050237, Safety Population

Treatment-Emergent Adverse Events, n(%)	Lurasidone 40-120 mg N=419	Risperidone 2-6 mg N=202
Patients with ≥1 TEAE	**354 (84.5)**	**171 (84.7)**
Akathisia	60 (14.3)	16 (7.9)
Anxiety	39 (9.3)	17 (8.4)
Constipation	8 (1.9)	14 (6.9)
Dizziness	25 (6.0)	8 (4.0)
Dystonia	13 (3.1)	12 (5.9)
Headache	42 (10.0)	30 (14.9)
Insomnia	66 (15.8)	27 (13.4)
Nasopharyngitis	22 (5.3)	13 (6.4)
Nausea	70 (16.7)	22 (10.9)
Parkinsonism	18 (4.3)	11 (5.4)
Psychotic disorder	21 (5.0)	15 (7.4)
Sedation	61 (14.6)	28 (13.9)
Somnolence	57 (13.6)	36 (17.8)
Vomiting	42 (10.0)	7 (3.5)
Weight decreased	31 (7.4)	9 (4.5)
Weight increased	39 (9.3)	40 (19.8)

Abbreviations: TEAE = treatment-emergent adverse event, N = number of patients.

The rate of SAEs was similar in each group (lurasidone = 11.0%, risperidone = 9.9%). The only SAEs at the reported by ≥1% of patients in either treatment group were psychotic disorder (2.9% in the lurasidone group compared with 4.0% in the risperidone group), schizophrenia (1.9% in the lurasidone group compared with 1.5% in the risperidone group), and suicidal ideation (0.5% in the lurasidone group compared with 1.0% in the risperidone group).

The median observed change from baseline to Month 12 in prolactin for lurasidone and risperidone treated patients was -0.4 ng/mL and 14.8 ng/mL, respectively. The median observed change from baseline to LOCF endpoint in prolactin for lurasidone and risperidone treated patients was 0.1 ng/mL and 9.1 ng/mL, respectively. Prolactin median change from baseline to endpoint by gender is presented in Table 47.

Table 47: Change from Baseline to Month 12 and LOCF Endpoint in Prolactin Levels, Study D1050237, Safety Population

Endpoint	Lurasidone 40-120 mg	Risperidone 2-6 mg
Prolactin (ng/mL; male), Month 12 / LOCF	**n=115 / n=268**	**n=64 / n=110**
Median change from Baseline to Month 12	-0.50	9.60
Median change from Baseline to LOCF	0.00	7.50
Prolactin (ng/mL; female), Month 12 / LOCF	**n=35 / n=110**	**n=29 / n=66**
Median change from baseline to Month 12	0.10	28.40
Median change from baseline to LOCF	0.95	26.40

Abbreviations: n = number of patients, LOCF = last observation carried forward.

Mean changes from baseline for metabolic endpoints are listed in Table 48. Laboratory specimens were taken from the patient in the fasting state before breakfast.

Table 48: Change from Baseline to Month 12 and LOCF Endpoint in Metabolic Endpoints, Study D1050237, Safety Population

Endpoint	Lurasidone 40-120 mg	Risperidone 2-6 mg
Total Cholesterol (mg/dL), Month 12 / LOCF	**n=150 / n=354**	**n=93 / n=169**
Mean change from baseline (SD) to Month 12	-2.5 (30.2)	-1.9 (41.1)
Mean change from baseline (SD) to LOCF	-3.7 (29.5)	-4.3 (34.0)
LDL (mg/dL), Month 12 / LOCF	**n=150 / n=354**	**n=93 / n=169**
Mean change from baseline (SD) to Month 12	-1.3 (26.3)	-2.7 (30.3)
Mean change from baseline (SD) to LOCF	-2.2 (25.1)	-3.6 (26.6)
HDL (mg/dL), Month 12 / LOCF	**n=150 / n=354**	**n=93 / n=169**

Endpoint	Lurasidone 40-120 mg	Risperidone 2-6 mg
Mean change from baseline (SD) to Month 12	-0.2 (9.6)	-2.8 (9.2)
Mean change from baseline (SD) to LOCF	-0.0 (9.0)	-2.2 (9.1)
Triglycerides (mg/dL), Month 12 / LOCF	**n=150 / n=354**	**n=93 / n=169**
Mean change from baseline (SD) to Month 12	-13.0 (68.5)	19.9 (113.1)
Mean change from baseline (SD) to LOCF	-8.4 (89.7)	8.5 (97.9)
Glucose, mg/dL, Month 12 / LOCF	**n=149 / n=354**	**n=93 / n=171**
Mean change from baseline to Month 12 (SD)	3.4 (27.7)	4.0 (16.4)
Mean change from baseline to LOCF (SD)	2.4 (26.1)	4.8 (20.4)
HbA1c (%), Month 12 / LOCF	**n=149 / n=352**	**n=90 / n=168**
Mean change from baseline to Month 12 (SD)	0.06 (0.46)	0.10 (0.25)
Mean change from baseline to LOCF (SD)	0.04 (0.34)	0.07 (0.32)
Insulin, mU/L, Month 12 / LOCF	**n=150 / n=378**	**n=93 / n=176**
Mean change from baseline to Month 12 (SD)	-0.72 (21.03)	6.61 (29.96)
Mean change from baseline to LOCF (SD)	2.31 (31.46)	6.13 (24.24)
Weight (kg), Month 12 / LOCF	**n=150 / n=410**	**n=98 / n=197**
Mean change from baseline to Month 12 (SD)	-0.93 (6.55)	2.59 (5.40)
≥7% increase, n (%)	9 (13)	19 (19)
≥7% decrease, n (%)	31 (21)	6 (6)
Mean change from baseline to LOCF (SD)	-0.97 (5.06)	1.47 (5.03)
≥7% increase, n (%)	30 (7)	27 (14)
≥7% decrease, n (%)	52 (13)	11 (6)

Abbreviations: HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SD = standard deviation, n = number of patients, LOCF = last observation carried forward.

Efficacy Results

There were no significant differences during the 12-month double-blind treatment period between lurasidone and risperidone in PANSS total and CGI-S. On a mixed model for repeated measures (MMRM) analysis, the least squares (LS) mean reduction in PANSS total score was -4.7 (95% CI: [-6.4, -3.0], n=410) for the lurasidone treatment group and -6.5 (95% CI: [-8.8, -4.3]; n=197) for the risperidone treatment group at month 12. On a MMRM analysis, the CGI-S score decreased from baseline to month 12 in both the lurasidone group (-0.4, 95% CI: [-0.5, -0.3]; n=410) and the risperidone group (-0.4, 95% CI: [-0.5, -0.2]; n=198). There were no significant differences between lurasidone and risperidone in MADRS at any time point except for Month 12.

Relapse was defined as the earliest occurrence of a worsening of >30% PANSS total score from Baseline and CGI-S >3; re-hospitalization for worsening of psychosis; or the emergence of suicidal

ideation, homicidal ideation, and/or risk of harm to self or others. Overall, 19% of patients relapsed at some point during the study, with 20% of lurasidone-treated patients and 16% of risperidone-treated patients experiencing a relapse. A summary of the secondary endpoint results are shown in Table 49 below.

Table 49: Secondary Efficacy Endpoints, Repeated Measures Model, Study D1050237, ITT Population

Endpoint[a]	Lurasidone 40-120 mg N=410	Risperidone 2-6 mg N=198
PANSS	**n=410**	**n=197**
PANSS Total, LS mean change (SE)	-4.7 (0.9)	-6.5 (1.1)
p-value vs. risperidone at Month 12	0.181	-
PANSS positive subscore, LS mean change (SE)	-1.6 (0.3)	-1.9 (0.3)
p-value vs. risperidone at Month 12	0.488	-
PANSS negative subscore, LS mean change (SE)	-1.3 (0.3)	-1.4 (0.4)
p-value vs. risperidone at Month 12	0.948	-
PANSS general psychopathology subscore, LS mean change (SE)	-2.3 (0.4)	-3.6 (0.6)
p-value vs. risperidone at Month 12	0.072	-
PANSS cognitive subscore, LS mean change (SE)	-0.8 (0.2)	-0.9 (0.2)
p-value vs. risperidone at Month 12	0.869	-
CGI-S	**n=410**	**n=198**
LS mean change (SE)	-0.4 (0.1)	-0.4 (0.1)
p-value vs. risperidone at Month 12	0.929	-
MADRS	**n=380**	**n=176**
LS mean change (SE)	-0.8 (0.4)	-2.4 (0.5)
p-value vs. risperidone at Month 12	0.007	-

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model with fixed effects for pooled center, visit as a categorical variable, and treatment by visit interaction, assuming an unstructured covariance matrix. This model includes Baseline data as a response variable and provides one Baseline estimate across all patients. Contrasts are from differences (lurasidone versus risperidone) at each visit versus Baseline.

Abbreviations: CGI-S = Clinical Global Impression – Severity Scale, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, PANSS = Positive and Negative Syndrome Scale, SE = standard error.

3.1.3.3. Study D1050231E

D1050231E was the six-month open-label extension phase of study D1050231. As described above, D1050231 was a six-week, randomized, double-blind, parallel-group, placebo- and active controlled (olanzapine) study in patients with an acute exacerbation of schizophrenia[9]

Study Design

Patients who completed the double blind treatment of study D1050231 were eligible for entry into an open-label (OL) extension study (D1050231E) in which safety and tolerability were evaluated for six months. After completing a single-blind, 3-day placebo washout, patients in all treatment arms were switched to lurasidone 80 mg daily in an OL fashion. Flexible dosing was permitted after one week, in the dosing range of 40 to 120 mg/day. Efficacy assessments included the PANSS total and subscale scores, the CGI-S, and the Montgomery-Asberg Depression Rating Scale (MADRS). Three safety endpoints of interest were AEs and laboratory values.

Study Patients

A total of 298 patients completed the double-blind phase and were eligible for enrollment into the extension study; 254 entered and 113 (44%) completed the open-label extension phase. A total of 246 patients were included in the safety population. Demographics, baseline characteristics and patient disposition for the extension phase are presented in Table 50.

Table 50: Baseline Characteristics, Study D1050231E, Safety Population

Baseline Characteristic	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=69	All Extension N=246
Sex, n (%) Male	55 (81)	35 (74)	54 (78)	45 (73)	189 (77)
Age, years, Mean (Range)	36.9 (18-58)	34.8 (18-61)	36.4 (19-62)	36.5 (18-64)	36.3 (18-64)
Race, n (%), White	21 (31)	14 (30)	23 (33)	19 (31)	77 (31)
DSM-IV subtype, n (%), paranoid	60 (88)	42 (89)	58 (84)	53 (85)	213 (87)
PANSS total Score, DB baseline (acute phase), mean ± SD	97.3 ± 11.1	100.0 ± 11.2	96.3 ± 11.0	93.8 ± 9.9	96.6 ± 10.9
PANSS total Score, OL baseline (extension phase), mean ± SD	63.6 ± 17.3	68.1 ± 12.8	64.7 ± 15.1	70.7 ± 20.3	66.6 ± 16.9
CGI-S, DB baseline (acute phase), mean ± SD	5.0 ± 0.6	4.9 ± 0.6	4.9 ± 0.7	4.8 ± 0.6	4.9 ± 0.6
CGI-S, OL baseline (extension phase), mean ± SD	3.2 ± 0.9	3.3 ± 0.7	3.3 ± 0.7	3.5 ± 1.1	3.3 ± 0.9
MADRS, DB baseline (acute phase), mean ± SD	10.4 ± 7.1	11.4 ± 8.2	10.0 ± 6.2	9.7 ± 5.5	10.3 ± 6.7
MADRS, OL baseline (extension phase), mean ± SD	5.1 ± 5.2	5.2 ± 4.9	4.7 ± 4.3	6.3 ± 5.5	5.3 ± 5.0

Abbreviations: CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, L40 = lurasidone 40 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone during open-label phase, OLZ = olanzapine 15 mg in double-blind treatment phase, PBO = placebo in double-blind treatment phase PANSS = Positive and Negative Syndrome Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SD = standard deviation, N = number of patients, DB = double-blind, OL = open-label

Safety Results

The majority of discontinuations during the extension phase were due to withdrawal of consent (N=41, 16%), insufficient clinical response or a worsening of existing condition (N=29, 11%), or loss to follow-up (N=29, 11%). The proportion of patients in the extension phase who experienced one or more TEAE or a serious TEAE was 65.9% and 11.4%, respectively. The most common (incidence ≥5%) treatment-emergent adverse events are presented in

Table 51.

Table 51: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050231E, Safety Population

Treatment-emergent Adverse Event, n (%)	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
Patients with ≥1 TEAE	**43 (63.2)**	**28 (59.6)**	**47 (68.1)**	**44 (71.0)**	**162 (65.9)**
Akathisia	8 (11.8)	4 (8.5)	11 (15.9)	9 (14.5)	32 (13.0)
Anxiety	3 (4.4)	6 (12.8)	2 (2.9)	4 (6.5)	15 (6.1)
Headache	4 (5.9)	5 (10.6)	2 (2.9)	7 (11.3)	18 (7.3)
Insomnia	7 (10.3)	2 (4.3)	10 (14.5)	8 (12.9)	27 (11.0)
Nausea	5 (7.4)	2 (4.3)	5 (7.2)	12 (19.4)	24 (9.8)
Parkinsonism	7 (10.3)	4 (8.5)	6 (8.7)	6 (9.7)	23 (9.3)
Somnolence	10 (14.7)	2 (4.3)	5 (7.2)	7 (11.3)	24 (9.8)
Vomiting	5 (7.4)	2 (4.3)	5 (7.2)	4 (6.5)	16 (6.5)
Weight Increased	3 (4.4)	4 (8.5)	2 (2.9)	4 (6.5)	13 (5.3)

Abbreviations: L40 = lurasidone 40 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone during open-label phase; N = number of patients, OLZ = olanzapine 15 mg in double-blind treatment phase, PBO = placebo in double-blind treatment phase; TEAE = treatment-emergent adverse event

There were 33 SAEs reported in 28 patients. The most common SAEs were related to a worsening of the underlying condition of schizophrenia, with 16 patients reporting a SAE with a Preferred Term including the terms “schizophrenia” (9 patients) or “psychosis” (7 patients). Of the 14 SAEs that were assessed by the investigators to be possibly related, probably related, or related to study medication, 8 SAEs were either schizophrenia or psychotic disorder SAEs. Headache and poor quality sleep (both in the same subject) and vomiting were the only nonpsychiatric disorder SAEs reported to be possibly related, probably related, or related to study medication.

Prolactin, which had increased during the DB phase of the study (+3.2 ng/mL on combined lurasidone; +3.4 ng/mL on olanzapine), showed a median decrease (-1.3 ng/mL) during the OL extension.

Median change from OL baseline to LOCF endpoint for prolactin and mean change from OL baseline to LOCF endpoint for metabolic endpoints are listed in Table 52 and Table 53, respectively.

Table 52: Summary of Prolactin Levels, Study D1050231E, Safety Population

Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
Prolactin (ng/mL; male), Month 8/LOCF	**n=24/n=51**	**n=18/n=33**	**n=24/n=51**	**n=18/n=38**	**n=84/n=173**
Median Change from OL Baseline Month 8	2.05	-2.15	-3.65	-0.85	-1.40
Median Change from OL Baseline LOCF	2.10	-1.90	-4.40	-0.25	-1.30
Prolactin (ng/mL; female), Month 8/LOCF	**n=9/n=12**	**n=5/n=11**	**n=6/n=15**	**n=10/n=17**	**n=30/n=55**
Median Change from OL Baseline Month 8	-0.70	-19.20	-10.55	10.55	-1.00
Median Change from OL Baseline LOCF	-1.00	-19.20	-10.90	5.70	-2.50

LOCF endpoint is defined as the last post-baseline measurement through seven days after open-label treatment completion or discontinuation.

Abbreviations: L40 = lurasidone 40 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LOCF = last observation carried forward, LUR = lurasidone during open-label phase; N = number of patients, OL = open-label, OLZ = olanzapine 15 mg in double-blind treatment phase, PBO = placebo in double-blind treatment phase

Table 53: Summary of Metabolic Endpoints, Study D1050231E, Safety Population

Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
Total Cholesterol (mg/dL), Month 8/LOCF	**n=32/n=57**	**n=23/n=43**	**n=31/n=58**	**n=28/n=51**	**n=114/n=209**
Mean change from OL baseline (SD) Month 8	-7.8 (37.4)	-0.8 (24.8)	-13.4 (31.5)	-2.9 (35.1)	-6.7 (32.9)
Mean change from OL baseline (SD) LOCF	-4.1 (32.8)	-0.4 (24.5)	-20.3 (30.6)	-1.0 (30.1)	-7.1 (30.9)
HDL (mg/dL), Month 8/LOCF	**n=32/n=57**	**n=23/n=43**	**n=31/n=58**	**n=28/n=51**	**n=114/n=209**
Mean change from OL baseline (SD) Month 8	-2.3 (8.7)	-2.0 (10.5)	3.8 (10.3)	-0.1 (9.0)	-0.1 (9.8)
Mean change from OL baseline (SD) LOCF	-2.4 (8.3)	-2.3 (9.0)	0.3 (11.1)	0.5 (9.4)	-0.9 (9.6)
LDL (mg/dL), Month 8/LOCF	**n=32/n=57**	**n=23/n=43**	**n=31/n=58**	**n=28/n=51**	**n=114/n=209**
Mean change from OL baseline (SD) Month 8	-1.1 (34.2)	5.7 (30.1)	-4.9 (22.3)	0.1 (30.7)	-0.5 (29.5)

Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
Mean change from OL baseline (SD) LOCF	-0.6 (30.8)	3.7 (26.4)	-9.6 (23.0)	-2.3 (26.5)	-2.6 (27.0)
Triglycerides (mg/dL), Month 8/LOCF	**n=32/n=57**	**n=23/n=43**	**n=31/n=58**	**n=28/n=51**	**n=114/n=209**
Mean change from OL baseline (SD) Month 8	-8.1 (69.5)	-16.6 (80.0)	-64.6 (131.5)	2.1 (64.8)	-22.7 (94.2)
Mean change from OL baseline (SD) LOCF	-1.5 (86.5)	-11.1 (69.9)	-57.2 (129.0)	1.0 (61.7)	-18.3 (95.3)
C-reactive protein (mg/dL), Month 8/LOCF	**n=32/n=63**	**n=23/n=44**	**n=31/n=66**	**n=27/n=55**	**n=113/n=228**
Mean change from OL baseline (SD) Month 8	-0.4 (0.30)	0.004 (0.53)	-0.06 (0.56)	0.15 (1.06)	0.01 (0.66)
Mean change from OL baseline (SD) LOCF	-0.03 (0.29)	0.06 (0.55)	-0.08 (0.53)	0.17 (0.81)	0.02 (0.57)
Glucose (mg/dL), Month 8/LOCF	**n=32/n=62**	**n=23/n=44**	**n=31/n=66**	**n=27/n=54**	**n=113/ n=226**
Mean change from OL baseline (SD) Month 8	9.6 (39.1)	2.7 (10.9)	-7.5 (41.9)	1.2 (28.8)	1.5 (33.9)
Mean change from OL baseline (SD) LOCF	8.3 (31.0)	3.3 (17.6)	-7.8 (35.2)	1.2 (22.1)	0.9 (28.8)
HbA1c (%), Month 8/LOCF	**n=31/n=57**	**n=22/n=42**	**n=31/n=56**	**n=28/n=50**	**n=112/n=205**
Mean change from OL baseline (SD) Month 8	-0.04 (0.27)	-0.11 (0.25)	-0.21 (0.81)	0.03 (0.33)	-0.08 (0.49)
Mean change from OL baseline (SD) LOCF	0.00 (0.25)	-0.11 (0.27)	-0.15 (0.64)	0.03 (0.28)	-0.06 (0.41)
Insulin (mU/L), Month 8/LOCF	**n=33/n=63**	**n=23/n=44**	**n=30/n=66**	**n=28/n=55**	**n=114/n=228**
Mean change from OL baseline (SD) Month 8	-5.95 (39.51)	0.70 (16.94)	-1.89 (25.81)	0.39 (20.88)	-1.98 (27.94)
Mean change from OL baseline (SD) LOCF	-3.23 (32.60)	1.28 (19.32)	-5.68 (37.44)	-0.49 (16.77)	-2.41 (28.92)
Weight (kg), Month 8/LOCF	**n=33/n=63**	**n=23/n=44**	**n=31/n=65**	**n=28/n=55**	**n=115/n=227**
Mean change from OL baseline (SD) Month 8	0.94 (4.23)	-0.35 (4.00)	-1.88 (5.72)	0.87 (3.86)	-0.10 (4.65)
≥7% increase, n (%)	2 (6.1)	2 (8.7)	1 (3.2)	5 (17.9)	10 (8.7)
≥7% decrease, n (%)	3 (9.1)	2 (8.7)	9 (29.0)	2 (7.1)	16 (13.9)
Mean change from OL baseline (SD) LOCF	0.38 (3.66)	-0.33 (3.36)	-1.80 (4.93)	0.88 (3.62)	-0.26 (4.12)
≥7% increase, n (%)	3 (4.8)	2 (4.5)	1 (1.5)	6 (10.9)	12 (5.3)
≥7% decrease, n (%)	4 (6.3)	3 (6.8)	12 (18.5)	3 (5.5)	22 (9.7)
BMI (kg/m^2), Month 8/LOCF	**n=33/n=63**	**n=23/n=44**	**n=31/n=65**	**n=28/n=55**	**n=115/n=227**

Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
Mean change from OL baseline (SD) Month 8	0.36 (1.41)	-0.12 (1.44)	-0.66 (2.02)	0.39 (1.41)	-0.00 (1.64)
Mean change from OL baseline (SD) LOCF	0.16 (1.24)	-0.11 (1.18)	-0.60 (1.65)	0.33 (1.26)	-0.07 (1.40)

LOCF endpoint is defined as the last post-Baseline measurement through 7 days after open-label treatment completion or discontinuation

Abbreviations: BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein, L40 = lurasidone 40 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LOCF = last observation carried forward, LUR = lurasidone during open-label phase, N = number of patients, OL = open-label, OLZ = olanzapine 15 mg in double-blind treatment phase, PBO = placebo in double-blind treatment phase, SD = standard deviation

Efficacy Results

Patients continuing in the OL phase maintained improvement, as measured by PANSS, CGI-S and MADRS, for up to 6 months of treatment with flexible doses of lurasidone in the range of 40 to 120 mg/day. The modal dose of lurasidone was 80 mg (63%), followed by 120 mg (27%) and 40 mg (10%).

The mean (SD) PANSS total score, for patients from all treatment arms (N=246) continuing into the OL phase, was 66.6 (16.9) at the baseline of the OL phase. Patients completing open-label treatment (n=117) had a mean (SD) PANSS total score of 54.9 (16.0) at the end of the extension phase. The efficacy endpoints are shown in Table 54.

Table 54: Summary of Efficacy Endpoints, Study D1050231E

Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
N (observed cases)	33	25	31	28	117
PANSS Total					
Change from OL baseline to Month 8 (SD)	-9.8 (14.1)	-7.1 (14.8)	-5.8 (11.1)	-12.0 (17.1)	-8.7 (14.4)
95% CI	-14.8, -4.8	-13.2, -1.0	-9.9, -1.8	-18.7, -5.4	-11.3, -6.1
PANSS positive subscale					
Change from OL baseline to Month 8 (SD)	-3.4 (5.4)	-1.6 (4.3)	-1.9 (3.3)	-3.5 (4.9)	-2.6 (4.6)
95% CI	-5.3, -1.5	-3.5, 0.2	-3.1, -0.7	-5.4, -1.6	-3.5, -1.8
PANSS negative subscale					
Change from OL baseline to Month 8 (SD)	-2.3 (4.4)	-3.3 (4.5)	-1.5 (3.3)	-3.0 (5.5)	-2.5 (4.5)

Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
95% CI	-3.9, -0.7	-5.2, -1.4	-2.7, -0.4	-5.1, -0.8	-3.3, -1.7
PANSS psychopathology subscale					
Change from OL baseline to Month 8 (SD)	-4.1 (6.1)	-2.2 (8.1)	-2.4 (6.7)	-5.6 (8.6)	-3.6 (7.4)
95% CI	-6.2, -1.9	-5.6, 1.1	-4.9, 0.1	-8.9, -2.2	-5.0, -2.2
CGI-S					
Change from OL baseline to Month 8 (SD)	-0.5 (1.2)	-0.4 (1.0)	-0.3 (0.7)	-0.5 (1.0)	-0.4 (1.0)
95% CI	-1.0, -0.1	-0.8, 0.1	-0.5, 0.0	-0.9, -0.1	-0.6, -0.2
MADRS					
Change from OL baseline to Month 8 (SD)	-0.1 (5.8)	0.1 (4.6)	1.8 (5.9)	-2.0 (5.3)	0.0 (5.6)
95% CI	-2.2, 1.9	-1.8, 2.0	-0.4, 3.9	-4.1, 0.0	-1.0, 1.0

Abbreviations: CGI-S = Clinical Global Impression scale – Severity of Illness, CI = confidence interval, L40 = lurasidone 40 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone during open-label phase, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, OL = Open-label, OLZ = olanzapine 15 mg in double-blind treatment phase, PBO = placebo in double-blind treatment phase, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

3.1.3.4. D1050229E

D1050229E is the 22-month open-label (OL), flexible-dose extension of study D1050229. As described above, D1050229 was a six-week, randomized, double-blind, multicenter, parallel-group, placebo-controlled study in patients with an acute exacerbation of schizophrenia.[8]

Study Design

The extension phase started at the end of Week 6 (42-day, Visit 10). Patients enrolled were switched to lurasidone 80 mg in an open-label fashion, regardless of the double-blind treatment assignment. There was no gap in study medication administration between the acute and extension phases. Patients who elected to continue in the extension phase received extension medication starting at Visit 10 and at monthly visits thereafter. Patients were contacted by the study center in between the monthly visits by telephone at weekly intervals to assess AEs, confirm medication compliance, and to assess general well-being. Safety and tolerability assessments were the primary objective. Efficacy was also evaluated during the extension trial period utilizing PANSS, CGI-S, and MADRS.

Study Patients

A total of 251 out of 328 patients who completed the double-blind phase of the study elected to participate in the OL extension phase. Assigned treatment groups were as follows: 62 in the lurasidone 40 mg, 65 in the lurasidone 80 mg, 65 in the lurasidone 120 mg, and 59 in the placebo group. A total of 67 out of 251 patients (27%) completed the OL extension phase of the study. The majority of discontinuations were due to withdrawal of consent (n=60, 24.0%), insufficient clinical response or worsening of condition (n=57, 23%), and AEs (n=37, 15.0%). A total of 250 patients were analyzed and included in the safety population. Baseline characteristics for the extension phase are presented in Table 55.

Table 55: Baseline Characteristics, Study D1050229E, Safety Population

Baseline Characteristic	L40 to LUR N=62	L80 to LUR N=65	LUR120 to LUR N=64	PBO to LUR N=59	All Extension N=250
Sex, n (%) Male	36 (58)	39 (60)	44 (69)	43 (73)	162 (65)
Age, years, Mean (Range)	40.9 (18-72)	36.2 (19-55)	38.1 (19-65)	38.8 (20-59)	38.5 (18-72)
Race, n (%), White	29 (47)	37 (57)	29 (45)	34 (58)	129 (52)
DSM-IV subtype, n (%), paranoid	54 (87)	55 (85)	57 (89)	55 (93)	221 (88)
PANSS total Score, DB baseline (acute phase), mean ± SD	98.3 ± 11.8	96.3 ± 9.4	95.9 ± 10.0	95.5 ± 10.1	96.5 ± 10.3
PANSS total Score, OL baseline (extension phase), mean ± SD	72.7 ± 18.0	68.8 ± 14.8	68.0 ± 15.6	68.4 ± 17.4	69.5 ± 16.5
CGI-S, DB baseline (acute phase), mean ± SD	5.0 ± 0.6	5.0 ± 0.5	4.9 ± 0.6	4.9 ± 0.5	4.9 ± 0.6
CGI-S, OL baseline (extension phase), mean ± SD	3.6 ± 1.0	3.4 ± 0.7	3.3 ± 0.8	3.5 ± 0.9	3.4 ± 0.8
MADRS, DB baseline (acute phase), mean ± SD	10.1 ± 5.9	10.7 ± 7.1	11.0 ± 7.2	11.4 ± 6.0	10.8 ± 6.6
MADRS, OL baseline (extension phase), mean ± SD	5.9 ± 5.2	5.8 ± 4.9	6.7 ± 5.9	6.2 ± 5.0	6.1 ± 5.3

Abbreviations: CGI-S = Clinical Global Impressions scale – Severity of Illness, DB = double-blind, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, L40 = lurasidone 40 mg in double-blind treatment phase, L80 = lurasidone 80 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone during open-label phase, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, OL = open-label, PANSS = Positive and Negative Syndrome Scale, PBO = placebo in double-blind treatment phase SD = standard deviation

Safety Results

The proportion of patients experiencing ≥1 AE in the OL extension phase was 172 (68.8%). Serious TEAE occurred in 49 (19.6%) of patients in the OL extension phase. The 5 most frequently reported TEAEs at the Preferred Term level were schizophrenia (12.4% of all patients), akathisia (10.8% of all patients), somnolence (10.8% of all patients), vomiting (8.8% of all patients), and nausea (8.4% of all patients). The majority of TEAEs reported were classified as either mild or moderate. Only 23 patients (9.2%) reported one or more TEAE that was classified as severe during the open-label extension. A total

of 48 patients (19.2%) were reported with one or more EPS-related TEAE. Akathisia was reported by the highest proportion of patients (10.8%) followed by Parkinsonism (6.4%) and tremor (2.4%). No other EPS-related TEAE was reported by more than 2% of patients. The most common treatment-emergent adverse events (occurring in ≥5%) are listed in Table 56.

Table 56: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1050229E, Safety Population

Treatment-Emergent Adverse Events, n(%)	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PBO to LUR N = 59	All Extension N = 250
Patients with ≥1 TEAE	**41 (66.1)**	**42 (64.6)**	**42 (65.6)**	**47 (79.7)**	**172 (68.8)**
Akathisia	5 (8.1)	8 (12.3)	9 (14.1)	5 (8.5)	27 (10.8)
Anxiety	4 (6.5)	4 (6.2)	1 (1.6)	10 (16.9)	19 (7.6)
Headache	7 (11.3)	3 (4.6)	2 (3.1)	3 (5.1)	15 (6.0)
Insomnia	5 (8.1)	8 (12.3)	3 (4.7)	4 (6.8)	20 (8.0)
Nausea	2 (3.2)	5 (7.7)	3 (4.7)	11 (18.6)	21 (8.4)
Parkinsonism	4 (6.5)	5 (7.7)	5 (7.8)	2 (3.4)	16 (6.4)
Schizophrenia	8 (12.9)	6 (9.2)	9 (14.1)	8 (13.6)	31 (12.4)
Somnolence	9 (14.5)	5 (7.7)	6 (9.4)	7 (11.9)	27 (10.8)
Vomiting	4 (6.5)	5 (7.7)	3 (4.7)	10 (16.9)	22 (8.8)
Weight decreased	5 (8.1)	2 (3.1)	3 (4.7)	5 (8.5)	15 (6.0)

Abbreviations: L40 = lurasidone 40 mg in double-blind treatment phase, L80 = lurasidone 80 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone during open-label phase, N = number of patients, PBO = placebo in double-blind treatment phase, TEAE = treatment emergent adverse event

A total of 49 patients (19.6%) reported one or more serious TEAE during the open-label extension. The only events at the Preferred Term level that were reported by ≥ 1% of patients were schizophrenia (10.0% of patients) and psychotic disorder (2.8%), both exacerbations of the underlying condition. The only other serious TEAE reported for more than one subject was akathisia, reported for 2 patients (0.8%).

Prolactin concentrations increased during the double-blind phase of the study for patients continuing into the open-label extension from a (mean ± SD) double-blind baseline of 13.41 ± 15.04 ng/mL to 17.24 ± 28.45 ng/mL. During the OL extension phase, median prolactin decreased overall from OL baseline to LOCF endpoint (-0.30 ng/mL, range: -108.4, 129.9 ng/mL). In females, the largest median decrease was in patients who had been randomized to double-blind phase lurasidone 120 mg (-5.00 ng/mL, range: -86.0, +129.9 ng/mL) and lurasidone 80 mg (5.00 ng/mL, range: -107.1, +36.6 ng/mL). In males, the median change from OL baseline to LOCF Endpoint tended to be smaller. Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 57.

Table 57: Summary of Prolactin Levels, Study D1050229E, Safety Population

Endpoint	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PBO to LUR N = 59	All Extension N = 250
Prolactin (ng/mL; male), Month 24/LOCF	**N=10/N=30**	**N=11/N=32**	**N=8/N=39**	**N=8/N=37**	**N=37/N=138**
Median Change from OL Baseline Month 24	-8.40	-5.07	-5.15	5.45 (17.28)	-3.71
Median Change from OL Baseline LOCF	0.35	-0.45	-4.10	-0.40	-0.65
Prolactin (ng/mL; female), Month 24/LOCF	**N=8/N=25**	**N=9/N=23**	**N=4/N=17**	**N=8/N=15**	**N=29/N=80**
Median Change from OL Baseline Month 24	3.69	-7.49	-25.20	6.93	-2.87
Median Change from OL Baseline LOCF	6.60	-5.00	-5.00	0.90	1.05

LOCF endpoint is defined as the last post-baseline measurement through seven days after open-label treatment completion or discontinuation.

Abbreviations: L40 = lurasidone 40 mg in double-blind treatment phase, L80 = lurasidone 80 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LOCF = last observation carried forward, LUR = lurasidone during open-label phase; N = number of patients, OL = open-label, PBO = placebo in double-blind treatment phase

Metabolic endpoints of interest included glucose, total cholesterol, HDL, LDL, and triglycerides. Glucose, total cholesterol, HDL, LDL, and triglycerides were to be collected with patients in a fasted state. Metabolic endpoints measured are presented in Table 58.

Table 58: Change from OL Baseline to Month 24 in Metabolic Endpoints, Study D1050229E, Safety Population

Endpoint	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PBO to LUR N = 59	All Extension N = 250
Total Cholesterol (mg/dL) Month 24/LOCF	**n=17/n=55**	**n=19/n=56**	**n=12/n=56**	**n=16/n=52**	**n=64/n=219**
Mean change from OL baseline (SD) Month 24	-2.9 (29.3)	-5.5 (31.6)	2.8 (24.9)	6.5 (40.7)	-0.3 (32.1)
Mean change from OL baseline (SD) LOCF	-4.0 (34.5)	-3.8 (27.5)	-0.4 (30.2)	0.8 (29.1)	-1.9 (30.3)
HDL (mg/dL) Month 24/LOCF	**n=17**	**n=19**	**n=12**	**n=16**	**N=64**
Mean change from OL baseline (SD) Month 24	-1.2 (6.6)	-1.8 (11.2)	-2.4 (13.0)	-0.8 (12.9)	-1.5 (10.8)
Mean change from OL baseline (SD) LOCF	-0.4 (9.5)	-2.0 (9.2)	-0.9 (12.9)	-0.7 (9.9)	-0.7 (10.4)
LDL (mg/dL) Month 24/LOCF	**n=17/n=55**	**n=19/n=56**	**n=12/n56**	**n=16/n=52**	**N=64/n=219**

Endpoint	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PBO to LUR N = 59	All Extension N = 250
Mean change from OL baseline (SD) Month 24	-1.9 (28.5)	-5.6 (21.2)	7.3 (21.9)	-2.8 (24.4)	-1.5 (24.1)
Mean change from OL baseline (SD) LOCF	-4.1 (26.9)	-2.5 (20.1)	1.0 (30.6)	-1.5 (21.2)	-1.7 (25.0)
Triglycerides (mg/dL) Month 24/LOCF	**n=17/n=55**	**n=19/n=56**	**n=12/n=56**	**n=16/n=52**	**n=64/n=219**
Mean change from OL baseline (SD) Month 24	-0.5 (117.7)	-2.3 (66.1)	-7.8 (61.7)	73.7 (159.0)	16.2 (112.1)
Mean change from OL baseline (SD) LOCF	-2.5 (90.0)	-2.7 (57.5)	-5.6 (52.8)	22.3 (107.2)	2.5 (79.7)
Glucose (mg/dL) Month 24/LOCF	**n=18/n=56**	**n=19/n=62**	**n=12/n=58**	**n=16/n=56**	**n=65/n=232**
Mean change from OL baseline (SD) Month 24	3.3 (12.6)	9.1 (19.1)	2.4 (10.5)	-3.4 (16.2)	3.2 (15.7)
Mean change from OL baseline (SD) LOCF	5.8 (15.9)	8.0 (20.7)	2.9 (13.9)	5.8 (26.0)	5.7 (19.6)
HbA1c (%) Month 24/LOCF	**n=17/n=53**	**n=18/n=55**	**n=11/n=55**	**n=15/n=51**	**n=61/n=214**
Mean change from OL baseline (SD) Month 24	0.09 (0.30)	0.25 (0.41)	0.15 (0.22)	0.08 (0.53)	0.15 (0.39)
Mean change from OL baseline (SD) LOCF	-0.02 (0.27)	0.10 (0.34)	0.05 (0.40)	-0.04 (0.43)	0.02 (0.36)
Weight (kg) Month 24/LOCF	**n=18/n=57**	**n=20/n=63**	**n=13/n=60**	**n=16/n=56**	**n=67/n=236**
Mean change from OL baseline (SD) Month 24	0.59 (6.74)	0.66 (4.72)	2.28 (5.16)	-0.97 (11.06)	0.56 (7.20)
≥7% increase, n (%)	3 (16.7)	4 (20.0)	4 (30.8)	5 (31.3)	16 (23.9)
≥7% decrease, n (%)	4 (22.2)	2 (10.0)	1 (7.7)	2 (12.5)	9 (13.4)
Mean change from OL baseline (SD) LOCF	-1.33 (6.61)	-0.14 (4.84)	0.32 (4.79)	-0.67 (6.76)	-0.44 (5.78)
≥7% increase, n (%)	3 (5.3)	7 (11.1)	7 (11.7)	7 (12.5)	24 (10.2)
≥7% decrease, n (%)	9 (15.8)	8 (12.7)	5 (8.3)	6 (10.7)	28 (11.9)
BMI (kg/m^2) Month 24/LOCF	**n=19**	**n=20**	**n=14**	**n=16**	**n=69**
Mean change from OL baseline (SD) Month 24	0.33 (2.67)	0.18 (1.75)	0.82 (1.88)	-0.17 (3.72)	0.26 (2.57)
Mean change from OL baseline (SD) LOCF	-0.33 (2.27)	-0.06 (1.68)	0.12 (1.67)	-0.19 (2.26)	-0.11 (1.97)

LOCF endpoint is defined as the last post-Baseline measurement through 7 days after open-label treatment completion or discontinuation

Abbreviations: BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, L40 = lurasidone 40 mg in double-blind treatment phase, L80 = lurasidone 80 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LDL = low-density lipoprotein , LOCF = last observation carried forward, LUR = lurasidone during open-label phase, N = number of patients, OL = open-label, PBO = placebo in double-blind treatment phase, SD = standard deviation

Efficacy Results

The PANSS total score (± SD) at double-blind baseline for all patients continuing into the OL phase was 96.5 ± 10.3, indicating marked illness at the time of enrollment. Patients continuing into the OL phase of the study had shown a substantial decrease in PANSS total score (OL baseline PANSS total score of 69.5 ± 16.5), indicating improvement of psychotic symptoms.

Patients who continued through Month 24 of the study (end of the OL extension) continued to show marked improvement in the PANSS total score, with an overall mean of 52.4 ± 12.6 (n = 69) at Month 24 and an overall change from open-label baseline of -12.3 ± 16.2 (95% CI: -16.2, -8.4). The largest change from OL baseline to Month 24 was in patients randomized to double-blind phase lurasidone 120 mg (-14.8 ± 17.4, 95% CI: -25.4, -4.3), followed by patients randomized to double-blind lurasidone 40 mg (-14.6 ± 17.8, 95% CI: -23.2, -6.1), double-blind lurasidone 80 mg (-10.6 ± 16.3, 95% CI: -18.2, -3.0), and double-blind placebo (-9.7 ± 13.8, 95% CI: -16.8, -2.6). Efficacy endpoints in the OL extension phase are presented below in Table 59.

Table 59: Summary of Efficacy Endpoints – Observed Change from Open-Label Baseline, Study D1050229E

Endpoint	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PBO to LUR N = 59	All Extension N = 250
n (observed cases)	19	20	13	17	69
PANSS Total					
Change from OL baseline to Month 24 (SD)	-14.6 (17.8)	-10.6 (16.3)	-14.8 (17.4)	-9.7 (13.8)	-12.3 (16.2)
95% CI	-23.2, -6.1	-18.2, -3.0	-25.4, -4.3	-16.8, -2.6	-16.2, -8.4
PANSS positive subscale					
Change from OL baseline to Month 24 (SD)	-4.3 (5.1)	-3.0 (4.1)	-4.4 (3.6)	-3.4 (4.3)	-3.7 (4.3)
95% CI	-6.7, -1.8	-4.9, -1.0	-6.6, -2.2	-5.6, -1.1	-4.7, -2.6
PANSS negative subscale					
Change from OL baseline to Month 24 (SD)	-2.5 (4.8)	-3.1 (4.3)	-3.6 (6.9)	-2.6 (4.5)	-2.9 (5.0)
95% CI	-4.8, -0.2	-5.1, -1.1	-7.8, 0.6	-5.0, -0.3	-4.1, -1.7
PANSS psychopathology subscale					
Change from OL baseline to Month 24 (SD)	-7.9 (9.2)	-4.6 (9.3)	-6.8 (8.5)	-3.7 (7.7)	-5.7 (8.7)
95% CI	-12.3, -3.5	-8.9, -0.2	-12.0, -1.7	-7.6, 0.2	-7.8, -3.6
CGI-S					
Change from OL baseline to Month 24 (SD)	-0.5 (0.7)	-0.5 (0.8)	-0.6 (0.7)	-0.4 (0.7)	-0.5 (0.7)

Endpoint	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PBO to LUR N = 59	All Extension N = 250
95% CI	-0.9, -0.2	-0.9, -0.1	-1.0, -0.2	-0.7, 0.0	-0.7, -0.3
MADRS					
Change from OL baseline to Month 24 (SD)	-0.9 (4.4)	-1.9 (4.8)	-2.8 (5.8)	2.7 (8.1)	-0.7 (6.1)
95% CI	-3.0, 1.2	-4.2, 0.4	-6.4, 0.7	-1.6, 7.0	-2.2, 0.7

Abbreviations: CGI-S = Clinical Global Impression scale – Severity of Illness, CI = confidence interval, L40 = lurasidone 40 mg in double-blind treatment phase, L80 = lurasidone 80 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone during open-label phase, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, OL = Open-label, PBO = placebo in double-blind treatment phase, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

3.1.3.5. Study D1001048

52-week long-term study of lurasidone in schizophrenia.[76]

Study Design

Study D1001048, a 52-week, open-label, flexible-dose study, evaluated the long-term safety and effectiveness of lurasidone compared with risperidone in clinically stable adult Japanese patients (≥18 years of age) with a primary diagnosis of schizophrenia. Patients were treated with lurasidone dosed 40 to 120 mg/day (initial dose 40 mg/day, to be adjusted in increments of 20 mg/dose), given once daily after meals. The study included a 14-day screening period, seven-day single-blind placebo washout period, a baseline assessment, and a 12-month double-blind treatment period.

Table 60 presents the inclusion and exclusion criteria of the trial.

Table 60: Summary of Inclusion and Exclusion Criteria (D1001048)*

Inclusion Criteria	Exclusion Criteria
18–65 years of age, inclusive	Parkinson's disease
Satisfied ICD-10 diagnosis criteria for schizophrenia	History of drug or alcohol abuse
Patients experiencing initial occurrence or relapse, or patients already undergoing treatment with antipsychotic drugs and presenting with any of the following at the time of registration: a) Hallucinations and delusions as presenting symptoms b) Delusions alone as presenting symptoms c) Loss of initiative and blunted affect as presenting symptom I (such as acute hebephrenic schizophrenia) d) Loss of initiative and blunted affect as presenting symptom II (associated with chronic or fixed symptomotology) e) Symptoms consistent with a neurosis-like disorder f) Symptoms consistent with a depressed state	$HbA1_C$ level of 8.0% or greater, or glycoalbumin level 23.0% or greater
	Complications of serious cardiovascular, hepatic, renal, organic brain, hematological, endocrine, or convulsive conditions, or history of the conditions in the judgment of the principal investigator or a subinvestigator, would render a subject inappropriate for the study.

* Table does not include a complete list of inclusion and exclusion criteria.

Abbreviations: ICD = International Classification of Diseases

Study Patients

A total of 182 patients met entry criteria and were enrolled in the study. A total of 80 (44%) patients completed the study. Among patients who discontinued, 44 (43.1%) patients discontinued treatment because of aggravation of the underlying disease, and 32 (31.4%) patients discontinued treatment because of adverse events: of the remaining 26 (25.5%) patients, 13 patients discontinued treatment because of a request for withdrawal from the study from the subject him/herself or from his/her guardian. A total of 174 patients were included in the ITT population, and 182 were analyzed for safety. Baseline characteristics are presented in Table 61.

Table 61: Baseline Characteristics, Study D1001048, Safety Population

Baseline Characteristic	Lurasidone 40-120 mg N=182
Sex, n (%), Male	172 (94.5)
Age, years, Mean (Range)	43.9 (20-64)
DSM-IV subtype, n (%), Paranoid	146.4 (80.4)
BPRS total score, mean ± SD*	43.9 ± 11.5
PANSS total score, mean ± SD*	78.3 ± 20.2

*ITT population n = 174

Abbreviations: ty of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psyxhiatric Rating Scale, N = number of patients, SD = standard deviation

Efficacy Results

The PANSS total scores decreased from 78.3 ± 20.2 at baseline prior to dosing to 72.6 ± 24.5 at the end of dosing (change from baseline: -5.7 ± 17.2), and the BPRS total scores likewise decreased from 44.2 ± 11.5 to 40.8 ± 13.9 (change from baseline: -3.4 ± 10.4). A summary of the efficacy endpoint results are shown in Table 62 below.

Table 62: Summary of Efficacy Endpoints, Study D1001048

Endpoint	Lurasidone 40-120 mg
PANSS Total	**N=168**
Mean change from OL baseline to Endpoint (SD)	-5.7 (17.2)
95% CI	-8.3, -3.1
BPRS Total	**N=174**
Mean change from OL baseline to Endpoint (SD)	-3.4 (10.4.2)
95% CI	-5.0, -1.9
PANSS positive subscale	**N=168**
Mean change from OL baseline to Endpoint (SD)	-0.5 (4.9)
95% CI	-1.2, 0.3
PANSS negative subscale	**N=168**
Mean change from OL baseline to Endpoint (SD)	-2.5 (5.0)
95% CI	-3.3, -1.8
PANSS psychopathology subscale	**N=168**
Mean change from OL baseline to Endpoint (SD)	-2.7 (10.0)
95% CI	-4.2, -1.8

Abbreviations: CI = confidence interval, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation

Safety Results

The proportion of patients experiencing a TEAE in the lurasidone treatment group was 83.0%. The most common treatment-emergent adverse events (occurring in ≥5%, either treatment group) are listed in Table 63.

Table 63: Number (%) of Patients Reporting the Most Common Treatment-emergent Adverse Events (Incidence ≥5%), Study D1001048, Safety Population

Treatment-Emergent Adverse Events, n(%)	Lurasidone 40-120 mg N=182
Patients with >1 TEAE	**151 (83.0)**
Akathisia	20 (11.0)
Blood prolactin increased	30 (16.5)
Deoxypyridinoline/creatinine ratio	13 (7.1)
Gastric Discomfort	10 (5.5)
Headache	13 (7.1)
Insomnia	26 (14.3)
Lassitude	10 (5.5)
Nausea	20 (11.0)
Somnolence	16 (8.8)
Tremors	16 (8.8)
Vomiting	10 (5.5)

Abbreviations: TEAE = treatment-emergent adverse event

There were 14 TEAEs that were rated as severe. Most severe adverse events were related to schizophrenia (aggravation of the underlying disease), but no consistent relationship with dosage was observed.

Prolactin median change from baseline to LOCF endpoint by gender is presented in Table 64.

Table 64: Summary of Prolactin Levels, Study D1001048 Safety Population

Endpoint[a]	Lurasidone
Prolactin (ng/mL; male) Month 12/LOCF	**N=93**
Median change from baseline LOCF	-4.30
Prolactin (ng/mL; female) Month 12/LOCF	**N=88**
Median change from baseline LOCF	-3.80

Mean changes from baseline for metabolic and endpoints are listed in Table 65.

Table 65: Summary of Metabolic Endpoints, Study D1001048, Safety Population

Endpoint[a]	Lurasidone
Total Cholesterol (mg/dL), Month 12/LOCF	**N=181**
Mean change from baseline (SD) LOCF	-7.5 (25.8)
Triglycerides (mg/dL), Month 12/LOCF	**N=181**
Mean change from baseline (SD) LOCF	-7.9 (56.9)
Glucose (fasting), mg/dL, Month 12/LOCF	**N=180**
Mean change from baseline (SD) LOCF	0.5 (9.8)
Weight (kg), Month 12/LOCF	**N=181**
Mean change from baseline (SD) LOCF	-1.53 (4.77)

Abbreviations: SD = standard deviation

3.1.3.6. Additional Longer-term Studies

In addition studies above, a number of uncontrolled longer-term studies (primarily OL extension studies) have been conducted. Pooled safety data from these studies are presented in the Package Insert and below.

In the uncontrolled longer-term studies (primarily OL extension studies), lurasidone was associated with a:

- Mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236), and +1.2 mg/dL at week 52 (n=244)[3]
- Mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n=238) and -3.5 (n=238) mg/dL at week 36, and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively[3]
- Mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303), and -0.71 kg at week 52 (n=244)[3]
- Median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189), and -3.3 ng/mL at week 52 (n=243)[1]

3.1.4. Ongoing Lurasidone Clinical Trials

Studies in patients with schizophrenia that are currently ongoing include: a double-blind, placebo-controlled study withdrawal study of lurasidone for the maintenance treatment of patients with

schizophrenia; a long-term, open-label, flexible-dose continuation study in patients who have completed a prior lurasidone study; a randomized, single blind study to assess cognitive remediation in patients stabilized on lurasidone; and a double-blind, parallel-group study of lurasidone in patients with schizophrenia.

Neither efficacy data from ongoing studies nor interim study reports are included in the dossier. Ongoing clinical trials of lurasidone for schizophrenia and links to their registry information are presented in Table 66.

Table 66: Ongoing Lurasidone Clinical Trials for Schizophrenia

Title	Study Number	Clinical Trial Identifier	Link
A long-term, multicenter, open-label, flexible-dose continuation study in patients who have completed a prior lurasidone study	D1050298	NCT01485640	http://clinicaltrials.gov/ct2/show/NCT01485640?term=lurasidone&recr=open&rank=2
A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance treatment of patients with schizophrenia	D1050238	NCT01435928	http://clinicaltrials.gov/ct2/show/NCT01435928?term=lurasidone&recr=open&rank=29
Randomized, placebo-controlled, double-blind, parallel-group, confirmatory study of SM-13496 (lurasidone HCl) in patients with schizophrenia (Phase III Study)	D1001002	NCT00711269	http://clinicaltrials.gov/ct2/show/NCT00711269?term=lurasidone&recr=open&rank=5

3.2. Clinical Evidence Table Spreadsheets

3.2.1. Short-Term (6-week) Studies

Table 67: Study D1050233

Citation	• Sunovion Pharmaceuticals Inc. (2011). Lurasidone: CSR D1050233: A phase 3 randomized, double-blind, placebo- and active comparator-controlled clinical trial to study the efficacy and safety of two doses of lurasidone in acutely psychotic patients with schizophrenia. • Clinicaltrials.gov Identifier: NCT00790192.				
Objective	To assess the efficacy, safety, and tolerability of lurasidone (80 or 160 mg/day) compared with placebo in the treatment of patients with acute schizophrenia				
Design	Multicenter, randomized, double-blind, placebo-and-active-controlled trial				
Duration	Six weeks				
Sample Size	N = 482 in the efficacy analysis (ITT); N = 486 in the safety population				
Inclusion/Exclusion Criteria	18 to 75 years, with a primary diagnosis of DSM-IV schizophrenia for ≥1 year, experiencing an acute psychotic exacerbation for ≤2 months and marked deterioration of function from baseline (by history) or must have been hospitalized for an acute exacerbation for ≤2 consecutive weeks immediately before screening; a CGI-S of ≥4 at screening and baseline, a PANSS total score of ≥80 at screening and baseline with a score of ≥4 on ≥2 of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content. Excluded if they had a decrease of ≥20% in the PANSS score between screening and baseline; deemed treatment resistant or had used quetiapine within 30 days prior to screening and/or had had an inadequate response or intolerability to quetiapine treatment.				
Treatments	Lurasidone 80 mg, 160 mg, quetiapine XR 600 mg (active control), or placebo				
Primary Endpoint	Change in PANSS total from baseline to week 6				
Secondary Endpoints	Change from baseline to week 6 in CGI-S, MADRS, PANSS at Day 4, and PANSS positive, negative, and general psychopathology subscales; PANSS responder rates (≥20% improvement from baseline) at week 6.				
Safety Endpoints	EPS evaluated using the BAS, AIMS, and SAS; clinical laboratory parameters; physical examinations; ECGs; and AEs				
Results—Efficacy Endpoints	Endpoint	Lurasidone 80 mg	Lurasidone 160 mg	Quetiapine XR 600 mg	Placebo
	PANSS total change from baseline to week 6 (SE)[a]	-22.2 (1.8)	-26.5 (1.8)	-27.8 (1.8)	-10.3 (1.8)
	p-value vs. placebo	<0.001b	<0.001 b	<0.001a	-

	CGI-S change from baseline to week 6 (SE)[a]	-1.5 (0.1)	-1.7 (0.1)	-1.7 (0.1)	-0.9 (0.1)
	p-value vs. placebo	<0.001[b]	<0.001[b]	<0.001[a]	-
	MADRS change from baseline to week 6 (SE)[c]	-4.0 (0.5)	-4.4 (0.5)	-4.3 (0.5)	-1.0 (0.5)
	p-value vs. placebo	<0.001[c]	<0.001[c]	<0.001[c]	-
	Responders[d] n (%)	81 (65)	95 (79)	92 (79)	49 (41)
	p-value vs. placebo	<0.001	<0.001	<0.001	-
Results—Safety Endpoints	The proportion of patients in the lurasidone groups (60.2%) reporting >1 TEAE was similar to the placebo group (62.0%). The five most frequent TEAEs in patients treated with lurasidone were headache, insomnia, akathisia, nausea, and vomiting. Change in EPS as measured by the SAS, BAS, and AIMS scores was generally absent to mild in lurasidone-treated patients. No ECG abnormalities were associated with lurasidone treatment. There were 15 SAEs reported by 12 patients during the six-week study period (2.0% in the combined lurasidone groups, 2.5% of the quetiapine XR group, and 3.3% of the placebo group). Laboratory data indicate an association between lurasidone treatment with a small increase in prolactin (median increase of 1.7 ng/mL in lurasidone-combined treatment groups vs. -0.80 ng/mL in the placebo group, p=0.004). The effect of lurasidone on metabolic parameters and weight and BMI was similar to that of placebo.				
Conclusion(s)	Lurasidone (80 mg and 160 mg) treatment once daily was shown to effectively treat patients with schizophrenia as demonstrated by change in PANSS total score.				

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.

[b] Adjusted p-values were adjusted with Hommel-based tree-gate keeping procedures.

[c] LS means and p-values were from an ANCOVA with treatment and pooled center as fixed factors and Baseline value as a covariate.

[d] Responder analysis of PANSS total score at LOCF Week 6 Endpoint was based on a logistic regression of response, with effects for treatment group and baseline score.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, EPS = extrapyramidal symptoms, ITT = intent to treat, Lura = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, NSA-16 = Negative Symptom Assessment score, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SE = standard error, TEAE = treatment-emergent adverse event

Table 68: Study D1050231

Citation	• Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011; 168:957-967. • Clinicaltrials.gov Identifier: NCT00615433.				
Objective	To assess the efficacy, safety, and tolerability of lurasidone (40 or 120 mg/day) compared with placebo in the treatment of patients with acute schizophrenia				
Design	Multicenter, randomized, double-blind, placebo-and-active-controlled trial				
Duration	Six weeks				
Sample Size	N = 473 in the efficacy analysis (ITT); N = 475 in the safety population				
Inclusion/Exclusion Criteria	18 to 75 years, with a primary diagnosis of DSM-IV schizophrenia for ≥1 year, experiencing an acute psychotic exacerbation for ≤2 months and marked deterioration of function from baseline (by history) or must have been hospitalized for an acute exacerbation for ≤2 consecutive weeks immediately before screening; a CGI-S of ≥4 at screening and baseline, a PANSS total score of ≥80 at screening and baseline with a score of ≥4 on ≥2 of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Excluded if they had a decrease of ≥20% in the PANSS score between screening and baseline; deemed treatment resistant or had used olanzapine within 30 days prior to screening and/or had had an inadequate response or intolerability due to olanzapine treatment.				
Treatments	Lurasidone 40 mg, 120 mg, olanzapine 15 mg (active control), or placebo				
Primary Endpoint	Change in PANSS total from baseline to week 6				
Secondary Endpoints	Change from baseline to week 6 in CGI-S and in MADRS; PANSS responder rates (≥20% improvement from baseline) at week 6. Other secondary endpoints included change in PANSS at Day 4, and PANSS positive, negative, and general psychopathology subscales (see Table 3.5).				
Safety Endpoints	EPS evaluated using the BAS, AIMS, and SAS; clinical laboratory parameters; physical examinations; ECGs; and AEs				
Results—Efficacy Endpoints	Endpoint[a]	Lurasidone 40 mg	Lurasidone 120 mg	Olanzapine 15 mg	Placebo
	PANSS total change from baseline to week 6 (SE)	-25.7 (2.0)	-23.6 (2.1)	-28.7 (1.9)	-16.0 (2.1)
	p-value vs. placebo	0.002[b]	0.022[b]	<0.001[a]	-
	CGI-S change from baseline to week 6 (SE)	-1.5 (0.1)	-1.4 (0.1)	-1.5 (0.1)	-1.1 (0.1)
	p-value vs. placebo	0.011[b]	0.040[b]	<0.001[a]	-
	MADRS change from baseline to week 6 (SE)	-3.5 (0.5)	-3.2 (0.6)	-5.0 (0.5)	-2.8 (0.6)

	p-value vs. placebo	0.571[b]	0.571[b]	0.003[a]	-
	Respondersc n (%)	73 (62)	71 (60)	89 (74)	56 (49)
	p-value vs. placebo	0.108[b]	0.108[b]	<0.001	-
Results—Safety Endpoints	The proportion of patients in the lurasidone groups (78.9%) reporting >1 TEAE was similar to the placebo group (72.4%). The five most frequent TEAEs in patients treated with lurasidone were headache, akathisia, somnolence, insomnia, and sedation. Change in EPS as measured by the SAS, BAS, and AIMS scores was generally absent to mild in lurasidone-treated patients. No ECG abnormalities were associated with lurasidone treatment. There were 23 SAEs reported by 18 patients during the six-week study period (3.4% in the combined lurasidone groups, 4.1% of the olanzapine group, and 4.3% of the placebo group). Laboratory data indicate an association between lurasidone treatment and a modest increase in prolactin (median increase of 2.15 ng/mL in lurasidone-combined treatment groups vs. -0.65 ng/mL in the placebo group, p<0.001). The effect of lurasidone on metabolic parameters and weight and BMI was similar to that of placebo.				
Conclusion(s)	Lurasidone (40 mg and 120 mg) treatment once daily was shown to effectively treat patients with schizophrenia as demonstrated by change in PANSS total score.				

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.

[b] Adjusted p-values were adjusted with Hommel-based tree-gate keeping procedures.

[c] Responder analysis of PANSS total score at LOCF Week 6 Endpoint was based on a logistic regression of response, with effects for treatment group and baseline score.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, EPS = extrapyramidal symptoms, ITT = intent to treat, Lura = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SE = standard error, TEAE = treatment-emergent adverse event

Table 69: Study D1050229

Citation	Sunovion Pharmaceuticals Inc. (2009). Lurasidone: CSR D1050229: A phase 3 randomized, placebo-controlled clinical trial to study the safety and efficacy of three doses of lurasidone HCL in acutely psychotic patients with schizophrenia. Clinialtrials.gov identifier: NCT00549718.				
Objective	To assess the efficacy, safety, and tolerability of lurasidone (40, 80, or 120 mg/day) compared with placebo in the treatment of patients with acute schizophrenia				
Design	Multicenter, randomized, double-blind, placebo-controlled trial				
Duration	Six weeks				
Sample Size	N = 489 in the efficacy analysis (ITT); N = 496 in the safety population				
Inclusion/Exclusion Criteria	18 to 75 years, primary diagnosis of DSM-IV schizophrenia for ≥1 year, experiencing an acute psychotic exacerbation for ≤2 months and marked deterioration of function from baseline (by history) or must have been hospitalized for an acute exacerbation for two consecutive weeks or less immediately before screening; a CGI-S of ≥4 at screening and baseline, a PANSS total score of ≥80 at screening and baseline with a score ≥4 on ≥2 of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Excluded if they had a decrease of ≥20% in the PANSS score between screening and baseline or deemed treatment-resistant.				
Treatments	Lurasidone 40 mg, 80 mg, 120 mg, or placebo				
Primary Endpoint	Change in PANSS total score from baseline to week 6				
Secondary Endpoints	Change from baseline to week 6 in CGI-S and MADRS; PANSS responder rates (≥20% improvement from baseline) at week 6. Other secondary endpoints included change in PANSS at Day 4; and PANSS positive, negative, and general psychopathology subscales (see Table 3.13).				
Safety Endpoints	EPS evaluated with the BAS, the AIMS, and the SAS; clinical laboratory tests; physical examinations; ECGs; and AEs				
Results—Efficacy Endpoints	Endpoint[a]	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Placebo
	PANSS total change from baseline to week 6 (SE)	-19.2 (1.7)	-23.4 (1.8)	-20.5 (1.8)	-17.0 (1.8)
	p-value vs. placebo	0.591[b]	0.034[b]	0.391[b]	-
	CGI-S change from baseline to week 6 (SE)	-1.1 (0.1)	-1.4 (0.1)	-1.2 (0.1)	-1.0 (0.1)
	p-value vs. placebo	0.591[b]	0.034[b]	0.543[b]	-
	MADRS change from baseline to week 6 (SE)	-3.3 (0.5)	-4.3 (0.5)	-2.9 (0.5)	-3.4 (0.5)
	p-value vs. placebo	0.876[b]	0.612[b]	0.876[b]	-

	Responders[c] n (%)	70 (58)	79 (67)	80 (65)	67 (54)
	p-value vs. placebo	0.545[b]	0.114[b]	0.152[b]	-
Results—Safety Endpoints	A larger proportion of patients in the lurasidone treatment groups (79.1%) reporting >1 TEAE compared with the placebo group (66.9%). The most frequently reported TEAEs in patients treated with lurasidone were akathisia, headache, somnolence, and nausea. Analyses of the BAS, AIMS, and SAS assessments showed a relatively low potential for moderate to severe EPS and akathisia in lurasidone-treated patients. No ECG abnormalities were associated with lurasidone treatment. The proportion of patients with SAEs was similar between the lurasidone-treated patients (3.0%, all doses combined) and the placebo patients (3.9%). Lurasidone treatment was associated with a small increase in prolactin (median increase of 0.70 ng/mL in lurasidone-combined treatment groups vs. 0.35 ng/mL in the placebo group, p=0.054). The effect of lurasidone on metabolic parameters and weight and BMI was similar to that of placebo.				
Conclusion(s)	Lurasidone 80 mg treatment once daily was shown to effectively treat patients with schizophrenia as demonstrated by change in PANSS total score.				

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.

[b] Adjusted p-values were adjusted with Hommel-based tree-gate keeping procedures.

[c] Responder analysis of PANSS total score at LOCF Week 6 Endpoint is based on a logistic regression of response, with effects for treatment group and baseline score.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BMI = body mass index, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, EPS = extrapyramidal symptoms, ITT = intent to treat, Lura = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SE = standard error, TEAE = treatment-emergent adverse event

Table 70: Study D1050006

Citation	• Sumitomo Pharmaceuticals America Ltd. (2003). A double-blind, randomized, fixed dose, placebo-controlled, parallel-group, 6-week, efficacy, safety, and tolerability study of two dose levels of SM-13496 in patients with schizophrenia by DSM-IV criteria who are experiencing an acute exacerbation of symptoms. • Clinical Study Report Protocol No. D1050006-P02.			
Objective	To assess the efficacy, safety, and tolerability of lurasidone 40 mg and 120 mg daily compared with placebo in the treatment of patients with acute schizophrenia			
Design	Multicenter, randomized, double-blind, placebo-controlled trial			
Duration	Six weeks			
Sample Size	N = 145 in the efficacy analysis (ITT); N = 149 in the safety population			
Inclusion/Exclusion Criteria	18 to 64 years; hospitalized for an acute exacerbation of schizophrenia meeting the DSM-IV criteria based on the SCID-CV; a duration of illness > 1 year; a BPRS total score ≥42 with a score of ≥4 on two or more positive symptom items; a CGI-S score of ≥4; a SAS score of ≤2 and an AIMS score of ≤3. Patients were excluded if they had a ≥25% decrease from washout to baseline on the BPRS. Patients were required not to be judged treatment-resistant.			
Treatments	Lurasidone 40 mg, 120 mg, or placebo			
Primary Endpoint	Mean change from baseline to week 6 in the BPRS as derived from PANSS			
Secondary Endpoints	Mean change from baseline to week 6 in PANSS, CGI-I, CGI-S; BPRS responder rate (≥20% improvement from baseline). Other secondary endpoints included CGI-I and PANSS positive, negative, and general psychopathology subscales (see Table 3.18).			
Safety Endpoints	EPS evaluated using the SAS, BAS, and AIMS assessments, clinical laboratory tests, physical examinations, ECGs, and AEs			
Results—Efficacy Endpoints	Endpoint[a]	Lurasidone 40 mg	Lurasidone 120 mg	Placebo
	BPRS total LS mean change from baseline to week 6 (SE)	-9.4 (1.58)	-11 (1.58)	-3.8 (1.57)
	p-value vs. placebo	0.018	0.004	-
	PANSS total LS mean change from baseline to week 6 (SE)	-14 (2.74)	-17 (2.73)	-6.2 (2.74)
	p-value vs. placebo	0.076	0.009	-
	CGI-S LS mean change from baseline to week 6 (SE)	-0.8 (0.15)	-0.8 (0.14)	-0.1 (0.14)
	p-value vs. placebo	0.002	0.001	-

	Responders[b] %	51.1	44.7	18.3
	p-value vs. placebo	0.000	0.003	-
Results—Safety Endpoints	Lurasidone 40 mg and 120 mg were well-tolerated. Dose relationships were suggested for nausea and akathisia. SAEs were reported by 8.0%, 8.0% and 4.1% of placebo, lurasidone 40 mg, and lurasidone 80 mg patients, respectively. All SAEs were related to the worsening of schizophrenia symptomatology, and their relationship to treatment was deemed unlikely. No statistically significant differences between lurasidone and placebo were observed for the AIMS, SAS, or BAS at week 6, and no statistically significant differences were observed for the AIMS and the SAS at any time point during the study. No important differences were found among groups in changes from baseline to week 6 in laboratory examination, ECG, or vital signs. Increased prolactin levels were observed with lurasidone 40 mg and 120 mg (median change from baseline: 3.5 ng/mL and 7.7 ng/mL, respectively) vs. placebo (-1.3 ng/mL); however, no prolactin-related clinical symptoms were reported.			
Conclusion(s)	Lurasidone (40 mg and 120 mg) treatment once daily was shown to effectively treat patients with schizophrenia as demonstrated by change in BPRS.			

[a] Each dose group of lurasidone compared to placebo with a 2-sided Dunnett's t-test. The analysis of variance model used was center, treatment, and the baseline efficacy parameter as the covariate. The p-value presented is the Dunnett's adjusted p-value.

[b] Each dose group of lurasidone compared to placebo with a Cochran-Mantel-Haenszel test.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions Improvement scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, EPS=extrapyramidal symptoms, ITT = intent to treat, LS = least squares, Lura = lurasidone, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SCID-CV = Structured Clinical Interview for the DSM-IV Disorders-Clinician's Version, SE = standard error

Table 71: Study D1050196

Citation	• Nakamura M, Ogasa M, et al. (2009). Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry 70(6): 829-36.3 • Clinicaltrials.gov Identifier: NCT00088634.		
Objective	To assess the efficacy, safety, and tolerability of lurasidone in patients hospitalized for acute exacerbation of DSM-IV-defined schizophrenia		
Design	Multicenter, randomized, double-blind, placebo-controlled trial		
Duration	Six weeks		
Sample Size	N = 180 in the efficacy analysis (ITT); N = 180 in the safety population		
Inclusion/ Exclusion Criteria	18 to 64 years; hospitalized for an acute exacerbation of schizophrenia meeting the DSM-IV criteria, based on the SCID-CV; had a duration of illness of ≥1 year, a BPRS total score of ≥42 with a score of ≥4 on two or more positive symptom items, a CGI-S score of ≥4, a SAS score of <2, and an AIMS score of <3. Patients were excluded if they had a ≥20% decrease from screening to baseline on the BPRS.		
Treatments	Lurasidone 80 mg or placebo		
Primary Endpoint	Mean change from baseline to week 6 in the BPRS as derived from the PANSS		
Secondary Endpoints	Mean change from baseline to week 6 in the PANSS total score; CGI-S; and the MADRS; BPRS responder rate (≥20% improvement from baseline). Other secondary endpoints included PANSS positive, negative, cognitive, and general psychopathology subscales (see Table 3.23).		
Safety Endpoints	EPS evaluated using the SAS, BAS, and AIMS assessments; clinical laboratory tests; physical examinations; ECGs; and AEs		
Results—Efficacy Endpoints	Endpoint[a]	Lurasidone 80 mg	Placebo
	BPRS LS mean change from baseline to week 6 (SE)	-8.9 (1.3)	-4.2 (1.4)
	p-value vs. placebo	0.0118	-
	PANSS total LS mean change from baseline to week 6 (SE)*	-14.1 (2.1)	-5.5 (2.2)
	p-value vs. placebo	0.0040	-
	CGI-S LS mean change from baseline to week 6 (SE)	-0.6 (0.1)	-0.2 (0.1)
	p-value vs. placebo	0.0072	-
	MADRS LS mean change from baseline to week 6 (SE)	-2.9 (0.8)	-0.1 (0.9)

	p-value vs. placebo	0.0187	-
	Responders[b], %	48.9	35.6
	p-value vs. placebo [a]	0.072	
Results—Safety Endpoints	The percentage of patients experiencing at least one adverse event was not significantly higher in the lurasidone arm than the placebo arm (76.7% vs. 68.9%). Only nausea was significantly more common in the lurasidone arm than the placebo arm (16.7% vs. 3.3%, p= 0.005). No clinically significant differences were seen for any physical examination and vital sign parameters, the AIMS, or the SAS. No ECG abnormalities were associated with lurasidone treatment. A modest but significant difference was observed for the BAS score (0.2 and -0.1 for lurasidone and placebo, respectively, p=0.03). The rate of serious adverse events was low in each group (lurasidone = 3.3%, placebo = 4.4%). Lurasidone was associated with a small but significant increase in prolactin compared to placebo at endpoint (median change 2.4 vs. -0.3 ng/mL, respectively, p=0.0129). Lurasidone was associated with a small increase in weight relative to placebo. Mean change from baseline in HbA1c was slightly greater in the lurasidone-treated patients, but the difference was only marginally significant (p=0.049). No clinically significant differences were seen in metabolic laboratory tests.		
Conclusion(s)	Lurasidone 80 mg treatment once daily was shown to effectively treat patients with schizophrenia as demonstrated by change in BPRS.		

*Results from PANSS subscales available in full text description of this study

[a] Lurasidone compared to placebo using analysis of covariance model including treatment, investigator, and baseline terms.

[b] Lurasidone compared to placebo using Cochran-Mantel-Haenszel test controlling for center and using the general association statistic.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, HbA1c = hemoglobin A1c, ITT = intent to treat, LS = least squares, Lura = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SCID-CV = Structured Clinical Interview for the DSM-IV Disorders-Clinician's Version, SE = standard error

Table 72: Study D1050049

Citation	• Sumitomo Pharmaceuticals America Ltd. (2003). A 6-week, double-blind, randomized, fixed dose, parallel-group study of the efficacy and safety of three dose levels of SM-13496 compared to placebo and haloperidol in patients with schizophrenia who are experiencing an acute exacerbation of symptoms. • Clinicaltrials.gov Identifier: NCT00044044.					
Objective	To assess the efficacy, safety, and tolerability of lurasidone compared with placebo and haloperidol in the treatment of patients with schizophrenia					
Design	Multicenter, randomized, double-blind, placebo-controlled trial					
Duration	Six weeks					
Sample Size	N = 349 in the efficacy analysis (ITT); N = 353 in the safety population					
Inclusion/Exclusion Criteria	18 to 64 years; hospitalized for an acute exacerbation of schizophrenia meeting the DSM-IV criteria, based on the SCID-CV; had a duration of illness ≥1 year, a BPRS total score of ≥42 with a score of ≥4 on two or more positive symptom items, a CGI-S score ≥4, a SAS score of ≤1, and an AIMS score of ≤2. Patients were excluded if a ≥20% decrease from screening to baseline on the BPRS. Patients were required not to be judged treatment-resistant.					
Treatments	Lurasidone 20 mg, 40 mg, 80 mg, haloperidol 10 mg (active control), or placebo					
Primary Endpoint	Mean change from baseline to week 6 in the BPRS as derived from the PANSS					
Secondary Endpoints	Mean change from baseline to week 6 in PANSS total, CGI-S, and MADRS. Other secondary endpoints included responder rates and PANSS positive, negative, cognitive, and general psychopathology subscales (see Table 3.28).					
Safety Endpoints	EPS evaluated using the SAS, BAS, and AIMS assessments; clinical laboratory tests; physical examinations; ECGs; and AEs					
Results—Efficacy Endpoints	Endpoint[a]	Lurasidone 20 mg	Lurasidone 40 mg	Lurasidone 80 mg	Haloperidol 10 mg	Placebo
	BPRS total mean change from baseline to week 6 (SE)	-5.2 (1.45)	-5.4 (1.66)	-7.8 (1.38)	-9.7 (1.28)	-8.6 (1.44)
	p-value vs. placebo	0.357	0.437	1.000	0.747	-
	PANSS total mean change from baseline to week 6 (SE)	-7.4 (2.52)	-7.6 (2.88)	-13.3 (2.21)	-15.7 (2.11)	-13.2 (2.31)
	p-value vs. placebo	0.109	0.126	0.694	0.252	-
	CGI-S mean change from baseline to day 4 (SE)	-0.5 (0.15)	-0.5 (0.12)	-0.7 (0.12)	-0.8 (0.12)	-0.7 (0.13)

	p-value vs. placebo	0.179	0.128	0.595	0.463	-
	MADRS mean change from baseline to week 6 (SE)	-0.9 (1.06)	-0.5 (1.18)	-2.4 (1.08)	-3.5 (1.07)	-2.5 (1.05)
	p-value vs. placebo	0.620	0.565	0.668	0.562	-
Results—Safety Endpoints	The AEs that occurred most frequently with lurasidone compared to placebo were nausea, vomiting, akathisia, somnolence, sedation, fatigue, and agitation, with all but agitation showing a dose response. Mean changes from baseline were generally comparable across treatment groups for the AIMS, SAS, and BAS; no significant differences between lurasidone and placebo were observed. No ECG abnormalities were associated with lurasidone treatment. The occurrence of SAEs was comparable among all five treatment groups. All lurasidone groups demonstrated slight increases in mean serum prolactin compared with placebo, but increases were less than those seen with haloperidol. No other notable trends in laboratory measures, vital signs, and physical examinations were seen.					
Conclusion(s)	No valid clinical conclusions regarding the efficacy of lurasidone can be made given the lack of sensitivity in this trial.					

[a] P-values from ANCOVA model with baseline as a continuous covariate and treatment and center as class variables.

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, EPS= Extrapyramidal symptoms, ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SCID-CV = Structured Clinical Interview for the DSM-IV Disorders-Clinician's Version, SE = standard error

3.2.2. Longer-term Studies

Table 73: Study D1050234

Citation	• Sunovion Pharmaceuticals Inc. (2011). Lurasidone: CSR D1050234: A Phase 3 Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of Lurasidone in Patients With Schizophrenia (PEARL 3 Extension Study). • Clinicaltrials.gov Identifier: NCT00789698.
Objective	To evaluate the long-term efficacy and safety of flexibly dosed lurasidone (40-160 mg/day) and quetiapine XR (200-800 mg/day) in a 12-month double-blind, parallel group study.
Design	Multicenter, randomized, double-blind, active-controlled trial (extension phase)
Duration	12-months
Sample Size	N = 256 in the efficacy analysis (ITT); N = 292 in the safety population
Inclusion/ Exclusion Criteria	Patients who demonstrated a clinical response (defined as Study D1050233 completion with ≥20% improvement in PANSS total score at Day 42 visit and CGI-S score ≤4) to either lurasidone (80 mg/day or 160 mg/day) or quetiapine XR (600 mg/day) in Study D1050233. Patients 18 to 75 years, with a primary diagnosis of DSM-IV schizophrenia for ≥1 year, experiencing an acute psychotic exacerbation for ≤2 months and marked deterioration of function from baseline (by history) or must have been hospitalized for an acute exacerbation for ≤2 consecutive weeks immediately before screening; a CGI-S of ≥4 at screening and baseline, a PANSS total score of ≥80 at screening and baseline with a score of ≥4 on ≥2 of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content. Excluded if they had a decrease of ≥20% in the PANSS score between screening and baseline; deemed treatment resistant or had used quetiapine within 30 days prior to screening and/or had had an inadequate response or intolerability to quetiapine treatment.
Treatments	Flexibly dosed lurasidone (40-160 mg/day) and active control, quetiapine XR (200-800 mg/day)
Primary Endpoint	Time to relapse for lurasidone versus quetiapine XR in a non-inferiority (NI) analysis utilizing a Cox proportional-hazards model
Secondary Endpoints	Change from core baseline to month 12 in PANSS and CGI-S. Other secondary endpoints included MADRS, AEs, and metabolic parameters.

Results—Safety Endpoints	Fifty-two percent and 39% of the LUR to LUR treatment group and QXR to QXR treatment group, respectively, completed the extension phase of the study. The majority of discontinuations were due to withdrawal of consent (19% and 22% for LUR to LUR and QXR to QXR, respectively), insufficient clinical response (9% and 21% for LUR to LUR and QXR to QXR, respectively), lost to follow-up (7% and 11% for LUR to LUR and QXR to QXR, respectively), and AEs (7% and 5% for LUR to LUR and QXR to QXR, respectively). The proportion of patients experiencing ≥1 AE in the extension phase was 97 (64.2%) and 61 (71.8%) for the LUR to LUR and QXR to QXR treatment groups, respectively. Serious TEAE occurred in 15 (9.9%) and 17 (20.0%) of patients in the LUR to LUR and QXR to QXR treatment groups, respectively. The most common adverse events (incidence ≥5%) in lurasidone treatment group were akathisia, headache, insomnia, anxiety, weight increased, and parkinsonism. The most common quetiapine XR adverse events (incidence ≥5%) included schizophrenia, headache, insomnia, psychotic disorder, increased weight and agitation. Median observed change in prolactin from core baseline at 12 months was +0.6 ng/mL for lurasidone-treated patients and -0.7 ng/mL for quetiapine XR-treated patients. Metabolic endpoints of interest included weight change, glucose, total cholesterol, HDL, LDL, and triglycerides. Mean observed weight change in patients who completed 12 months of treatment was 0.7 kg for lurasidone and 1.2 kg for quetiapine XR. A ≥7% weight gain was observed at Month 12 endpoint in 11.5% of lurasidone-treated patients compared to 15.2% of quetiapine XR treated patients. Median observed changes in total cholesterol, triglycerides, and glucose were 0.0 mg/dL, -18.0 mg/dL, and +1.0 mg/dL for lurasidone-treated patients and +4.0 mg/dL, -7.0 mg/dL, and +1.0 mg/dL for quetiapine XR-treated patients.		
Results—Efficacy Endpoints	The primary Kaplan-Meier (KM) survival analysis showed a hazard ratio of 0.728 (indicating lower risk of relapse for lurasidone, 95% confidence interval (CI): 0.410, 1.295. The protocol pre-specified NI margin was 1.9. Since the CI 1.295 is well within this pre-specified margin, NI of lurasidone compared to QXR was clearly demonstrated in this study. Therefore this study successfully met its primary endpoint. The observed relapse rate for lurasidone (n=139) was 21.0% versus 27.0% for quetiapine XR (n=79).		
	Endpoint	LUR to LUR (N=132)	QXR to QXR (N=72)
	PANSS Total		
	Change from core baseline to Month 12 (SE)	-34.6 (1.8)	-25.7 (2.6)
	p-value	0.006	-
	CGI-S		
	Change from core baseline to Month 12 (SE)	-1.9 (0.1)	-1.6 (0.1)
	p-value	0.069	-
Conclusion(s)	Flexibly dosed lurasidone (40-160 mg) treatment once daily was shown to effectively treat patients with schizophrenia as demonstrated by non-inferiority analysis comparing time to relapse vs. quetiapine XR.		

*Results from PANSS subscales available in full text description of this study

Abbreviations: AE = adverse event, CGI-S = Clinical Global Impressions scale – Severity of Illness, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, HDL = high density lipoprotein, ITT = intent to treat, LDL = low density lipoprotein, LUR to LUR = lurasidone 80 mg or 160 mg in the acute treatment phase followed by flexibly dosed lurasidone 40-160 mg in the extension phase, QXR to QXR = quetiapine XR 600 mg in the acute treatment phase followed by flexibly dosed quetiapine XR 200-800 mg in the extension phase, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, PANSS = Positive and Negative Syndrome Scale, SE = standard error, TEAE = treatment emergent adverse event

Table 74: Study D1050237

Citation	• Sumitomo Pharmaceuticals America Ltd. (2011). Long-term safety, tolerability, and effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder: a randomized, active comparator-controlled trial (double-blind phase). Clinical Study Report Protocol No. D1050237. • Clinialtrials.gov identifier: NCT00641745.		
Objective	To assess the safety and tolerability of lurasidone in clinically stable patients with chronic schizophrenia or schizoaffective disorder.		
Design	Multicenter, randomized, double-blind, parallel-group trial		
Duration	12 months		
Sample Size	N = 608 in the efficacy analysis (ITT); N = 621 in the safety population		
Inclusion/ Exclusion Criteria	18 to 75 years; meeting the DSM-IV criteria for schizophrenia, had a duration of illness of ≥1 year, and clinically stable: CGI-S ≤ 4; no change in antipsychotic medications ≥6 weeks prior to Screening; no hospitalizations at ≥8 weeks prior to Screening; and a score of ≤4 (moderate or less) on PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content). Patients were excluded if judged to be treatment-resistant.		
Treatments	Flexible-dosing of lurasidone 40-120 mg or risperidone 2-6 mg		
Primary Endpoint	Safety was assessed by the proportion of patients with AEs, discontinuation due to AEs, and SAEs.		
Secondary Endpoints	Mean change from baseline to month 12 in the PANSS total score; CGI-S; and the MADRS. Other secondary endpoints included PANSS positive, negative, cognitive, and general psychopathology subscales (see Table 3.7).		
Results—Safety Endpoints	The proportion of patients experiencing ≥1 AE in the lurasidone treatment group (84.5%) was similar compared to the risperidone group (84.7%). Change in movement disorder signs or symptoms as measured by change in SAS, BAS, and AIMS scores, was generally absent to mild in patients treated with either lurasidone or risperidone. No ECG abnormalities were associated with lurasidone treatment. The rate of SAEs was similar in each group (lurasidone = 11.0%, risperidone = 9.9%). The only SAEs at the reported by ≥ 1% of patients in either treatment group were psychotic disorder (2.9% in the lurasidone group compared with 4.0% in the risperidone group), schizophrenia (1.9% in the lurasidone group compared with 1.5% in the risperidone group), and suicidal ideation (0.5% in the lurasidone group compared with 1.0% in the risperidone group). For lurasidone-treated patients, there was little change (mean ± SD) from baseline to LOCF Endpoint in prolactin concentrations in either male (2.51 ± 13.46 ng/mL, n = 268) or female (5.16 ± 34.89 ng/mL, n = 110) patients. There were larger increases in prolactin concentrations in male (9.45 ± 14.13 ng/mL, n = 110) and female (33.90 ± 53.31 ng/mL, n = 66) patients treated with risperidone. Clinically significant differences were seen in metabolic endpoints including weight and glucose.		
Results—Efficacy Endpoints	Endpoint[a]	Lurasidone	Risperidone
	PANSS total LS mean change from baseline to month 12 (SE)*	-4.7 (0.9)	-6.5 (1.1)
	p-value vs. risperidone	0.181	-

	CGI-S LS mean change from baseline to month 12 (SE)	-0.4 (0.1)	-0.4 (0.1)
	p-value vs. risperidone	0.929	-
	MADRS LS mean change from baseline to month 12 (SE)	-0.8 (0.4)	-2.4 (0.5)
	p-value vs. risperidone	0.007	-
Conclusion(s)	This study demonstrated the safety and tolerability of lurasidone (flexibly dosed 40 to 120 mg) once daily over 12 months of treatment compared to risperidone.		

*Results from PANSS subscales available in full text description of this study

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model with fixed effects for pooled center, visit as a categorical variable, and treatment by visit interaction, assuming an unstructured covariance matrix. This model includes Baseline data as a response variable and provides one Baseline estimate across all patients. Contrasts are from differences (lurasidone versus risperidone) at each visit versus Baseline.

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, ITT = intent to treat, LS = least squares, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SD = standard deviation, SE = standard error

Table 75: Study D1050231E

Citation	• Sumitomo Pharmaceuticals America Ltd. (2011). A Phase 3 Randomized, Placebo- and Active Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of Two Doses of Lurasidone HCl in Acutely Psychotic Patients with Schizophrenia (Open-Label Extension Phase). Clinical Study Report Protocol No. D1050231. • Clinialtrials.gov identifier: NCT00615433.
Objective	The objective of the open-label extension phase was to evaluate the safety and tolerability of lurasidone in patients with schizophrenia.
Design	Multicenter, open-label, extension phase
Duration	6 months
Sample Size	N = 246 safety population
Inclusion/ Exclusion Criteria	Patients who successfully completed the 6-week, double-blind treatment phase of the study had the option to continue into the 6-month, open-label extension phase. At the beginning of the extension phase, patients entered a single-blind, 3-day placebo washout, then switched to lurasidone 80 mg daily in an open-label fashion; the dose of study medication could be titrated up by 40 mg to a ceiling of 120 mg daily or down by 40 mg to a minimum of 40 mg daily, if deemed clinically appropriate. The dose could be changed a total of 4 times in the extension phase. Patients 18 to 75 years; meeting the DSM-IV criteria for schizophrenia, had a duration of illness of ≥1 year; CGI-S ≥ 4; subject had an acute exacerbation of psychotic symptoms (no longer than 2 months) and marked deterioration of function from Baseline (by history) or subject had been hospitalized for the purpose of treating an acute psychotic exacerbation for 2 consecutive weeks or less immediately before screening; and a PANSS total score ≥80, with a score of ≥4 (moderate or less) on two or more PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content, suspiciousness). Patients were excluded if judged to be treatment-resistant.
Treatments	Flexible-dosing of lurasidone 40-120 mg
Primary Endpoint	Evaluate the safety and tolerability of lurasidone in patients with schizophrenia.
Secondary Endpoints	Mean change from OL baseline to month 8 in the PANSS total score; CGI-S; and the MADRS. Other secondary endpoints included PANSS positive, negative, cognitive, and general psychopathology subscales.
Results—Safety Endpoints	The majority of discontinuations during the extension phase were due to withdrawal of consent (N=41, 16%), insufficient clinical response or a worsening of existing condition (N=29, 11%), or loss to follow-up (N=29, 11%). The proportion of patients in the extension phase who experienced one or more TEAE or a serious TEAE was 65.9% and 11.4%, respectively. There were 33 SAEs reported in 28 patients. The most common SAEs were related to a worsening of the underlying condition of schizophrenia, with 16 patients reporting a SAE with a Preferred Term including the terms “schizophrenia” (9 patients) or “psychosis” (7 patients). Of the 14 SAEs that were assessed by the investigators to be possibly related, probably related, or related to study medication, 8 were either schizophrenia or psychotic disorder SAEs. Headache and poor quality sleep (both in the same subject) and vomiting were the only nonpsychiatric disorder SAEs reported to be possibly related, probably related, or related to study medication.Median change from OL baseline to LOCF endpoint for prolactin and mean

	change from OL baseline to LOCF endpoint for metabolic endpoints are listed in Table 3.11 and Table 3.12, respectively. Prolactin, which had increased during the DB phase of the study (+3.2 ng/mL on combined lurasidone; +3.4 ng/mL on olanzapine), showed a median decrease (-1.3 ng/mL) during the OL extension.					
Results—Efficacy Endpoints	Endpoint	L40 to LUR N=68	L120 to LUR N=47	OLZ to LUR N=69	PBO to LUR N=62	All Extension N=246
	n (observed cases)	33	25	31	28	117
	PANSS* Total Change from OL baseline to Month 8 (SD)	-9.8 (14.1)	-7.1 (14.8)	-5.8 (11.1)	-12.0 (17.1)	-8.7 (14.4)
	CGI-S, Change from OL baseline to Month 8 (SD)	-0.5 (1.2)	-0.4 (1.0)	-0.3 (0.7)	-0.5 (1.0)	-0.4 (1.0)
	MADRS, Change from OL baseline to Month 8 (SD)	-0.1 (5.8)	0.1 (4.6)	1.8 (5.9)	-2.0 (5.3)	0.0 (5.6)
Conclusion(s)	Flexibly dosed lurasidone (40-120 mg, daily) was well-tolerated and effective in treating patients with schizophrenia during this 6-month open-label extension study.					

*Results from PANSS subscales available in full text description of this study

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions scale – Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, HbA1c = hemoglobin A1c, ITT = intent to treat, LS = least squares, Lura = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SCID-CV = Structured Clinical Interview for the DSM-IV Disorders-Clinician's Version, SE = standard error

Table 76: Study D1050229E

Citation	• Sumitomo Pharmaceuticals America Ltd. (2011). A Phase 3 Randomized, Placebo-Controlled, Clinical Trial to Study the Safety and Efficacy of Three Doses of Lurasidone HCl in Acutely Psychotic Patients with Schizophrenia (Open-Label Extension Phase). Clinical Study Report Protocol No. D1050229. • Clinialtrials.gov identifier: NCT00549718.
Objective	The objective of the open-label extension phase was to evaluate the safety and tolerability of lurasidone in patients with schizophrenia.
Design	Multicenter, open-label, extension phase
Duration	22 months
Sample Size	N = 250 safety population
Inclusion/ Exclusion Criteria	Patients who successfully completed the 6-week, double-blind treatment phase of the study had the option to continue into the 22-month, open-label extension phase, for a total treatment duration of 24 months. The extension phase of this study was an open-label, multicenter study designed to evaluate the safety and tolerability of flexibly dosed lurasidone (40, 80, and 120 mg/day) in the treatment of patients with schizophrenia. The dose could be changed a total of 4 times in the extension phase. Patients 18 to 75 years; meeting the DSM-IV criteria for schizophrenia, had a duration of illness of ≥1 year; CGI-S ≥ 4; subject had an acute exacerbation of psychotic symptoms (no longer than 2 months) and marked deterioration of function from Baseline (by history) or subject had been hospitalized for the purpose of treating an acute psychotic exacerbation for 2 consecutive weeks or less immediately before screening; and a PANSS total score ≥80, with a score of ≥4 (moderate or less) on PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content, suspiciousness). Patients were excluded if judged to be treatment-resistant.
Treatments	Flexible-dosing of lurasidone 40-120 mg
Primary Endpoint	Evaluate the safety and tolerability of lurasidone in patients with schizophrenia.
Secondary Endpoints	Mean change from OL baseline to month 24 in the PANSS total score; CGI-S; and the MADRS. Other secondary endpoints included PANSS positive, negative, and general psychopathology subscales.
Results—Safety Endpoints	A total of 250 patients were analyzed and included in the safety population. The majority of discontinuations were due to withdrawal of consent (n=60, 24.0%), insufficient clinical response or worsening of condition (n=57, 23%), and AEs (n=37, 15.0%). The proportion of patients experiencing ≥1 AE in the OL extension phase was 172 (68.8%). Serious TEAE occurred in 49 (19.6%) of patients in the OL extension phase. The 5 most frequently reported TEAEs at the Preferred Term level were schizophrenia (12.4% of all patients), akathisia (10.8% of all patients), somnolence (10.8% of all patients), vomiting (8.8% of all patients), and nausea (8.4% of all patients). The majority of TEAEs reported were classified as either mild or moderate. Only 23 patients (9.2%) reported one or more TEAE that was classified as severe during the open-label extension. A total of 48 patients (19.2%) were reported with one or more EPS-related TEAE. Akathisia was reported by the highest proportion of patients (10.8%) followed by Parkinsonism (6.4%) and tremor (2.4%). No other EPS-related TEAE was

	reported by more than 2% of patients.					
Results—Efficacy Endpoints	Endpoint	L40 to LUR N = 62	L80 to LUR N = 65	L120 to LUR N = 64	PLB to LUR N = 59	All Extension N = 250
	N	19	20	13	17	69
	PANSS* Total Change from OL baseline to Month 24 (SD)	-14.6 (17.8)	-10.6 (16.3)	-14.8 (17.4)	-9.7 (13.8)	-12.3 (16.2)
	CGI-S Change from OL baseline to Month 24 (SD)	-0.5 (0.7)	-0.5 (0.8)	-0.6 (0.7)	-0.4 (0.7)	-0.5 (0.7)
	MADRS Change from OL baseline to Month 24 (SD)	-0.9 (4.4)	-1.9 (4.8)	-2.8 (5.8)	2.7 (8.1)	-0.7 (6.1)
Conclusion(s)	Flexibly dosed lurasidone (40-120 mg) was well tolerated and effective in treating patients with schizophrenia during this 22-month open-label extension study.					

*Results from PANSS subscales available in full text description of this study

Abbreviations: AE = adverse event, CGI-S = Clinical Global Impressions scale – Severity of Illness, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, EPS = extrapyramidal symptoms, L40 = lurasidone 40 mg in double-blind treatment phase, L80 = lurasidone 80 mg in double-blind treatment phase, L120 = lurasidone 120 mg in double-blind treatment phase, LUR = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients, OL = open-label, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, TEAE = treatment emergent adverse event

Table 77: Study D1001048

Citation	• Sumitomo Pharmaceuticals America Ltd. (2009). 52-week long-term administration study of SM-13496 in schizophrenia. Clinical Study Report Protocol No. D1001048.	
Objective	To evaluate the efficacy and safety of lurasidone during ong-term administration using a flexible-dose methodology.	
Design	Uncontrolled, open-label, flexible dose trial	
Duration	52 weeks	
Sample Size	N = 174 in the efficacy analysis (ITT); N = 182 in the safety population	
Inclusion/ Exclusion Criteria	18 to 65 years; meeting the ICD-10 criteria for schizophrenia, patients experiencing initial occurrence or relapse, or patients already undergoing treatment with antipsychotic drugs and presenting with any of the following at the time of registration: a) Hallucinations and delusions as presenting symptoms; b) Delusions alone as presenting symptoms; c) Loss of initiative and blunted affect as presenting symptom I (such as acute hebephrenic schizophrenia); d) Loss of initiative and blunted affect as presenting symptom II (associated with chronic or fixed symptomotology); (e) Symptoms consistent with a neurosis-like disorder; f) Symptoms consistent with a depressed state. Patients were excluded if complications of serious cardiovascular, hepatic, renal, organic brain, hematological, endocrine, or convulsive conditions, or history of the conditions in the judgment of the principal investigator or a subinvestigator, would render a subject inappropriate for the study.	
Treatments	Lurasidone 40-120 mg/day	
Primary Endpoint	Change in BPRS and PANSS total scores from baseline to the end of dosing.	
Secondary Endpoints	Change in PANSS and BPRS cluster scores and symptom scores and PANSS 5-factor scores.	
Results—Efficacy Endpoints	Endpoint	Lurasidone 40-120 mg
	PANSS Total	N=168
	Mean change from OL baseline to Endpoint (SD)	-5.7 (17.2)
	95% CI	-8.3, -3.1
	BPRS Total	N=174
	Mean change from OL baseline to Endpoint (SD)	-3.4 (10.4.2)
	95% CI	-5.0, -1.9
	PANSS positive subscale	N=168

	Mean change from OL baseline to Endpoint (SD)	-0.5 (4.9)
	95% CI	-1.2, 0.3
	PANSS negative subscale	N=168
	Mean change from OL baseline to Endpoint (SD)	-2.5 (5.0)
	95% CI	-3.3, -1.8
	PANSS psychopathology subscale	N=168
	Mean change from OL baseline to Endpoint (SD)	-2.7 (10.0)
	95% CI	-4.2, -1.8
Results—Safety Endpoints	The proportion of patients experiencing a TEAE in the lurasidone treatment group was 83.0%. There were 14 TEAEs that were rated as severe. Most severe adverse events were related to schizophrenia (aggravation of the underlying disease), but no consistent relationship with dosage was observed. Adverse events leading to discontinuation of study drug occurred in 68 patients (37.4%), while adverse events leading to a reduction in the dosage occurred in 41 patients (22.5%). The majority of the adverse events that led to discontinuation or dose-decrease were schizophrenia (aggravation of underlying disease) or extrapyramidal symptoms, with most patients showing improvement or recovery following discontinuation or dose-decrease. Adverse events of increased serum prolactin occurred in 34 patients (18.7%), which were mild in each case.	
Conclusion(s)	This study demonstrated the safety and tolerability of lurasidone (flexibly dosed 40 to 120 mg) once daily over 12 months of treatment.	

Abbreviations: AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions scale-Severity of Illness, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ECG = electrocardiogram, HbA1c = hemoglobin A1c, ITT = intent to treat, LS = least squares, Lura = lurasidone, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAE = serious adverse event, SAS = Simpson-Angus Scale, SCID-CV = Structured Clinical Interview for the DSM-IV Disorders-Clinician's Version, SE = standard error

4. ECONOMIC VALUE AND MODELING REPORTS

The economic value of lurasidone compared with other atypical antipsychotics is demonstrated below from three economic models:

4.1 CVD Incidence Related Cost-Consequence Model **Page 161**
4.2 Relapse and Relapse-Related Hospitalization Model **Page 174**
4.3 Budget Impact Model **Page 188**

4.1. CVD Incidence Related Cost-Consequence Model

4.1.1. Overview and Objectives

A cost-consequence health economic model was developed to estimate the potential impact of changes in cardiometabolic parameters on the incidence of diabetes and CV events after one year of treatment with lurasidone versus other selected atypical antipsychotics in adult patients diagnosed with schizophrenia.

4.1.2. Model Type and Time Horizon

The model was constructed using a discrete event simulation (DES) approach. DES is a modeling technique that conceptualizes the course of a disease and its management in terms of events that occur over time and examines the impact that these events have on patients and other components of the system (i.e., clinical outcomes and costs). A three-year time horizon was chosen for the base-case analysis and a longer model timeframe was used in the sensitivity analysis.

4.1.3. Methodological Overview

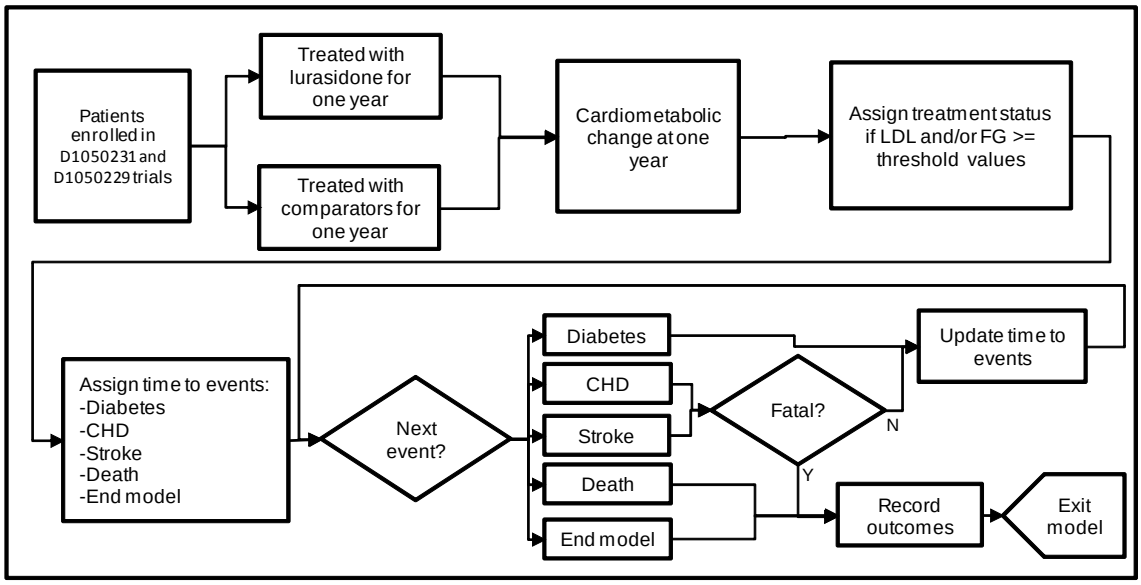
The DES model was built in a Microsoft Excel® interface. It simulates individual patients using a discrete event approach that conceptualizes the course of a disease and its management in terms of events that occur over time.[84] The model assesses the three-year clinical and economic consequences due to changes in cardiometabolic parameters (e.g., LDL, HDL, triglycerides, total cholesterol, fasting glucose, and BMI) after one year of treatment with lurasidone vs. risperidone, olanzapine or quetiapine XR. Specifically, the model estimates are based on (i) the proportion of patients requiring medication treatment for hyperlipidemia and pre-diabetes after 1-year treatment and (ii) predicted incidence of cardiometabolic events due to cardiometabolic parameter changes. The default model data inputs were derived from the published literature, publicly available data sources, and lurasidone clinical trial data (studies D1050237 [long-term safety study], D1050234, D1050231, and D1050229).[3,4,6,7] Further information on the studies can be found in Section 3.1 of the dossier. The model perspective is that of a US third-party payer. The time horizon for the base case analysis is three years, although this value is a user-modifiable input that can be changed to examine the impact for a longer time horizon. All costs were measured in 2011 values and were discounted at 3.5% per annum after the first year.

4.1.4. Model Structure

A schematic presentation of the model structure is shown in Figure 4. At the beginning of the simulation, a hypothetical cohort of 1,000 adults with schizophrenia is created for each treatment group by sampling patient profiles from patients enrolled in studies D1050231 and D1050229. Each patient carries the relevant demographic (e.g., age, gender, and race) and cardiometabolic parameters at baseline. The model then updates the baseline cardiometabolic parameters with the one-year values associated with each specific atypical antipsychotic treatment. Based on the updated values at one year and relevant patient characteristics, the model projects the number of cases with pre-diabetes or hyperglycemia (i.e., fasting glucose [FG]=100–126 mg/dL) and hyperlipidemia (i.e., LDL≥130 mg/dL) using the threshold values from clinical guidelines and simulates the clinical course of disease for each patient in terms of the occurrence of diabetes, coronary heart disease (CHD), stroke, and death over three years using risk equations from the Framingham Heart Study and the US life table (with risk adjustment for schizophrenia). CHD and stroke may be fatal and occurrence of diabetes leads to increased risk of CHD event and death. Costs associated with antipsychotic drugs and treatments for hyperlipidemia, hyperglycemia, diabetes, and cardiovascular events are accrued according to each patient's specific experience with these events over the course

of simulation. Finally, the model tallies the net difference between lurasidone and the other comparators at three years for the potential cardiometabolic outcomes and associated projected medical costs.

Figure 4: Model Structure



CHD = coronary heart disease, FG = fasting glucose, LDL = low-density lipoprotein

4.1.5. Patient Characteristics

Patient demographic and disease characteristics used to drive the model include age, gender, race, body mass index (BMI), height, weight, waist circumference, systolic and diastolic blood pressure, LDL, HDL, total cholesterol (TC), triglycerides, FG, smoking status, and parental history of diabetes (Table 78). Data for these characteristics were obtained directly from trials D1050231 and D1050229. Although baseline patient data from other lurasidone trials were not used, the exclusion of patient data from studies D1050237 and D1050234 at baseline does not impact the model results because each treatment arm in the model (lurasidone, olanzapine, risperidone, and quetiapine XR) has the same cohort at baseline based on trials D1050231 and D1050229. Smoking status and parental history of diabetes at baseline were not included in these trials and were imputed with data obtained from the literature, 67.4% and 27.0%, respectively.[85,86]

Table 78: Baseline Patient Characteristics from Patients Used in the Simulation (Pooled Across Studies D1050231 and D1050229, Safety Population)

Patient Characteristics	Input value†
Age (Years), mean (SD)	38.3 (10.7)
Gender (% female)*	26.3
Race (%)**	
Mexican American	10.2
Black	33.7
Other	56.1
BMI (kg/m^2), mean (SD)	26.3 (5.7)
Height (cm), mean (SD)	170.9 (10.1)
Weight (kg), mean (SD)	77.3 (19.5)
Waist circumference (cm) mean (SD)	91.1 (15.1)
Systolic blood pressure (mmHg), mean (SD)	120.3 (12.4)
Diastolic blood pressure (mmHg), mean (SD)	77.4 (8.7)
LDL (mg/dL)	111.7 (34.4)
HDL (mg/dL)	47.7 (13.1)
Cholesterol (mg/dL)	191.8 (44.0)
Triglycerides (mg/dL)	138.8 (86.2)
Fasting Glucose (mg/dL)	95.2 (20.2)
Diabetic (%)	5.5
Parental history of diabetes (%)	27.0
Current smoker (%)	67.4

*ITT population: n=473 in study D1050231, n=489 in study D1050229.

**For the purpose of the simulation, if the subject's baseline race was listed as "Black or African American," the subject was categorized as "Black," irrespective of the ethnicity; if the subject's baseline was *not* listed as "Black or African American" and the subject's ethnicity was listed as "Hispanic or Latin," the subject was categorized as "Mexican American." Any other combination was categorized as "other."

†Four patients were excluded from the simulation because baseline data for one or more fields was missing.

BMI = body mass index, cm = centimeters, HDL = high-density lipoprotein, kg = kilograms, LDL = low-density lipoprotein, SD = standard deviation

4.1.6. Cardiometabolic Treatment Effect

The model predicts the impact of treatment with an atypical antipsychotic over one year on cardiometabolic parameters, including LDL, HDL, triglycerides, TC, FG, weight, and BMI. The comparators of interest for the model were olanzapine, risperidone, and quetiapine XR, as these are established therapies that have been associated with hyperglycemia, hyperlipidemia, and body weight gain.[87,88,89] The mean changes for cardiometabolic parameters from baseline to one year for lurasidone were pooled from trials D105237, D1050234, D1050231 and D1050229.[3,4,6,7] For risperidone and quetiapine XR, these data were drawn from clinical trials D1050237 and D1050234, respectively. Because olanzapine patients crossed over to lurasidone after six weeks in lurasidone trial D1050231, one-year olanzapine data were obtained from the literature (Table 79).[90] Mean change data for lurasidone and quetiapine XR were derived from Phase III clinical trials enrolling schizophrenia patients experiencing an acute exacerbation, with PANSS items scores ≥4 (moderate) and CGI-S score ≥4. Mean change data for risperidone were obtained from a long-term safety study in which enrolled patients were required to be "clinically stable" (i.e., in a non-acute phase of illness [CGI-S score ≤4, PANSS items scores ≤4 (moderate), and no hospitalizations for at least 8 weeks prior to baseline]).

Table 79. Cardiometabolic Treatment Effect: Mean Change from Baseline After One Year

Treatment	Weight (kg)	LDL (mg/dL)	HDL (mg/dL)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	Glucose (mg/dL)
Lurasidone[7-10]	0.5	-0.5	-1.2	-2.3	-9.5	3.7
Olanzapine[11]	3.0	17.0	-3.0	20.0	30.1	12.0
Risperidone[9]*	2.6	-4.1	-2.6	-3.8	15.1	4.4
Quetiapine XR[10]	1.2	-1.7	5.2	3.9	-11.4	6.0

Laboratory specimens were taken with patients in the fasting state.

HDL = high-density lipoprotein, IR = immediate release, LDL = low-density lipoprotein, XR = extended release
*Mean change data for risperidone were obtained from a long-term safety study in which enrolled patients were required to be "clinically stable" (non-acute phase of illness) for at least 8 weeks prior to baseline. In other lurasidone clinical trials, the included patients were acutely hospitalized adults with schizophrenia.

4.1.7 Cardiometabolic Events

The model predicts the following clinical outcomes:

- Number of patients with hyperlipidemia and hyperglycemia based on LDL and FG values after one year of treatment. Threshold values used to determine a hyperlipidemic or hyperglycemic case were based on the following assumptions:
  - Hyperlipidemia: LDL≥130 mg/dL (National Cholesterol Education Program [NCEP] Guidelines)[91]
  - Hyperglycemia: FG between 100 and 126 mg/dL (American Diabetes Association [ADA, 2011] Guidelines). Any patient with a FG >126 mg/dL was considered a diabetic case in this model (ADA 2011 guidelines).[92]

For purposes of this model, it is assumed that only a proportion of patients with either of these conditions received pharmacological treatments per published literature: 55% for hyperglycemia[93] and 89% for hyperlipidemia[94] in the base-case analysis.

- Occurrence of CHD, stroke, diabetes (only for those remaining free of diabetes at the end of year one), and death over three years, which was based on the following assumptions:
  - The occurrence of these clinical events was influenced by patients' baseline characteristics (e.g., gender, race, height, waist circumference) and cardiometabolic parameters after one year of antipsychotic treatment (i.e., LDL, HDL, triglycerides, TC, FG, and BMI).
  - Published risk equations from the Framingham Heart Study (FHS)[95] were used to assign risks of CHD, stroke, and diabetes based on patients' baseline characteristics and cardiometabolic parameters after one year of antipsychotic treatment and to calculate the time to each specific event.
  - If patients developed diabetes, risks for CHD were updated based on the FHS risk equation.[90]
  - Time to death was predicted based on the patient's age and gender using mortality data from the 2006 US Life Table.[96] The risk of death was affected by the occurrence of diabetes.[97] CHD or a stroke event could also lead to death, which was determined based on an event-specific case-fatality rate obtained from literature [98]

4.1.8 Costs

Specific costs items considered in this model included antipsychotic drug costs, treatment for hyperlipidemia and hyperglycemia, and management of clinical events (i.e., CHD, stroke, and diabetes). Costs were reported in 2011 values. Where up-to-date values were not available, those

costs were inflated to 2011 values using the Medical Component of the Consumer Price Index.[99] Cost inputs used in the base case analysis are shown in Table 80.

- Costs of treatment for hyperlipidemia were estimated based on a weighted average cost of six statin drugs (i.e., atorvastatin 10/20 mg/day, rosuvastatin 20 mg/day, simvastatin 20-40 mg/day, pravastatin 40 mg/day, lovastatin 20 mg/day), plus the costs of one visit per year to a primary care physician and specialist as well as laboratory tests.
- Costs of treatment for hyperglycemia included annual cost for metformin (500 mg twice daily) plus the costs of one visit per year to a primary care physician, specialist and laboratory tests (i.e., HbA1c blood test, fasting plasma glucose test, oral glucose tolerance test).
- Generic equivalents that were available in the market were used in the sensitivity analysis referenced in Section 4.1.11.

Table 80. Costs Inputs ($2011)

Parameter	Cost	Source
Atypical antipsychotic (Branded) drug costs, $ per year*		
Lurasidone (Latuda®) (40/80 mg/once a day)	5,617.35	RedBook (WAC), 2011[100]
Olanzapine (Zyprexa®) (15 mg/once a day)	10,095.90	
Risperidone (Risperdal®) (4 mg/twice a day)	10,335.63	
Quetiapine XR (Seroquel XR®) (300 mg/twice a day)	9,018.93	
Drug costs for treating high cholesterol, $ per year (% usage)		
Atorvastatin (10/20 mg/once a day)	1,580.59 (63.5%)	RedBook (WAC), 2011[100] Fox, 2007[101] Stacy, 2006[93]
Crestor®) (Rosuvastatin) (20 mg/once a day)	1,590.55 (7.2%)	
Simvastatin (20-40 mg/once a day)	135.66 (15.2%)	
Pravastatin (40 mg/once a day)	105.01 (7.2%)	
Lovastatin (20 mg/once a day)	14.43 (6.9%)	
Drug costs for treating pre-diabetes ($ per year)		
Metformin (500 mg/ twice a day)	25.71	RedBook (WAC), 2011[100] Fox, 2007[101] Stacy, 2006[93]
Physician ($ per visit)		
Primary care physician	70.86	CMS, 2011[102]
Specialist	105.61	
Laboratory tests ($ per visit)		
Cholesterol panel blood test	18.32	CMS, 2011[102]
HbA1c blood test	13.47	
Fasting plasma glucose test (FPG)	5.51	
Oral glucose tolerance test (OGTT)	6.61	
Clinical events ($)		
CHD, per event	18,261.00	HCUP[103] Bureau of Labor Statistics[99]
Stroke, per event	13,423.00	
Diabetes, per year	7,501.62	ADA[104] Bureau of Labor Statistics[99]

*All costs are for branded agents. Costs chosen to reflect effective dose ranges recommended in prescribing information for schizophrenia; median dose was chosen if a range was presented.
ADA = American Diabetes Association, CMS = Centers for Medicare & Medicaid Services, FPG = Fasting plasma glucose test, HbA1c = hemoglobin A1c, HCUP = Healthcare Cost and Utilization Project, IR = immediate release, OGTT = Oral glucose tolerance test, XR = extended release

4.1.9 Assumptions

The assumptions regarding the base-case analysis are detailed below.

- Due to unavailability of longer-term data, the cardiometabolic parameters were assumed to remain unchanged after one year (i.e., no additional cardiometabolic outcomes were attributed to the remaining model timeframe). The mean changes in these parameters from baseline to one year were assumed to be the same for all patients within a treatment arm.
- The effect of olanzapine on cardiometabolic parameters was drawn from the literature due to lack of availability of long-term data on olanzapine in the lurasidone clinical trial program. For modeling purposes, patients in this trial were assumed to have similar baseline characteristics as those in the lurasidone trials.
- While patients enrolled in the long-term safety study (D1050237) were a stable, out-patient population, it was assumed that they may be comparable in baseline demographic (age, gender, etc) characteristics to patients enrolled in studies D1050234, D1050231 and D1050229.
- Since patient-level data was unavailable, only indirect comparison of changes in cardiometabolic parameters between antipsychotic treatments was performed (i.e., the values extracted from literature for olanzapine were used in the model directly without adjustment to a common comparator).
- The model assumes 100% treatment compliance among patients that are treated with atypical antipsychotics, cholesterol-lowering drugs (if relevant), and pre-diabetes medication (if relevant).
- Due to the short model time horizon and because incident CVD events occur in the long-term, recurrent CHD and stroke events were not considered in the model.

4.1.10 Results: Base Case Analysis

To obtain reliable results, the base-case analysis simulated 1,000 patients per treatment arm per run. The simulation was repeated for a total of 100 runs, which is consistent with other recently published health economic simulation models in this disease area.[105],[106],[107] The results of the analysis are shown in Table 81. Treatment with lurasidone for one year is predicted to result in the fewest number of patients initiating therapy for pre-diabetes among all the comparators included in this analysis. Per every 1,000 patients treated with antipsychotics for one year and assuming no additional clinical impact attributable to the remaining model time frame after one year, lurasidone is predicted to:

- avoid 271, 35, and 82 cases with pre-diabetes when compared with olanzapine, risperidone, and quetiapine XR, respectively.
- avoid 194 cases with hyperlipidemia compared with olanzapine, but is associated with 31 and eight more cases with hyperlipidemia compared with risperidone and quetiapine XR, respectively.
- result in 119, 15, and seven fewer incident cases of diabetes during the three-year time horizon when compared with olanzapine, risperidone, and quetiapine XR, respectively.

Although treatment with lurasidone is predicted to yield potentially fewer cardiovascular events (fatal and non-fatal CHD) and all-cause deaths over three years, the differences are small due to the short model time horizon used in the analysis.

Table 81. Model Results: Estimated Outcomes and Costs for Lurasidone and Comparators

Outcome Measure	Lurasidone	Olanzapine	Risperidone	Quetiapine XR
Number of cases requiring treatment (after one year) for:				
High cholesterol (hyperlipidemia)	281	475	250	273
Pre-diabetes* (hyperglycemia)	268	539	303	350
Number of clinical events over 3 years				
CHD	11.85	13.59	12.02	11.19
Fatal CHD	4.44	5.08	4.61	4.44
Stroke	1.27	1.27	1.27	1.27
Fatal Stroke	0.32	0.32	0.32	0.32
Diabetes Total new cases of diabetes	218	337	233	225
New cases after one year	54	82	55	56
New cases after 2-3 years	164	255	178	169
Deaths	12.58	13.36	12.58	12.58
Discounted costs per patient				
Antipsychotic treatment	$15,861.39	$28,490,22	$29,181.35	$25,469.89
Treatment of high cholesterol	$947.63	$1,600.90	$843.88	$921.59
Treatment of high glycemia	$73.53	$146.17	$83.40	$100.33
CHD	$204.88	$235.27	$207.99	$193.39
Stroke	$15.87	$15.94	$15.90	$15.84
Diabetes	$4,283.43	$5,993.11	$4,476.32	$4,379.02
Total, excluding antipsychotic treatment	$5,525.34	$7,991.39	$5,627.48	$5,610.17
Total including antipsychotic treatment	$21,386.73	$36,481.61	$34,808.83	$31,080.06

*Patients who become diabetic during the model time horizon no longer accrue the costs associated with pre-diabetes.
CHD = chronic heart disease, IR = immediate release, XR = extended release

These differences in cardiometabolic parameter changes are expected to translate to potential net savings (discounted) of $2,466 per patient over three years compared to olanzapine, $102 compared to risperidone, and $85 compared to quetiapine XR, when excluding the cost of antipsychotic treatment. If the costs of antipsychotics are included, the total net savings associated with the use of lurasidone may be even greater: $15,095 per patient compared to olanzapine, $13,422 compared to risperidone, and $9,693 compared to quetiapine XR (Table 82).

Table 82. Model Results: Estimated Net Savings in Costs and Outcomes Between Lurasidone and Comparators

Outcome Measure	Olanzapine vs. Lurasidone	Risperidone vs. Lurasidone	Quetiapine XR vs. Lurasidone
Number of cases requiring treatment (after one year) for:			
High cholesterol (hyperlipidemia)	194	-31	-8
Pre-diabetes* (hyperglycemia)	271	35	82
Number of clinical events over 3 years			
CHD	1.74	0.17	-0.66
Fatal CHD	0.64	0.17	0.00
Stroke	0.00	0.00	0.00
Fatal stroke	0.00	0.00	0.00
Diabetes Total new cases of diabetes	119	15	7
New cases after one year	28	1	3
New cases after 2-3 years	91	14	5
Deaths	0.78	0.00	0.00
Discounted costs per patient			
Antipsychotic treatment	$12,628.54	$13,319.96	$9,608.50
Treatment of high cholesterol	$653.27	-$103.75	-$26.04
Treatment of hyperglycemia*	$72.64	$9.87	$26.80
CHD	$30.39	$3.11	-$11.49
Stroke	$0.07	$0.03	-$0.03
Diabetes	$1,709.68	$192.89	$95.59
Total, excluding antipsychotic treatment	**$2,466.06**	**$102.14**	**$84.83**
Total, including antipsychotic treatment	**$15,094.88**	**$13,422.10**	**$9,693.33**

*Patients who become diabetic during the model time horizon no longer accrue the costs associated with pre-diabetes.
CHD = coronary heart disease, IR = immediate release, XR = extended release

4.1.11 Results: Sensitivity Analyses

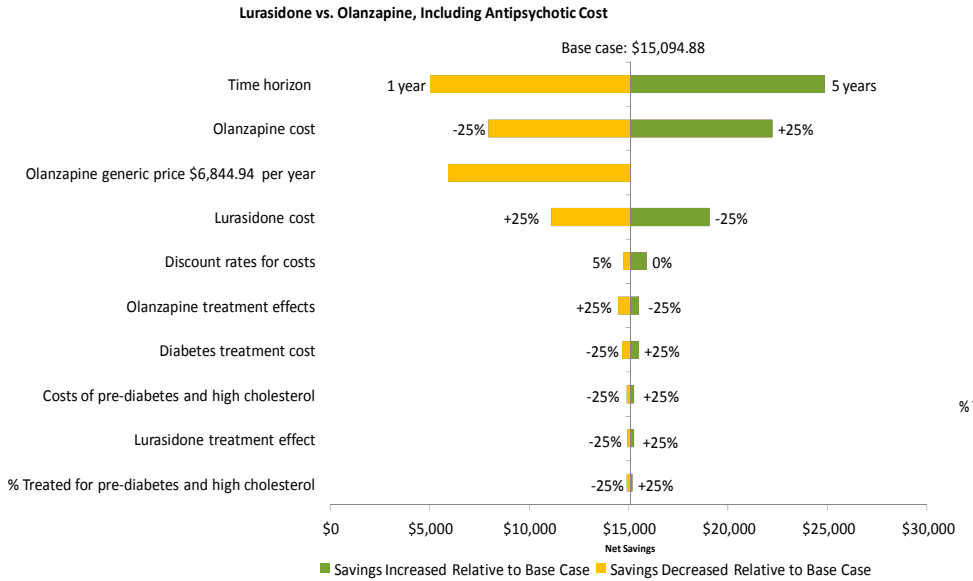
Univariate sensitivity analyses were carried out to evaluate the potential impact of varying model parameters on the cost savings relative to the base case by systematically varying one model input value while holding all other model input values constant. Parameters included in the univariate sensitivity analyses were: (1) model time horizon, (2) treatment effects, (3) drug cost, (4) discount rate for costs, (5) diabetes risk equation (FHS, Atherosclerosis Risk in Communities Study [ARIC], or San Antonio Heart Study [SAHS]), (6) cost of clinical events, (7) mortality hazard ratio for diabetes patients, (8) percent of patients treated for pre-diabetes or hyperlipidemia, and (9) CHD and stroke case-fatality rates. The sensitivity analyses considered a relative change of ± 25% from base-case value for all parameters. These analyses also assessed the impact of using a generic drug cost for olanzapine or risperidone. A tornado chart (Figure 4.2) compares the resulting change in the overall net savings (including or excluding the cost of antipsychotics) observed with lurasidone compared with the base case results when each parameter value is either reduced or increased.

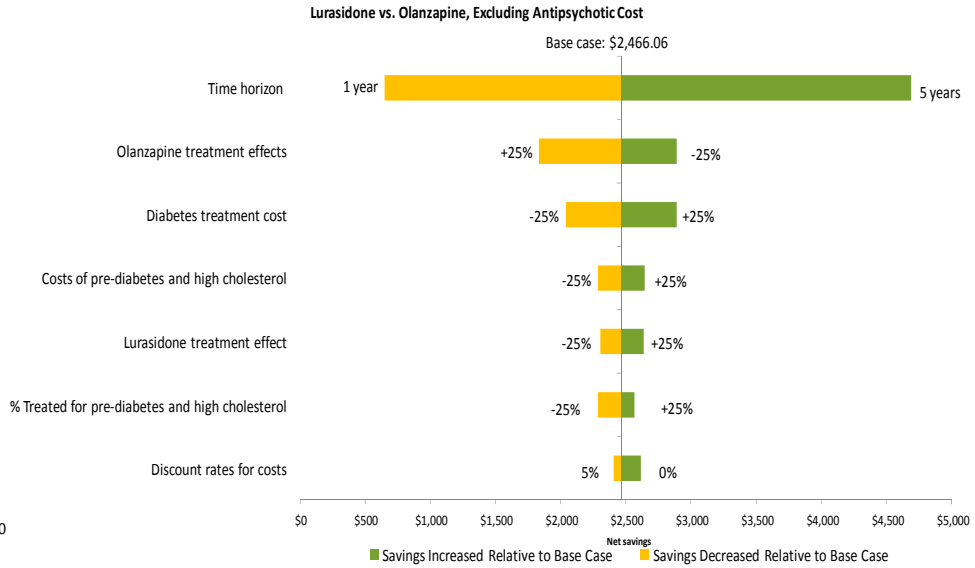
- The model is more sensitive to changes in the model time horizon, costs of lurasidone and comparators, and the treatment effects of lurasidone and comparators (Figure 5).

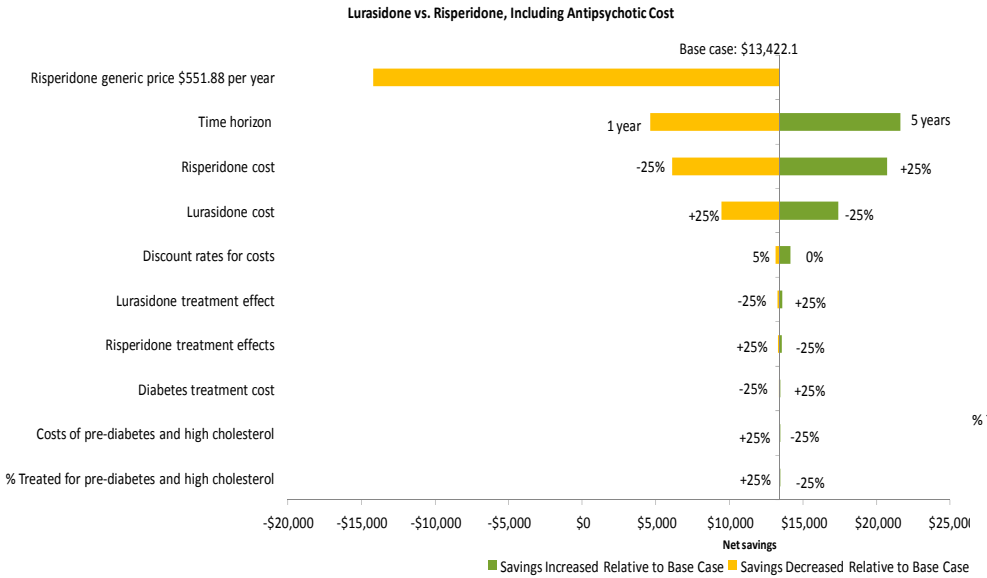
- The magnitude of cost savings with lurasidone differed based on the diabetes risk equation used in the analysis; however, cost savings with lurasidone were consistently observed. Compared with olanzapine, risperidone, and quetiapine, sensitivity analysis suggests that lurasidone may:

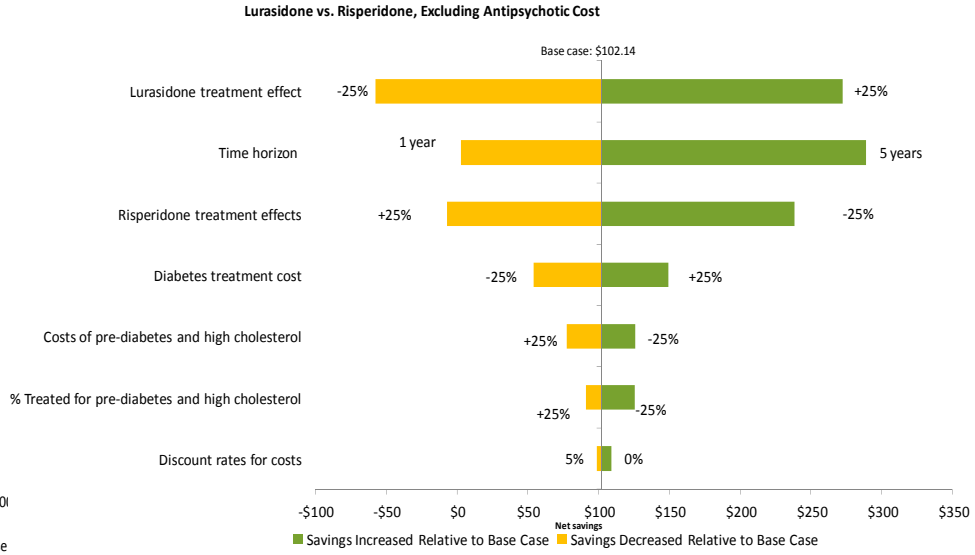
- avoid 119, 15, and seven diabetes cases and saves $1,710, $193, and $96 per patient, excluding the costs of antipsychotics and other events, respectively, when using FHS risk equation.
- avoid 52, 7, and 7 diabetes cases and saved $900, $76, and $87 when using ARIC risk equation, and
- avoid 58, 8, and 0 diabetes cases and saved $1,037, $115, and $23 when using SAHS risk equation.

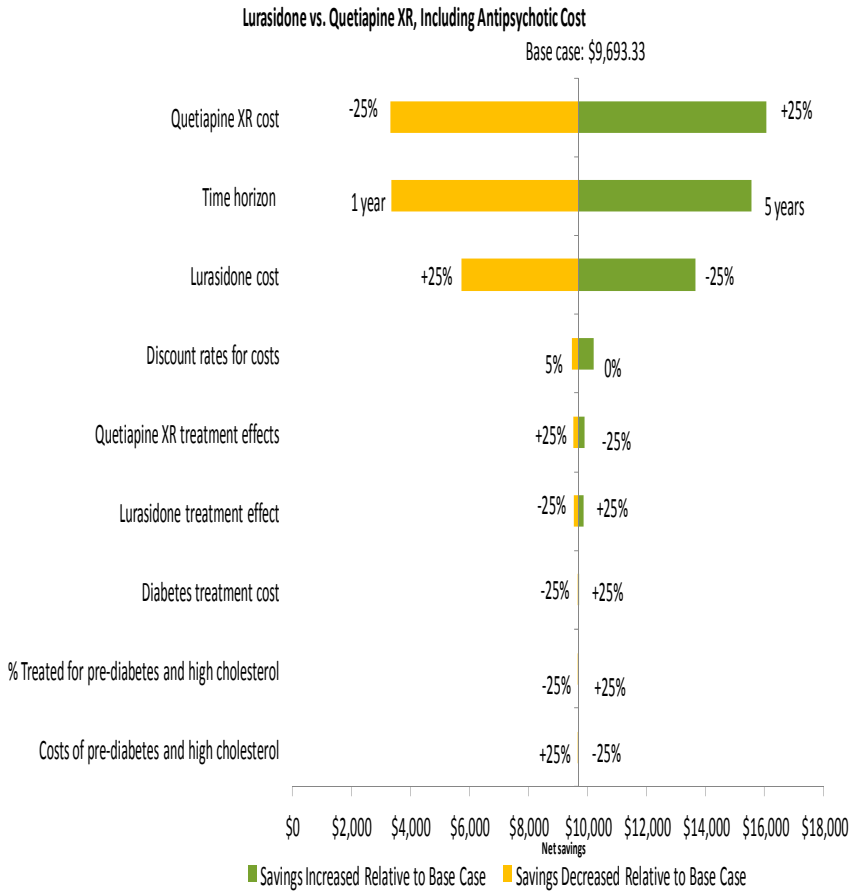
Figure 5:Univariate Sensitivity Analysis of Various Parameters

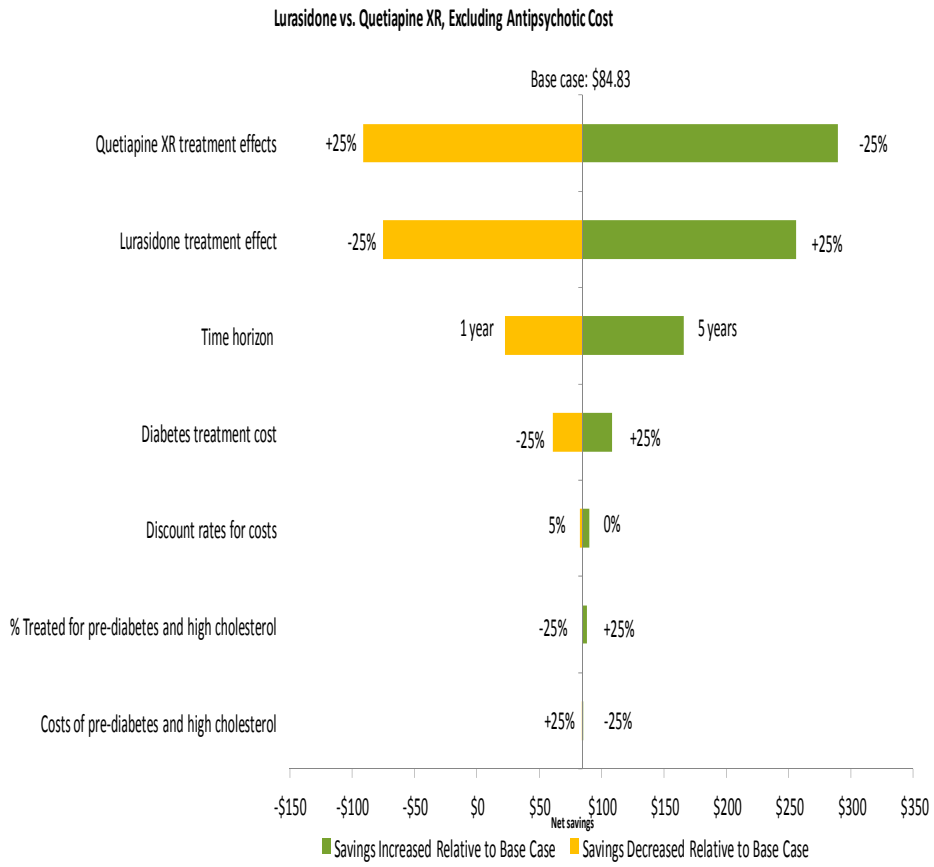

Lurasidone vs. Olanzapine, Including Antipsychotic Cost
Base case: $15,094.88
Time horizon
1 year
5 years
Olanzapine cost
-25%
+25%
Olanzapine generic price $6,844.94 per year
Lurasidone cost
+25%
-25%
Discount rates for costs
5%
0%
Olanzapine treatment effects
+25%
-25%
Diabetes treatment cost
-25%
+25%
Costs of pre-diabetes and high cholesterol
-25%
+25%
Lurasidone treatment effect
-25%
+25%
% Treated for pre-diabetes and high cholesterol
-25%
+25%
$0
$5,000
$10,000
$15,000
$20,000
$25,000
$30,000
Net Savings
Savings Increased Relative to Base Case
Savings Decreased Relative to Base Case


Lurasidone vs. Olanzapine, Excluding Antipsychotic Cost
Base case: $2,466.06
Time horizon
1 year
5 years
Olanzapine treatment effects
+25%
-25%
Diabetes treatment cost
-25%
+25%
Costs of pre-diabetes and high cholesterol
-25%
+25%
Lurasidone treatment effect
-25%
+25%
% Treated for pre-diabetes and high cholesterol
-25%
+25%
Discount rates for costs
5%
0%
$0
$500
$1,000
$1,500
$2,000
$2,500
$3,000
$3,500
$4,000
$4,500
$5,000
Net savings
Savings Increased Relative to Base Case
Savings Decreased Relative to Base Case


Lurasidone vs. Risperidone, Including Antipsychotic Cost
Base case: $13,422.1
Risperidone generic price $551.88 per year
Time horizon
1 year
5 years
Risperidone cost
-25%
+25%
Lurasidone cost
+25%
-25%
Discount rates for costs
5%
0%
Lurasidone treatment effect
-25%
+25%
Risperidone treatment effects
+25%
-25%
Diabetes treatment cost
-25%
+25%
Costs of pre-diabetes and high cholesterol
+25%
-25%
% Treated for pre-diabetes and high cholesterol
+25%
-25%
-$20,000
-$15,000
-$10,000
-$5,000
$0
$5,000
$10,000
$15,000
$20,000
Net savings
Savings Increased Relative to Base Case
Savings Decreased Relative to Base Case


Lurasidone vs. Risperidone, Excluding Antipsychotic Cost
Base case: $102.14
Lurasidone treatment effect
-25%
+25%
Time horizon
1 year
5 years
Risperidone treatment effects
+25%
-25%
Diabetes treatment cost
-25%
+25%
Costs of pre-diabetes and high cholesterol
+25%
-25%
% Treated for pre-diabetes and high cholesterol
+25%
-25%
Discount rates for costs
5%
0%
-$100
-$50
$0
$50
$100
$150
$200
$250
$300
$350
Net savings
Savings Increased Relative to Base Case
Savings Decreased Relative to Base Case


Lurasidone vs. Quetiapine XR, Including Antipsychotic Cost
Base case: $9,693.33
Quetiapine XR cost
-25%
+25%
Time horizon
1 year
5 years
Lurasidone cost
+25%
-25%
Discount rates for costs
5%
0%
Quetiapine XR treatment effects
+25%
-25%
Lurasidone treatment effect
-25%
+25%
Diabetes treatment cost
-25%
+25%
% Treated for pre-diabetes and high cholesterol
-25%
+25%
Costs of pre-diabetes and high cholesterol
+25%
-25%
$0
$2,000
$4,000
$6,000
$8,000
$10,000
$12,000
$14,000
$16,000
$18,000
Net savings
Savings Increased Relative to Base Case
Savings Decreased Relative to Base Case


Lurasidone vs. Quetiapine XR, Excluding Antipsychotic Cost
Base case: $84.83
Quetiapine XR treatment effects
+25%
-25%
Lurasidone treatment effect
-25%
+25%
Time horizon
1 year
5 years
Diabetes treatment cost
-25%
+25%
Discount rates for costs
5%
0%
% Treated for pre-diabetes and high cholesterol
-25%
+25%
Costs of pre-diabetes and high cholesterol
+25%
-25%
-$150
-$100
-$50
$0
$50
$100
$150
$200
$250
$300
$350
Net savings
Savings Increased Relative to Base Case
Savings Decreased Relative to Base Case

4.1.7. Limitations

As with all models, this model too has some key strengths and limitations:

- The cardiometabolic treatment effect (i.e., changes from baseline to end of year one) was assumed to be the same for all patients within the same treatment arm. Because changes in cardiometabolic parameters may be conditional on individual patient baseline characteristics, this assumption may not fully capture the real impact of treatment on each patient's change in cardiometabolic parameters and associated disease.
- The cardiometabolic treatment effect was assumed to remain unchanged after one year due to lack of availability of longer-term data, and consequently may underestimate the cost-savings associated with this cost-consequence model.
- The comparative cardiometabolic treatment effect data for olanzapine was obtained directly from the published report without adjusting for differences across trials, such as baseline patient characteristics, etc. The model estimates could be different if it was possible to use a common-reference comparator to obtain these data.
- Risperidone has been directly compared to lurasidone in one trial (D1050237), but patients enrolled in this trial are distinct from those enrolled in other lurasidone clinical trials (D1050234, D1050231 and D1050229). Study D1050237 required patients to be "clinically stable" at baseline, while studies D1050234, D1050231 and D1050229 required patients to be experiencing an acute exacerbation of symptoms at baseline. It is possible that the impact of atypical antipsychotics on cardiometabolic parameters is different in stable patients compared with acute patients, thus biasing comparisons between lurasidone and risperidone in favor of risperidone.
- The recurrence of CV events is not considered in the model, which results in an underestimation of the number of CV events and associated costs.
- The model does not incorporate changes in other parameters such as EPS, QTC, and prolactin levels. Additional analyses regarding the impact of lurasidone on relapse rates and side effects (EPS, QTC, and prolactin levels) are currently being conducted, and an update to the economic impact section that incorporates these parameters may occur at a future date.
- Despite the limitations cited above, the model is conservative for the following reasons:
  - Only a proportion of patients with pre-diabetes and hyperlipidemia were assumed to receive treatment for these conditions and incur the associated costs of management.
  - The model assumes that the values of cardiometabolic parameters remain unchanged after one year due to the lack of availability of long-term data. Although this assumption is unlikely to closely reflect the changes in cardiometabolic parameters over the longer term, it is believed to be more likely to yield conservative estimates of cardiometabolic changes associated with the use of lurasidone relative to other treatments because a better cardiometabolic profile is expected over a longer term for treatment with lurasidone vs. other comparators.
  - While treatment effect data for olanzapine was directly obtained from the literature without performing indirect comparisons analyses, the unfavorable impact of olanzapine on cardiometabolic parameters is consistently observed across trials in the literature, which include heterogeneous groups of patients.[63,64] This finding suggests that olanzapine's association with weight gain, hyperlipidemia, and hyperglycemia is unlikely to be affected by baseline patient characteristics. As such inclusion of alternative or pooled olanzapine data is unlikely to have an impact on the direction of the model results.

- The model uses a three-year time horizon in the base case analysis; sensitivity analyses indicate that cost savings are increased with lurasidone as the model time horizon is extended beyond three years.
- Although recurrent CV events are not considered in the model, due to the short model time horizon and the low incidence of CV events, this assumption should have no substantial impact on the model results.

4.1.8. Discussion and Conclusions

- The present analysis predicts that treatment of schizophrenia with lurasidone for one year may result in a better cardiometabolic profile compared with olanzapine, quetiapine XR, and risperidone, consequently leading to potentially fewer cases with diabetes, hyperglycemia, and hyperlipidemia over three years.
- These results are consistent with other analyses of CHD risk based on lurasidone clinical trial data (study D1050231) and FHS risk equations, which reported that lurasidone and placebo had similar acute effects on CHD risk factors and 10-year CHD risk in patients with schizophrenia, whereas olanzapine was associated with increases in CHD risk factors and greater 10-year CHD risk among male patients versus placebo.[108]
- Bsaed on the results of this model, the differences in cardiometabolic changes associated with the use of lurasidone are expected to result in cost savings. Assuming that 10,000 patients with schizophrenia within a health care plan are treated with lurasidone, the plan, without considering costs of antipsychotic treatment, would be expected to save about $8.2 million per year compared with olanzapine, $340,000 compared with risperidone, and $283,000 compared with quetiapine XR. If the costs of branded antipsychotic treatment are considered, the estimated potential savings may be even greater, amounting to approximately:
  - $50.3 million per year compared with olanzapine;
  - $44.7 million compared with risperidone; and
  - $32.3 million compared with quetiapine XR.
- The model results are sensitive to changes in the model time horizon, costs of lurasidone and comparators, and the treatment effects of lurasidone and comparators, but the results are robust to changes in the costs of diabetes, hyperglycemia, or hyperlipidemia, and the diabetes risk equation used in the analysis.

4.2. Relapse and Relapse-Related Hospitalization Cost Model

4.2.1. Model Overview and objectives

A model was developed to estimate the potential economic impact of annual relapses and relapse-related hospitalizations among adults treated for schizophrenia with lurasidone or quetiapine XR. The model compares direct mental health care costs from the perspective of a third-party payer over a 1-year time horizon.[109]

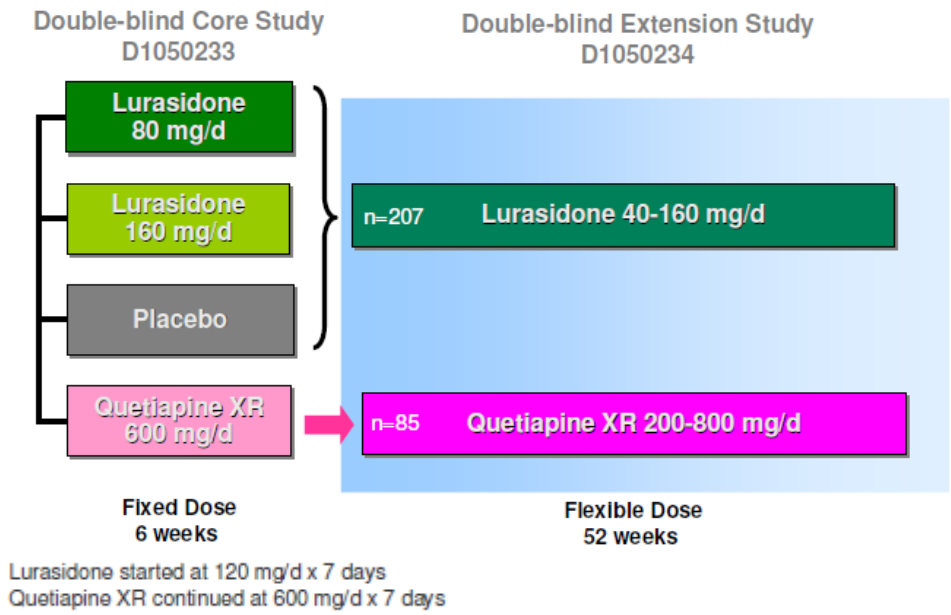
4.2.2. Methods

4.2.2.1. Methodological Overview

An interactive cost model was built using a Microsoft Excel® interface. The model objective was to estimate the per patient per year direct mental health costs for patients treated with lurasidone or quetiapine XR based on relapse and hospitalization data from Study D1050234 (hereinafter "Study 234").

Study 234 was a double-blind, parallel group study that compared the efficacy and safety of lurasidone (flexibly dosed 40-160 mg/day) and quetiapine XR (flexibly dosed 200-800 mg/day) for relapse prevention in patients with schizophrenia.[6] Patients who entered Study 234 had all completed the preceding Study D1050233, which was a 6-week, double-blind, placebo-controlled study involving fixed doses of lurasidone (80 mg/day or 160 mg/day) and quetiapine XR (600 mg/day) in patients with acute schizophrenia.[5] Further information on Study D1050233 and Study D1050234 can be found in section 3.1.4 of the dossier.

Figure 6: Study Design

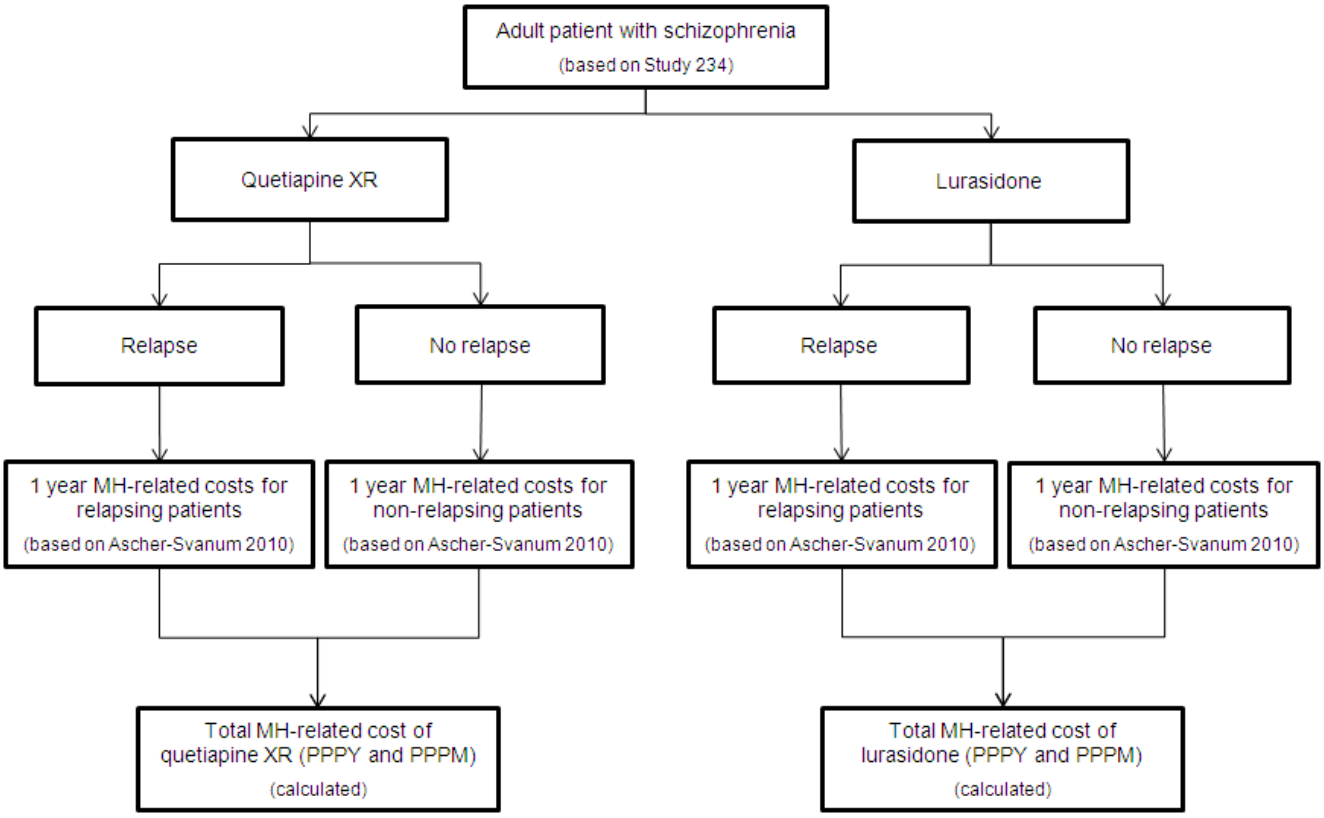


4.2.3. Model Structure

Figure 7 provides a schematic presentation of the model structure. The model population is based on the entire Study 234 population (N=236) (ALL cohort), but also allows for selection of only patients who were deemed responders (based on PANSS 20% change from baseline; N=217).

The absolute rates of relapses and relapse-related hospitalizations among patients treated with lurasidone or quetiapine XR from Study 234 formed the basis of the economic model. Annual direct mental health care costs incurred during a 1-year period among relapsing and non-relapsing patients with schizophrenia from a published study (Ascher-Svanum et al., 2010)[47] were used to estimate cost of relapses and relapse-related hospitalizations. Distributions for model parameters were created based on standard errors obtained from clinical trial data or estimates from the published literature. A probabilistic sensitivity analysis with 1,000 Monte Carlo simulations was conducted to simultaneously sample all parameter distributions to test the robustness of the model. The resulting costs were summed to estimate the total per patient per year (PPPY) mental health-related costs per patient treated with lurasidone or quetiapine XR.

Figure 7:Model Structure



MH = mental health; PPPM = per patient per month; PPPY = per patient per year; XR = extended-release

4.2.4. Treatment Options

Treatment options evaluated in the model included lurasidone and quetiapine XR. In Study 234, patients received either lurasidone 40-160 mg/day or quetiapine XR 200-800 mg/day for 12 months. The mean dose of lurasidone in Study 234 was 124 mg per day (all patients started the extension study at 120 mg per day for 7 days) and the mean dose of quetiapine XR was 629.6 mg per day (all patients started extension study at 600 mg per day for 7 days).

4.2.5. Patient Population

The patient population of interest was adult patients with schizophrenia. The model allows the selection of one of two patient populations based on Study 234:

- All patients enrolled in Study 234

- Responders, defined as patients who demonstrated a clinical response in Study D1050233. Response was defined as ≥20% improvement in PANSS total score (Day 42). This was the patient population for the primary endpoint in Study 234.

4.2.6. Perspective and Time Horizon

The analysis was conducted from a US third party payor perspective. The model analysis was conducted over a 1-year period. No discounting was performed since only annual costs were estimated based on 1-year outcomes.

4.2.7. Model Inputs

4.2.7.1. Rate of Clinical Relapse and Rehospitalization

The proportion of patients who relapsed during treatment with lurasidone and quetiapine XR was obtained from Study 234.

Relapse: In the study, relapse was defined as: either a worsening of ≥30% PANSS total score from D1050233 Day 42 and CGI-S ≥3; rehospitalization for worsening of psychosis; or emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others.

The observed relapse rates for lurasidone and quetiapine XR in the overall population and the responder population are shown in Table 83. The mean relapse rate and standard error were obtained from Study 234.

Table 83. Observed Relapse Rates from Study 234

	Lurasidone	Quetiapine XR
All patients		
Mean relapse rate (standard error)	19.9% (±3.3%)	28.2% (±4.9%)
Responders only		
Mean relapse rate (standard error)	20.9% (±3.4%)	26.6% (±5.0%)

Relapse-related hospitalization: Since hospitalizations were reported as a sub-set of the relapse definition used in the trial, we referred to hospitalizations as “relapse-related hospitalizations”. The observed rehospitalization rates for lurasidone and quetiapine XR in the overall population and the responder population are shown in Table 84. The mean relapse rate and standard error were obtained from Study 234.

Table 84. Observed Rehospitalization Rates from Study 234

	Lurasidone	Quetiapine XR
All patients		
Mean rehospitalization rate (standard error)	7.3% (±2.1%)	17.6% (±4.1%)
Responders only		
Mean relapse rate (standard error)	7.2% (±2.2%)	16.5% (±4.2%)

4.2.7.2. Mental Health-Related Costs

Direct costs associated with inpatient and outpatient mental health-related services for relapsing and non-relapsing patients were obtained from a large (N=2,327) prospective observational study of schizophrenia treatment in usual-care settings (US Schizophrenia Care and Assessment Program) (Ascher-Svanum et al., 2010). The authors identified patients with and without a relapse in the 6-month pre-period, and calculated subsequent total 1-year direct mental health costs based on data from 1557 patients who had complete 1-year follow-up data. Relapse was defined as having any of the following recorded in a patient's medical record: psychiatric hospitalization, use of emergency services, use of a crisis bed, or a suicide attempt.

Costs were aggregated into the following components:

- medications (antipsychotics, other psychotropics, such as mood stabilizers, anticholinergics, antidepressants, antianxiety, and sleep agents),
- psychiatric hospitalizations,
- day treatment,
- emergency services,
- psychosocial group therapy,
- medication management,
- individual therapy, and
- ACT/case management.

Medication costs in this study were obtained from published average wholesale prices discounted by 15%, costs of hospitalization were based on daily per diem costs at study sites, and costs of mental health services were obtained from management information systems at each study site based on their relative value units.

The authors evaluated the total 1-year direct mental health costs for patients who had a relapse in the 6-month period ("relapsing patients") and who did not ("non-relapsing patients") (Table 85).

Table 85. Cost Inputs in 2000 USD (Ascher-Svanum et al., 2010)

Parameter	Relapsing Patients (n=310)			Non-relapsing Patients (n=1,247)		
	Mean	SD	SE	Mean	SD	SE
Medications	$5,647	$3,810	$216	$4,613	$3,844	$109
Psychiatric Hospitalizations	$19,298	$48,545	$2,757	$1,055	$6,404	$181
Day Treatment	$1,816	$3,968	$225	$1,510	$3,672	$104
Emergency Services	$166	$271	$15	$64	$167	$5
Psychosocial Group Therapy	$1,541	$3,060	$174	$1,463	$3,143	$89
Medication Management	$1,436	$1,666	$95	$1,125	$1,227	$35
Outpatient Individual Therapy	$1,987	$2,555	$145	$1,088	$1,644	$44
ACT/Case Management	$1,406	$987	$56	$907	$925	$26

Source: Ascher-Svanum, 2010.

As the costs were published in 2000 US dollars (USD), all cost estimates were adjusted for inflation to 2011 USD, using the Medical Care Component of the Bureau of Labor Statistics Consumer Price Index.[110] The estimated costs associated with relapsing and non-relapsing patients used in the model are shown in Table 86.

Table 86. 2011 Inflation Adjusted Cost Inputs: Relapsing and Non-relapsing Patients

Parameter	Relapsing Patients (n=310)			Non-relapsing Patients (n=1,247)		
	Mean	SD	SE	Mean	SD	SE
Medications	$8,612	$5,810	$330	$7,035	$5,862	$166
Psychiatric Hospitalizations	$29,430	$74,033	$4,205	$1,609	$9,766	$277
Day Treatment	$2,769	$6,051	$344	$2,303	$5,600	$159
Emergency Services	$253	$413	$23	$98	$255	$7
Psychosocial Group Therapy	$2,350	$4,667	$265	$2,231	$4,793	$136
Medication Management	$2,190	$2,541	$144	$1,716	$1,871	$53
Outpatient Individual Therapy	$3,030	$3,896	$221	$1,659	$2,355	$67
ACT/Case Management	$2,144	$1,505	$85	$1,383	$1,411	$40

Source: Ascher-Svanum et al., 2010[3]; Bureau of Labor Statistics 2011[4]

4.2.8. Calculation of Model Outcomes

The outcome of interest was the per patient direct mental health cost for a patient treated with lurasidone compared with quetiapine XR. Conceptually, the estimated PPPY cost was calculated as the sum of the product of the proportion of relapsing patients on each treatment and each mental health cost component for relapsing patients and the product of the proportion of non-relapsing patients on each treatment and each mental health cost component for non-relapsing patients.

$$\text{Total Cost of LUR} = \Sigma\ (\text{Relapse Rate}_{LUR}) * (\text{Cost Component}_{Relapse}) + \Sigma\ (1 - \text{Relapse Rate}_{LUR}) * (\text{Cost Component}_{No\ Relapse})$$

$$\text{Total Cost of QXR} = \Sigma\ (\text{Relapse Rate}_{QXR}) * (\text{Cost Component}_{Relapse}) + \Sigma\ (1 - \text{Relapse Rate}_{QXR}) * (\text{Cost Component}_{No\ Relapse})$$

When rehospitalization rates are selected for the rehospitalization cost, the estimated PPPY cost is calculated as described above for relapse rates, with the exception of the psychiatric hospitalization cost component. For this component, the rehospitalization rate for patients treated with either lurasidone or quetiapine XR was applied to the proportion of patients relapsing or not relapsing, and then multiplied by the PPPY cost of a psychiatric hospitalization.

The probabilistic simulation in the model uses the mean value, standard error, and the identified sample distribution for each model parameter simultaneously and runs 1,000 Monte Carlo simulations to estimate the mean and 95% confidence intervals for all of the cost estimates. The respective probabilities for relapses during lurasidone or quetiapine XR treatment were modeled as a beta distribution using the mean observed relapse rate and standard errors from Study 234. The 1-year costs were modeled as a normal distribution using the mean costs and standard errors from the retrospective analysis (Ascher-Svanum et al., 2010).

4.2.9. Sensitivity Analysis

The probabilistic simulation also yields an estimate of the proportion of simulations in which lurasidone would be less costly than quetiapine XR.

Univariate sensitivity analysis was conducted to determine which factors have the most influence on the estimated net cost savings for lurasidone. Each model parameter was varied using the 95% CI for the low and high, while holding all other parameters constant.

4.2.10. Assumptions

The primary assumptions used in the model are detailed below:

- The model only evaluates treatment comparisons of lurasidone and quetiapine XR, based on Study 234. Other monotherapy or adjunctive treatments for schizophrenia are not included in this analysis and would be important to model for future purposes.
- While the definition of relapse was similar in both Study 234 and Ascher-Svanum et al., 2010. Study 234 also included additional criteria of "PANSS and CGI worsening threshold scores from their core study baseline to Day 42" in addition to rehospitalization for worsening of psychosis; or emergence of suicidal ideation,
- The model assumed that the 12-month direct costs reported in Ascher-Svanum et al., 2010 captures 12-month direct costs adequately and is applicable to Study 234.
- The model estimated cost only for the duration of Study 234 and only for one year; it did not involve extrapolations beyond one year..Future models may evaluate overall cost saving for a longer time-horizon.
- The model estimates are conservative insofar as costs are based on only 1 year costs.
- All cost estimates were adjusted for inflation to 2011 USD, using the Medical Care Component of the Bureau of Labor Statistics Consumer Price Index.
- The model included "an average cost of antipsychotic treatment" based on patient relapse status in the estimation of annual antipsychotic costs.

4.2.11. Results

Results of four scenarios are presented in the following sections of this report as a reference for further consideration:

- All patients, using relapse rate for the rehospitalization cost
- All patients, using rehospitalization rate for the rehospitalization cost
- Responder population, using relapse rate for the rehospitalization cost
- Responder population, using rehospitalization rate for the rehospitalization cost

4.2.11.1. All Patients

Treatment with lurasidone resulted in a significantly fewer relapses compared to treatment with quetiapine XR, as described in Section 4.2.7. In the all patients analysis, over a 1-year period, lurasidone could be esitmated to result in a total annual cost per patient of $24,567, compared to $27,269 for quetiapine XR, amounting to a cost savings of $2,702 per patient compared with

quetiapine XR (Table 87). The estimated total per patient per month (PPPM) costs for lurasidone was $2,047, representing a $225 cost savings compared with quetiapine XR ($2,272 PPPM). In the probabilistic analysis, there was a 99.7% likelihood that the mental health-related direct costs would be less for lurasidone than for quetiapine XR.

Table 87. Estimated Per Patient Per Year Costs (All Patients; Relapse Rates)

Cost Component	Lurasidone Mean (95% CI)		Quetiapine XR Mean (95% CI)		Difference*
Medication	$7,359	($7071, $7656)	$7,488	($7173, $7790)	-$129
Psychiatric hospitalization	$7,160	($5245, $8979)	$9,458	($6961, $12513)	-$2,298
Day treatment	$2,395	($2107, $2685)	$2,433	($2123, $2745)	-$38
Emergency services	$129	($115, $145)	$142	($124, $160)	-$13
Psychosocial group therapy	$2,249	($1987, $2490)	$2,259	($1991, $2507)	-$10
Medication management	$1,809	($1715, $1910)	$1,848	($1742, $1960)	-$39
Outpatient individual therapy	$1,931	($1787, $2076)	$2,044	($1875, $2206)	-$113
ACT/Case management	$1,533	($1460, $1605)	$1,596	($1512, $1676)	-$63
Total	**$24,567**	**($22509, $26550)**	**$27,269**	**($24526, $30602)**	**-$2,702**

*Difference calculated as lurasidone minus quetiapine XR

When the rate of relapse-related hospitalization rates from Study 234 was used for the hospitalization cost, cost savings were greater with lurasidone compared with quetiapine XR. In the all patients analysis, over a 1-year period, lurasidone could be expected to result in a total cost per patient of $21,025, compared to $24,301 for quetiapine XR, amounting to annual per patient cost savings of $3,277 per patient compared with quetiapine XR (Table 88). The total PPPM for lurasidone was $1,752, representing a potential $273 cost savings compared with quetiapine XR ($2,025 PPPM). In the probabilistic analysis, there was a 100% likelihood that the mental health related direct costs would be less for lurasidone than for quetiapine XR.

Table 88. Estimated Per Patient Per Year Costs (All Patients; Hospitalization Rates)

Cost Component	Lurasidone Mean (95% CI)		Quetiapine XR Mean (95% CI)		Difference*
Medication	$7,346	($7069, $7626)	$7,477	($7194, $7791)	-$131
Psychiatric hospitalization	$3,635	($2863, $4533)	$6,502	($4750, $8380)	-$2,867
Day treatment	$2,389	($2089, $2671)	$2,428	($2115, $2720)	-$38
Emergency services	$129	($114, $143)	$142	($124, $161)	-$13
Psychosocial group therapy	$2,256	($2021, $2492)	$2,266	($2035, $2511)	-$10
Medication management	$1,808	($1712, $1904)	$1,847	($1738, $1949)	-$39
Outpatient individual therapy	$1,928	($1786, $2063)	$2,043	($1872, $2216)	-$114
ACT/Case management	$1,533	($1458, $1609)	$1,597	($1517, $1678)	-$64
Total	**$21,025**	**($20059, $21979)**	**$24,301**	**($22479, $26295)**	**-$3,277**

*Difference calculated as lurasidone treatment minus Quetiapine XR

4.2.11.2. Responder Population

In the responder analysis, over a 1-year period, lurasidone could be estimated to result in a total cost per patient of $24,920, compared to $26,835 for quetiapine XR, amounting to a potential cost savings of $1,914 per patient compared with quetiapine XR. The total PPPM for lurasidone was $2,077, representing a $160 cost savings compared with quetiapine XR ($2,236 PPPM). In the probabilistic analysis, there was a 96.5% likelihood that the mental health-related direct costs would be less for lurasidone than for quetiapine XR.

Table 89. Estimated Per Patient Per Year Costs (Clinical Responders; Relapse Rates)

Cost Component	Lurasidone Mean (95% CI)		Quetiapine XR Mean (95% CI)		Difference*
Medication	$7,361	($7069, $7645)	$7,453	($7161, $7756)	-$92
Psychiatric hospitalization	$7,472	($5706, $9446)	$9,098	($6741, $11929)	-$1,626
Day treatmen	$2,397	($2118, $2654)	$2,424	($2139, $2700)	-$27
Emergency services	$131	($116, $146)	$140	($124, $158)	-$9
Psychosocial group therapy	$2,254	($2010, $2485)	$2,262	($2017, $2494)	-$8
Medication management	$1,816	($1712, $1915)	$1,843	($1734, $1954)	-$27
Outpatient individual therapy	$1,950	($1795, $2098)	$2,031	($1858, $2209)	-$80
ACT/Case management	$1,541	($1469, $1618)	$1,585	($1506, $1670)	-$44
Total	**$24,920**	**($23078, $27072)**	**$26,835**	**($24312, $29839)**	**-$1,914**

*Difference calculated as LATUDA minus Seroquel XR

When the rate of rehospitalization from Study 234 was used for the relapse-related hospitalization cost, similar cost savings could be expected with lurasidone. In the responder analysis, over a 1-year period, lurasidone could be expected to result in a total cost per patient of $21,069, compared to $23,956 for quetiapine XR, amounting to a potential cost savings of $2,888 per patient compared

with quetiapine XR. The total PPPM for lurasidone was $1,756, representing a $241 cost savings compared with quetiapine XR ($1,996 PPPM). In the probabilistic analysis, there was a 100% likelihood that the mental health-related direct costs would be less for lurasidone than for quetiapine XR.

Table 90. Estimated Per Patient Per Year Costs (Clinical Responders; Hospitalization Rates)

Cost Component	Lurasidone Mean (95% CI)		Quetiapine XR Mean (95% CI)		Difference*
Medication	$7,361	($7076, $7658)	$7,453	($7160, $7759)	-$92
Psychiatric hospitalization	$3,618	($2795, $4463)	$6,218	($4589, $7990)	-$2,600
Day treatment	$2,399	($2108, $2683)	$2,427	($2123, $2729)	-$28
Emergency services	$130	($116, $146)	$139	($123, $156)	-$9
Psychosocial group therapy	$2,262	($2013, $2502)	$2,268	($2027, $2517)	-$6
Medication management	$1,812	($1712, $1912)	$1,840	($1733, $1954)	-$28
Outpatient individual therapy	$1,944	($1796, $2100)	$2,025	($1862, $2199)	-$80
ACT/Case management	$1,541	($1468, $1613)	$1,586	($1503, $1669)	-$45
Total	**$21,069**	**($20051, $22040)**	**$23,956**	**($22181, $25799)**	**-$2,888**

*Difference calculated as LATUDA minus Seroquel XR

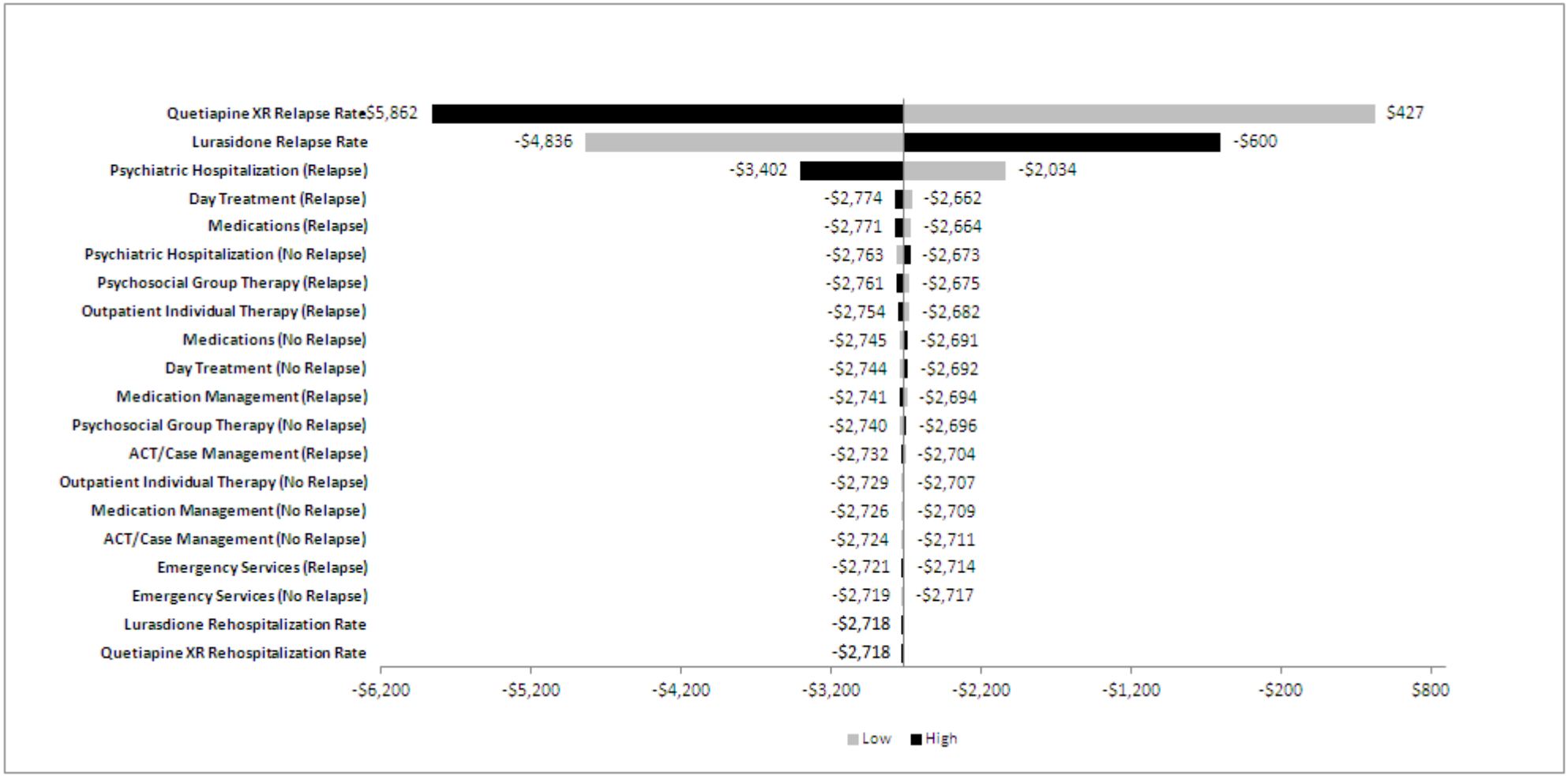
4.2.12. Univariate Sensitivity Analysis

A univariate sensitivity analysis was conducted to test the sensitivity of the model to variation in all model parameters. The output of the one-way sensitivity analysis is depicted as a tornado diagram, in which the width of the arms represents the influence of that parameter on the model results while holding all other parameters constant.

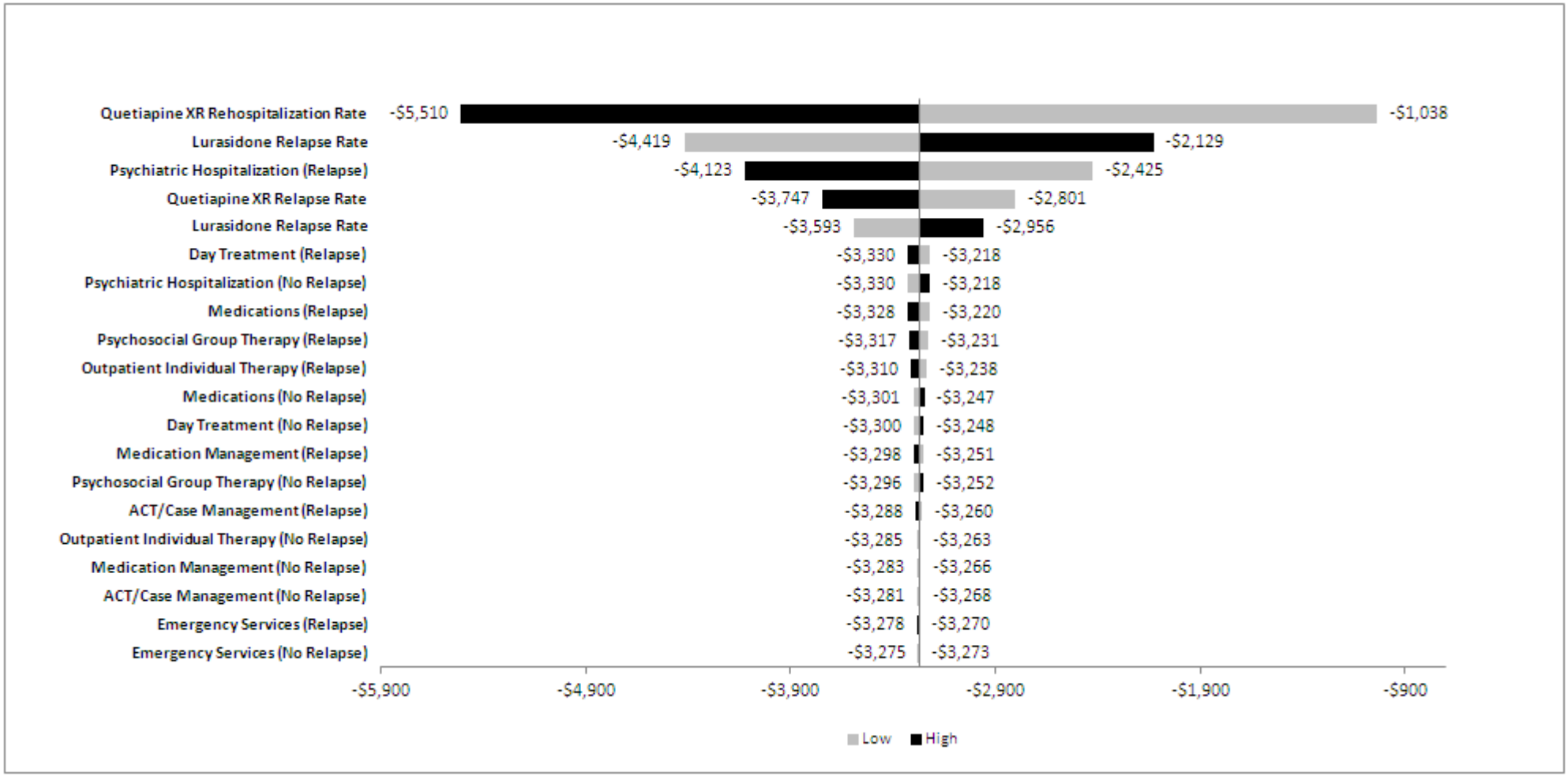
In each of the scenarios tested (Figure 8), the model results (net cost savings of lurasidone) were most sensitive to the relapse or relapse-related hospitalization rates for lurasidone and quetiapine XR. The model was also moderately sensitive to the annual cost of hospitalizations. The model was insensitive to changes in the costs of medication management, psychosocial group therapy, ACT/case management, outpatient individual therapy, and emergency services.

Figure 8: Univariate Sensitivity Analyses for 4 Model Scenarios

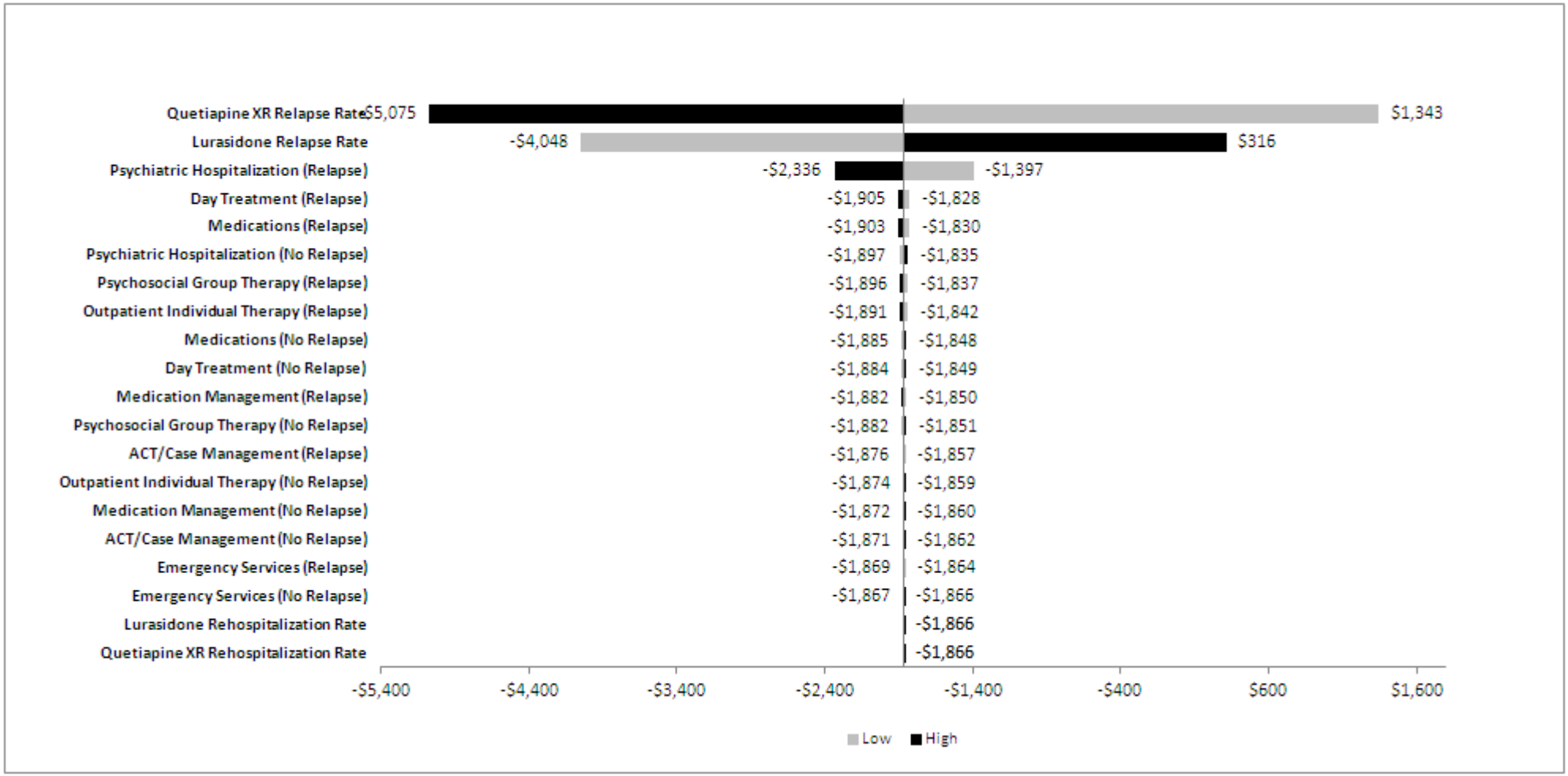
All Patients; Relapse Rate



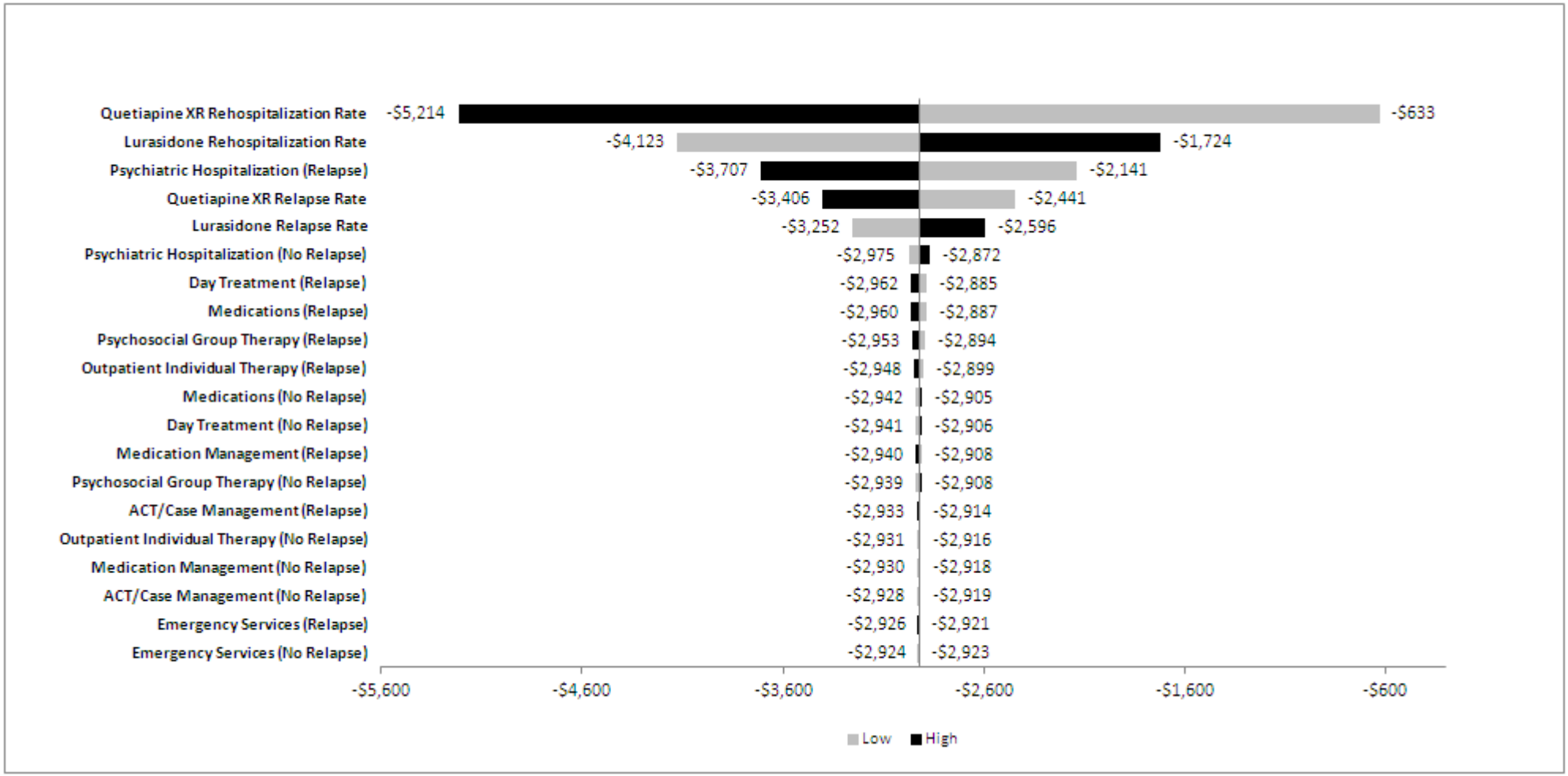
All Patients; Relapse-related Hospitalization Rate



Responder Population; Relapse Rate



Responder Population; Relapse-related Hospitalization Rate



4.2.13. Strengths & Limitations

As with every economic model, there are strengths and limitations with this relapse and relapse-related hospitalization cost model.

- In general, modeling involves a variety of assumptions regarding the disease, treatment patterns, and costs. Patients with schizophrenia represent a diverse population; as such, this model may represent a simplification of treatment patterns and response to treatment from what may be seen in actual practice based on the estimates from the 3-yr US-SCAP project.
- The model only evaluated the costs associated with relapses and relapse-related hospitalizations for two atypical antipsychotics, lurasidone and quetiapine XR. The cost of these agents was not considered, nor was the potential use of adjunctive therapies.
- Drug-specific characteristics that may impact patient response to treatment, including adverse events, adherence, and persistence, were not evaluated in the model.
- The model did not consider costs that would be incurred in this patient population, including adverse events associated with treatment and indirect costs such as lost productivity and caregiver time. Indirect Costs not related to mental health care were also excluded from the model.
- The only outcome evaluated was relapse and relapse-related hospitalizations; other relevant clinical outcomes such as cardiometabolic conditions and other comorbidities common in schizophrenia patients were not included.
- Notwithstanding some of the limitations mentioned above, this model is conservative and is likely that true annual total costs of relapse and relapse-related hospitalizations among adults with schizophrenia are possibly underestimated in this model for many of the reasons mentioned above. Consequently, this model may be underestimating the cost-savings associated with fewer relapses and fewer relapse-related hospitalizations.

4.2.14. Discussions and Conclusions

Patients with schizophrenia have a disproportionately high cost of illness compared with the general population and other mental health and substance abuse disorders (AHRQ 2004). Relapses represent a substantial driver of the costs of schizophrenia; patients with a relapse incur 3-times higher 1-year costs than patients without a relapse (Ascher-Svanum et al., 2010). The present economic analysis was undertaken to estimate the 1-year costs of adult patients with schizophrenia treated with lurasidone and quetiapine XR, based on the observed relapse rate from Study 234, a one-year, double-blind, study that compared the efficacy and safety of lurasidone (flexibly dosed 40-160 mg/day) and quetiapine XR (flexibly dosed 200-800 mg/day) for relapse prevention in patients with schizophrenia.

Based on the results from this model, the differences in relapse and relapse-related hospitalization rates associated with the use of lurasidone compared with quetiapine XR are expected to result in potential cost savings. The results of this model found that adults treated for schizophrenia with lurasidone have lower estimated annual direct mental health care costs than those treated with quetiapine XR, due to fewer relapses and relapse-related hospitalizations. Regardless of study population (all patients or responders only) and the outcome (relapses or relapse-related hospitalizations), the estimated PPPY cost was substantially lower for lurasidone versus quetiapine XR ($1,914-$2,702) in all four scenarios. Similar, yet higher cost savings were found when the observed rate of relapse-related hospitalization from Study 234 was used to calculate the relapse-related hospitalization cost (-$3,277 PPPY for all patients and -$2,888 PPPY for the

responder population). Overall model results suggest that lurasidone represents a potential cost-saving option over quetiapine XR due to fewer relapses and relapse-related hospitalizations.

4.3. Budget Impact Model

4.3.1. Overview and Objectives

The objective of the Budget Impact Model (BIM) was to determine the potential budgetary impact to the payer after the introduction of Latuda® to its formulary over a one-year time horizon. The BIM provides a valid computing framework to understand the relationship between the characteristics of their setting and the possible budget consequences after adopting Latuda®. A copy of the BIM is available upon request.

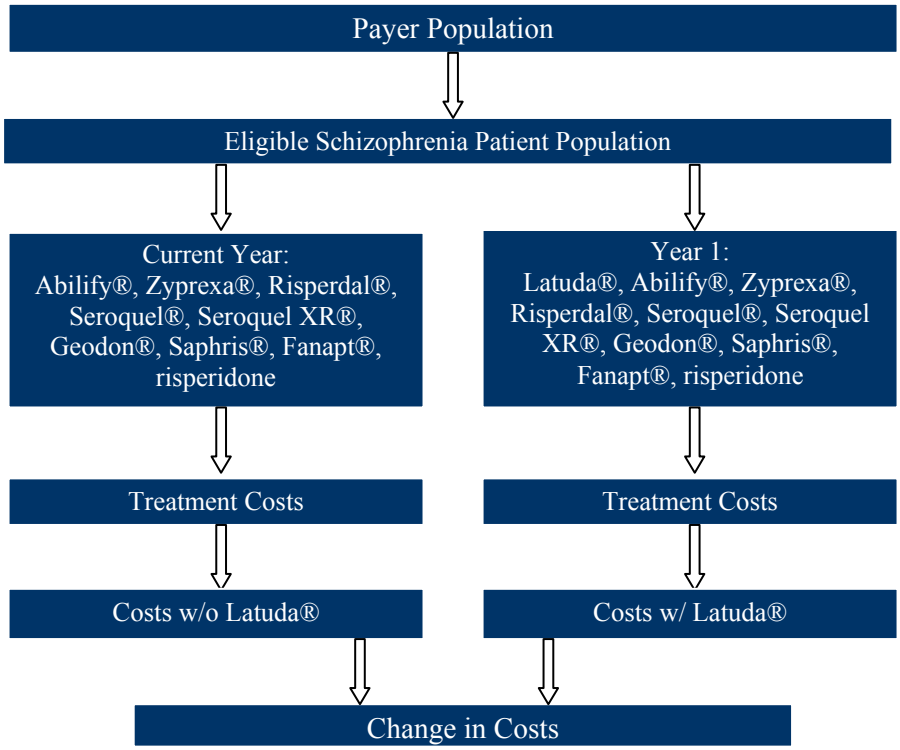
4.3.2. Methodological Overview

The model was built in Microsoft Excel®. It estimates the incremental budget impact after Latuda® (lurasidone HCl) is adopted as a treatment option for adult patients diagnosed with schizophrenia, combining epidemiological data, market uptake assumptions from market research forecasting, and drug treatment costs. The current model was populated with US data based on published prevalent schizophrenia population. The default model data inputs and assumptions were derived from the published literature, publicly available data sources. The perspective undertaken in the model is that of a US third-party payer (or pharmacy directors), and the time horizon for the analysis can be extended up to five years, with the base-case analysis set to one year.

4.3.3. Model Structure

A decision analytic model was developed using the model structure shown in Figure 9. The model calculates the estimated total annual budget impact of adding Latuda® as a treatment option for schizophrenia to a health plan formulary. The calculation is determined by multiplying the proportion of patients with schizophrenia treated with each of the respective treatment options by the drug acquisition costs associated with the drug used in a given year.

Figure 9: Budget Impact Model Structure



w/o = without, w/ = with, XR = extended release

There are three basic types of data inputs included in the BIM: population inputs, market dynamics, and cost inputs. These inputs, as well as the default values, are detailed next.

4.3.4. Population Inputs

The model employed a default health plan population of 1,000,000 members. Using a literature-based estimate of 1.0% for the US prevalence of schizophrenia (including diagnosed and undiagnosed patients), the model estimated that approximately 10,000 plan members would be affected by schizophrenia.[15] The percentage of patients with schizophrenia diagnosed and treated was approximated as 51%. This estimate was calculated by dividing the proportion of patients diagnosed with schizophrenia[16] by the prevalence of schizophrenia (0.51/1.00).[15] Based on this estimate, the model estimated that 5,100 patients would be treated within the default health plan. It is anticipated that the Patient Protection and Affordable Care Act may increase the number of patients receiving care; however, this does not affect the base case as the full enactment of the Act's provisions are not scheduled until 2014. The default population inputs are listed in Table 91, below.

Table 91. Plan Inputs – Default Values

Parameter	Default Value	Source
Number of Plan Members	1,000,000	User input
Prevalence of Schizophrenia in the US	1.00%	Narrow et al. 2002[1]
Estimated Number of Affected Members	*10,000*	*Calculation*
Percent Diagnosed and Treated	51%	Wu et al. 2006[2]; Narrow et al. 2002[1]
Estimated Number of Affected Members (Diagnosed/Treated)	*5,100*	*Calculation*
Percent Growth in the Number of Patients Treated	0%	Assumption

US = United States

The default time horizon for the base case analysis was one year, and drug cost data were based on RedBook 2012.[111] Treatments included in the base-case analysis were Abilify®, Zyprexa®, Risperdal®, Seroquel IR®, Seroquel XR®, Geodon®, Saphris®, Fanapt®, and risperidone (generic).

4.3.5. Market Dynamics

The projected default market share inputs for the current year (without Latuda®) and year 1 (with Latuda®) are presented in Table 92. Market share reductions for comparators, as Latuda® enters the market, were assumed to be proportional to each comparator's original market share.

Table 92. Market Share Inputs – Default Values

Drug	Current	Year 1
Latuda®	0.0%	0.5%
Abilify®	20.7%	20.6%
Zyprexa®	10.6%	10.5%
Risperdal®	1.6%	1.6%
Seroquel IR®	29.3%	29.1%
Seroquel XR®	6.5%	6.4%
Geodon®	6.9%	6.8%
Saphris®	0.5%	0.5%
Fanapt®	0.2%	0.2%
risperidone	23.9%	23.8%

Source: Sunovion Pharmaceuticals. Atypical Antipsychotics for Schizophrenia – Internal Market Research 11/1/2010.[112]
Note: Market share changes may not be visible due to rounding.
IR = immediate release, XR = extended release

4.3.6. Drug Treatment Costs

The default unit price and dosing information are presented in Table 93. Default daily cost of Latuda® is $15.39, irrespective of dose (40-mg and 80-mg doses are priced equally).[111] The unit cost is used to calculate the daily cost and the monthly cost of each treatment.

Table 93. Dosing and Unit Prices

Drug*	mg per Day*	Number per Day**	Unit Cost[3]**	Total Cost per Day
Latuda®[1]	40 mg or 80 mg	1	$15.39	$15.39
Abilify®[11]	15 mg	1	$18.24	$18.24
Zyprexa®[12]	10 mg	1	$18.44	$18.44
Risperdal®[113]	4 mg	2	$15.56	$31.12
Seroquel IR®[13]	200 mg	2	$11.98	$23.96
Seroquel XR®[13]	400 mg	2	$15.97	$31.94
Geodon®[114]	60 mg	2	$10.07	$20.14
Saphris®[14]	10 mg	2	$9.60	$19.21
Fanapt®[115]	6 mg	2	$9.62	$19.23
Risperidone[113]	4 mg	2	$0.76	$1.51

*All comparators included in the model are branded, except for Risperdal®/risperidone, for which both branded and generic forms are included in the base case.
**Dosing for comparators was based on prescribing information.
IR = immediate release, XR = extended release
Source: RedBook, 2012

The base case analysis assumed a co-pay of $0. Rebates can be applied as a user-defined percentage discount off the total annual cost of the drug; however, the default value for this input was set to 0%.

4.3.7. Model Assumptions

The assumptions regarding the base-case analysis are detailed below.

Epidemiology

- The model assumes all patients diagnosed with schizophrenia are treated.

Market Share

- The market share data were adjusted to fit the comparators selected for this budget impact model. To do this, the market share assigned to a comparator of interest was divided by the sum of all the market shares for the comparators included.
- Latuda® takes market share away from each of the comparators based on the proportion of market share allocated in the current year.

Drug Costs

- Treatment duration is assumed to be one year (365 days).
- Co-pays are assigned for each 30.4-day period that drug is taken; in the base-case analysis, copays are assumed to be $0.
- Rebates are assigned as a percent discount on the annual cost of the drug; in the base-case analysis, rebates are assumed to be 0%.

4.3.8. Results

The projected annual drug budget impact for a health plan of 1 million enrollees, before and after addition of Latuda®, is presented in Table 94. The addition of Latuda® to the health plan formulary in year 1 resulted in an estimated decrease in the annual drug budget to $31,927,074 (an estimated cost-saving of $16,475) for the overall population. The estimated cost per member per year (PMPY) was $31.94 in the current year and $31.93 in year 1 (a net difference of -$0.02). The estimated cost per member per month (PMPM) was $2.66 in the current year and remained the same in year 1. The estimated cost per treated member per month (PTMPM) was $521.95 in the current year and $521.68 in year 1, a net difference of -$0.27. Overall, Latuda® demonstrated budget savings in the base-case analysis.

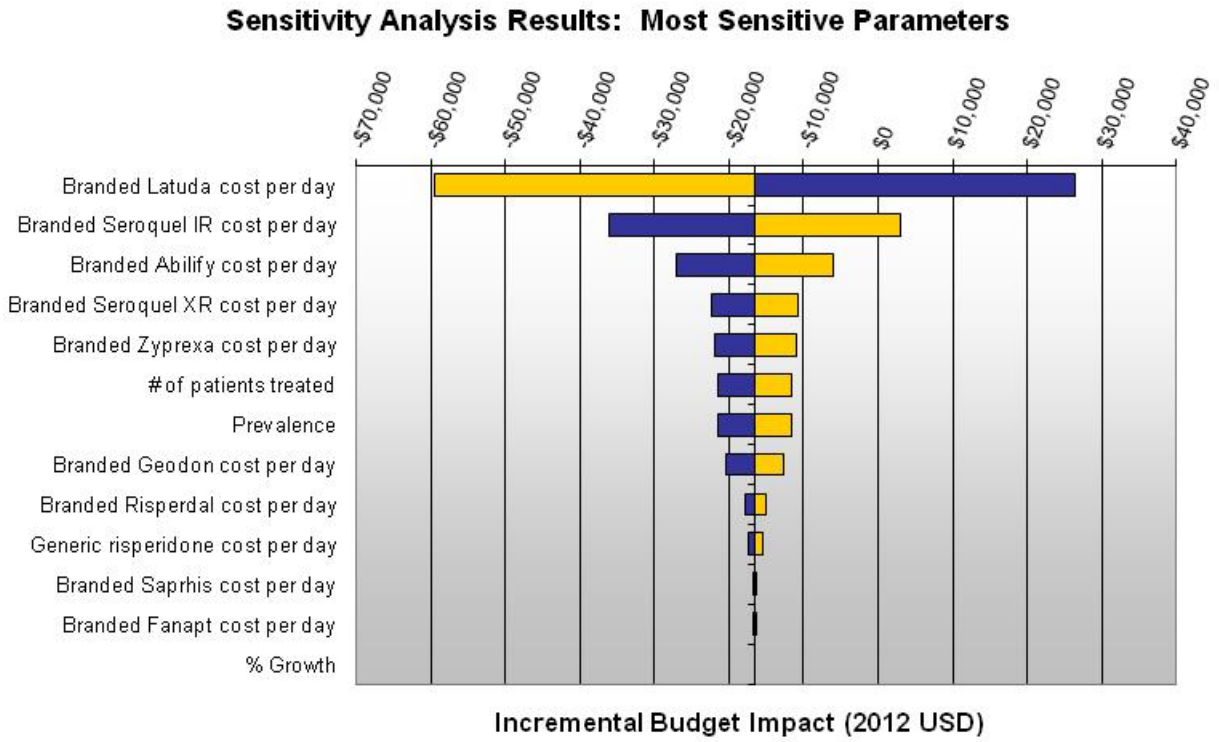
Table 94. Estimated Annual Budgetary Impact of Latuda® Treatment

Drug Budget	Current Formulary	Year 1	Difference
Total	$31,943,549	$31,927,074	-$16,475
PMPY	$31.94	$31.93	-$0.02
PMPM	$2.66	$2.66	$0.00
PTMPM	$521.95	$521.68	-$0.27

PMPY = per member per year, PMPM = per member per month, PTMPM = per treated member per month

Univariate sensitivity analyses were carried out to evaluate the impact of varying model parameters on the incremental change in the calculated costs and budget impact. Univariate sensitivity analyses are conducted by systematically varying one model input value while holding all other model input values constant. Key parameters included in the univariate sensitivity analyses were: (1) prevalence of schizophrenia, (2) the number of patients diagnosed and treated, and (3) the daily cost of all treatments included in the base case analysis. The sensitivity analyses considered a relative change of ± 30% from base-case value for all parameters. A tornado chart (Figure 10) compares the resulting change in the overall budget for year 1 compared to the current overall budget when each parameter value is either reduced or increased.

Figure 10. Univariate Sensitivity Analysis of Various Parameters for the Overall Population



Base case budget impact for year 1 relative to current year: -$16,475
Blue bars indicate the budget impact change if the base case value is increased.
Gold bars indicate the budget impact change if the base case value is decreased.
IR = immediate release, XR = extended release, USD = United States dollars, # = number, % = percent

- The model was not particularly sensitive to the number of patients treated or prevalence of schizophrenia because the same number of patients is treated in the current year and year 1; therefore, the variation in these parameters does not affect the annual total cost difference between the years.
- The base-case analysis results were most sensitive to a change in the price. Specifically, a ±30% variation in the unit cost of Latuda® [i.e., range of $10.77 to $20.01 (base-case unit cost, $15.39)] resulted in an incremental budget impact, ranging from -$59,448 to $26,497. The model was also sensitive to the variations in unit costs of other branded agents that had significant market share (Seroquel IR®, Abilify®, Seroquel XR®, Zyprexa®, and Geodon®).

4.3.9. Limitations

- The model assumes that all patients diagnosed are treated. This assumption was made out of necessity, as there were no available data regarding the percentage of diagnosed schizophrenia patients treated and untreated. While the model assumes all diagnosed patients were treated, some patients may refuse treatment after diagnosis. However, this is a conservative approach for a budget impact model, because this assumption will not lead to an underestimation of the costs and, therefore, the budget impact.

- There are numerous approaches to drug costing. The base-case analysis employs unit drug costs as reported by Redbook 2012; however, it should be noted that this approach may not reflect actual costs paid by health plan formularies due to variations in dose, discontinuation rates, and changes in current treatment patterns.. Future models with cost inputs based on daily consumption data, which incorporate dose intensity or medication possession ratio, may reflect drug utilization in this population more accurately.
- The base-case analysis assumed treatment duration of 365 days, without treatment gaps. Published literature suggests that patients frequently have treatment gaps which may reduce treatment duration per year. However, a consistent approach of applying universal treatment duration to all comparators was employed. Thus, the assumption does not bias the incremental budget impact results of adding Latuda® to the health plan formulary, but may equally overestimate this cost for all comparators.

4.3.10. Conclusions

The base-case analyses results suggest that over a one-year time horizon, the incremental budgetary impact of adding Latuda® to a health plan formulary for the management of schizophrenia may result in potential cost savings.

5. OTHER SUPPORTING EVIDENCE

5.1 Early Clinical Development Studies (Phase I/Ib Studies) **Page 194**

5.2 Humanistic Benefits (Post-Hoc/Secondary Analyses) **Page 203**

The following section summarizes data from early clinical development studies (Phase I studies) and post-hoc/secondary analyses, in order to provide further information on efficacy, safety/tolerability, and pharmacokinetic profile of lurasidone. The early clinical development studies described in this section include a food effect study, a dedicated QTc study, and a Phase Ib study that evaluated the efficacy and safety of lurasidone compared to ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. The post-hoc/scondary analyses summarized below were based on study D1050233 (PEARL 3) and include the following, cognition assessment based on Cogstate composite score analysis; quality-of-life assessment based on Quality of Well-Being scale, Self-Administered version (QWB-SA); and Epworth Sleepiness Scale (ESS) evaluation.

5.1. Early Clinical Development Studies (Phase I/Ib Studies)

5.1.1. Food Effect Study – (D1050267)

A Phase I, open-label study to determine the effect of calories and fat content on the pharmacokinetics of repeated dose lurasidone 120 mg in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder.[116]

Food-effect studies are usually conducted to assess the effects of food on the rate and extent of absorption of a drug when administered shortly after a meal, as compared to administration under fasting conditions

Study D1050267 was an open-label, randomized, repeat-dose, 6-period cross-over study that evaluated the effect of calorie and fat content on the steady-state pharmacokinetics of 120 mg lurasidone film-coated tablets in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder. Breakfast meals in various fat and calorie compositions were examined in this study. Lurasidone administered after a 10-hr fast was the reference treatment for all meal comparisons. Patients (N = 26) were randomized to one of six sequences to receive each of the six treatments (fasted, low calorie/high-fat, medium-calorie/low-fat, medium-calorie/high-fat, high-calorie/low-fat, and high-calorie/high-fat, corresponding to treatments A, B, C, D, E, and F, respectively) during six treatment periods. Table 95 shows the meal conditions that were tested.

Table 95: Meal Conditions and Meal Composition

Calorie Content	Fat Content	
	Low (15% of total calories)	High (50% of total calories)
Low (350 calories)	-	Treatment A[a] and Treatment B
Medium (500 calories)	Treatment C	Treatment D
High (800 to 1000 calories)	Treatment E	Treatment F

Note: While the percent content of carbohydrate in all breakfasts varied across treatment, the protein content was approximately 15% of total calories.

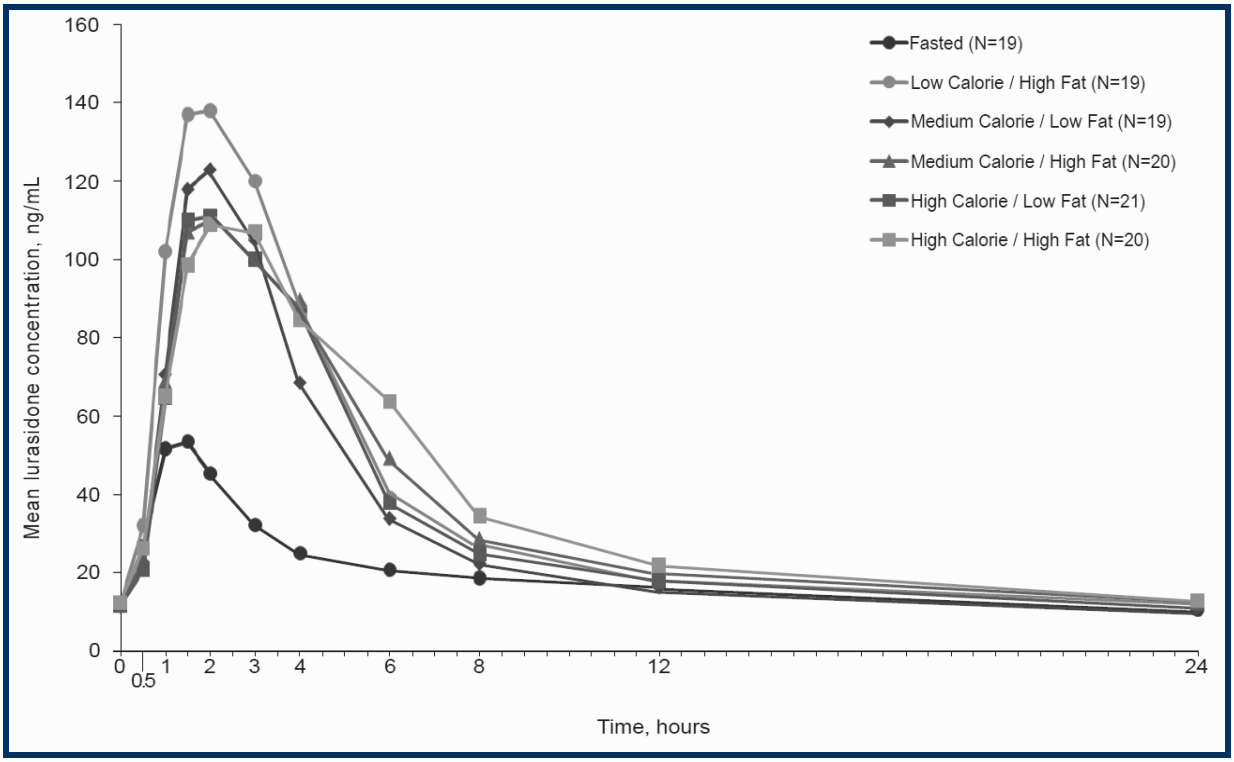
[a] Days 1 and 2 were fed conditions; and Days 3, 4, and 5 were fasted conditions.

Patients were administered lurasidone 120 mg once daily for a total of 30 days, 5 days each for one of six meal conditions. Breakfast was served 30 minutes prior to the planned dosing. There was no washout between treatments. Pharmacokinetic data obtained under the five fed conditions (Treatments B through F) were compared to that obtained under fasted conditions (Treatment A) to determine the effect of calorie and fat content on the pharmacokinetics of lurasidone. Serial blood samples were collected for lurasidone following the final dose on Day 5 of each treatment period to determine the steady-state PK parameters of lurasidone for each meal condition. Pharmacokinetic parameters evaluated included C_{max}, time to maximum concentration (t_{max}), and AUC over a dosing interval for steady state ($AUC_{0\text{-}tau}$), i.e., from time 0 to 24 hours.

The C_{max} and $AUC_{0\text{-}tau}$ for lurasidone were distinctly increased when administered under fed compared to fasted conditions but appeared essentially independent of meal composition. Mean

lurasidone concentration-time profiles after multiple dose administration of lurasidone 120 mg under fasted and fed conditions are shown in Figure 11.

Figure 11: Mean Lurasidone Concentration-time Profiles After Multiple-dose Administration of Lurasidone 120 mg Under Fasted and Fed Conditions



Meal composition (low, medium, or high-calorie and/or low versus high-fat content) had little effect on the magnitude of increase in lurasidone exposure. The 90% confidence intervals (CIs) of the geometric mean ratio of all fed to fasted comparisons fell entirely outside of the 80% to 125% range for both $AUC_{0\text{-}tau}$ and C_{max}. The geometric least-squares means for $AUC_{0\text{-}tau}$ increased by approximately 1.65 to 1.97 fold when lurasidone was administered under the various fed conditions while the geometric least-squares means for C_{max} increased by approximately 2.41 to 3.05 fold (Table 96). While increases in overall exposure ($AUC_{0\text{-}tau}$) appeared to be slightly higher following a meal with high-fat content (low-calorie/high-fat [1. fold], medium-calorie/high-fat [1.86 fold], and high-calorie/high-fat [1.97 fold]) compared to a meal with low-fat content (medium-calorie/low-fat [1.65 fold] and high-calorie/low-fat [1.77 fold]), increases in C_{max} did not appear to be related to meal composition.

Table 96: Ratios (with 90%-CIs) for Lurasidone PK Parameters Under Fed/Fasted Conditions

Meal Condition	$AUC_{0\text{-}tau}$ (ng•hr/mL)		C_{max} (ng/mL)	
	Geometric LS mean	Fed/Fasted ratio, % [90%-CI]	Geometric LS mean	Fed/Fasted ratio, % [90%-CI]
Fasted (A)	390	---	52.9	---
Low-calorie/ High-fat (B)	743	190.5 [175.4, 206.9]	161	305.0 [267.6, 347.6]
Medium-calorie/ Low-fat (C)	642	164.6 [151.6, 178.8]	149	281.3 [246.9, 320.6]
Medium-calorie/ High-fat (D)	727	186.5 [171.7, 202.5]	135	255.2 [224.0, 290.7]
High-calorie/ Low-fat (E)	691	177.3 [163.3, 192.5]	128	241.0 [211.7, 274.4]
High-calorie/ High-fat (F)	769	197.2 [181.6, 214.0]	131	248.4 [218.1, 282.9]

Median lurasidone t_{max} did not increase compared to fasting conditions when lurasidone was administered with a low-calorie/high-fat (Treatment B) or a medium-calorie/low-fat (Treatment C) breakfast. However, median lurasidone t_{max} increased by 0.5 to 1.0 hours compared to fasting conditions when lurasidone was administered with either a medium-calorie/high-fat (Treatment D), a high-calorie/low-fat (Treatment E), or a high-calorie/high-fat (Treatment F) breakfast.

The lurasidone treatments administered under fasting or fed conditions were generally well tolerated. Five patients withdrew due to non-serious adverse events (AEs) of nausea (two patients), akathisia, acute dystonia, and worsening of schizoaffective disorder. The most frequently occurring treatment-emergent adverse events (two or more patients) were nausea (9/26, 34.6%), akathisia (9/26, 34.6%), somnolence (9/26, 34.6%), sedation (7/26, 26.9%), vomiting (4/26, 15.4%), dystonia (4/26, 15.4%), anxiety (3/26, 11.5%), and dizziness (2/26, 7.7%). Overall, there were no trends or clinically significant changes noted in mean or median clinical laboratory, vital sign, or ECG data following dosing.

5.1.2. QTc Study – (D1050249)

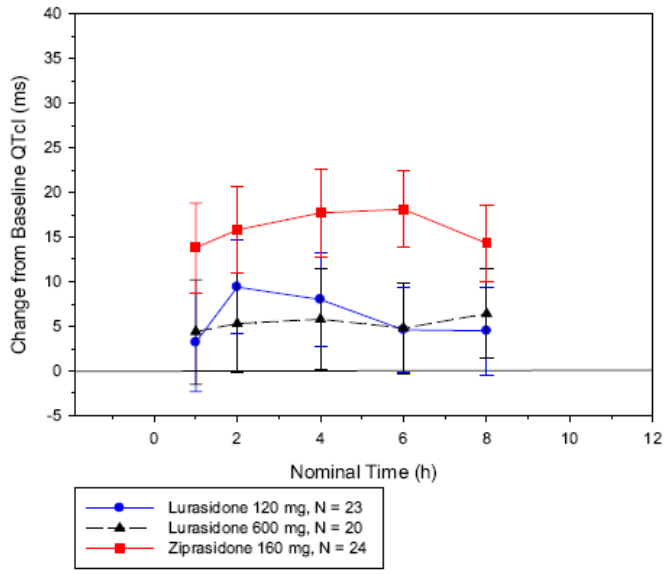
A double-blind, double-dummy, active controlled, randomized, 3-arm, parallel study to evaluate the effects of therapeutic and supratherapeutic doses of lurasidone on QTc interval in male and female schizophrenic or schizoaffective patients.[117]

Study D1050249 was a double-blind, double-dummy, randomized, three-arm, parallel study in male and female schizophrenic or schizoaffective patients to evaluate the effects of two doses of lurasidone and one dose (titrated to 160 mg total daily dose) of ziprasidone, as a positive control, on QTc interval. The two doses of lurasidone included a therapeutic 120 mg dose administered once daily without titrations and a supratherapeutic dose titrated to a total daily dose of 600 mg. The primary endpoint of this study was change in QTc corrected from baseline. The QT interval was

corrected for heart rate using different methods: Fridericia's correction (QTcF), Bazett's correction (QTcB), individual subject correction (QTcI), population based correction (QTcP), and model-based correction. QTcI was selected as the primary variable.

A total of 87 patients (67 male and 20 female) were enrolled in this study and received at least one dose of study drug. Of these, 73 patients received all doses of study drug and completed all study procedures. The LS mean and 90% CI for time-matched change-from-baseline QTcI (dQTcI) at each protocol-specified time-point for all 3 study arms are depicted in Figure 12.

Figure 12: Least-squares Mean dQTcI with 90% CI for Each Treatment



Note(s): CI=confidence interval.
Analyzed value is for average of the replicates at each timepoint on Day 11 minus the average of the replicates of each corresponding timepoint on Day 0.
Results are based on a linear mixed-effect model, with treatment, time, and interaction of treatment by time plus covariates for gender, time-matched baseline value, and prior exposure to aripiprazole with time as a repeated measure. Covariance structure: UN.

In the lurasidone 120-mg study arm, dQTcI increased between 1-hour to 2-hour post-dose. Thereafter, a trend in declining dQTcI was observed between 2-hour to 8-hour post-dose. The upper bound of the two-sided 90% CI was greater than 10 ms at 2-hour and 4-hour post-dose. In the lurasidone 600 mg study arm, the dQTcI versus time profile remained relatively constant with small fluctuations during 8 hours post-dose. The upper bound of the two-sided 90% CI was greater than 10 ms at 1-hour, 2-hour, 4-hour and 8-hour post-dose. At the supratherapeutic lurasidone dose (600 mg), the time-matched least-squares mean dQTcI values were generally similar to or lower than the therapeutic dose (120 mg). In the lurasidone 120-mg study arm, the maximum upper bound of the two-sided 90% CI dQTcI of 14.7 ms occurred at 2-hour post-dose at which time the mean change from baseline was 9.4 ms. In the lurasidone 600-mg study arm, the maximum upper bound of the two-sided 90% CI of 11.5 ms occurred at 4-hour post-dose at which time the mean change from baseline was 5.8 ms. In the positive control ziprasidone 160 mg study arm, the maximum upper bound of the two-sided 90% CI dQTcI of 22.6 ms occurred at 4-hour post-dose at which time the mean change from baseline was 17.7 ms. The time-matched least-squares mean dQTcI values in the ziprasidone 160-mg study arm were higher than those in both lurasidone study arms at all time-points.

The number and percentage of clinically noteworthy absolute QTcI and dQTcI values on Day 0 and Day 11 in each study arm are summarized in Table 97.

Table 97: Summary of Clinically Noteworthy QTcI and dQTcI (msec)

Study Day	Outlier Criteria	Lurasidone 120 mg (N=23)	Lurasidone 600 mg (N=20)	Ziprasidone 160 mg (N=24)
0	Max QTcI >500 ms	0 (0%)	0 (0%)	0 (0%)
	Max QTcI >480 ≤500 ms	0 (0%)	0 (0%)	0 (0%)
	Max QTcI >450 ≤480 ms	0 (0%)	0 (0%)	0 (0%)
11	Max QTcI >500 ms	0 (0%)	0 (0%)	0 (0%)
	Max QTcI >480 ≤500 ms	0 (0%)	0 (0%)	0 (0%)
	Max QTcI >450 ≤480 ms	0 (0%)	0 (0%)	1 (4.2%)
	Max dQTcI >60 ms	0 (0%)	0 (0%)	0 (0%)
	Max dQTcI >30 ≤60 ms	0 (0%)	0 (0%)	4 (16.7%)

dQTcI: time-matched change from baseline QTcI; Max: maximum: ms: milliseconds.

In this study no patients treated with lurasidone experienced QTc increases >60 msec from baseline, nor did any patient experience a QTc of >500 msec.

It is important to note that electrocardiogram (ECG) measurements were taken at various time points during the overall lurasidone clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with lurasidone. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.[1]

5.1.3. Phase Ib Study – (D1050254)

Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder.[118,119]

Study D1050254 was a 3 week, randomized, double-blind, fixed-dose, parallel-group study designed to evaluate the safety and tolerability profile of lurasidone (120 mg/day, n=150) and an active comparator ziprasidone (160 mg/day, n=151) in clinically stable outpatients with chronic schizophrenia or schizoaffective disorder. The study consisted of three phases: taper off of prior antipsychotics (3-5 days), placebo run-in period (1-3 days), and double-blind treatment (21 days). A total of 307 patients met entry criteria and were randomized to either 80 mg once daily lurasidone, to be increased to 120 mg once daily on Day 4, or 40 mg twice daily ziprasidone, increased to 80 mg twice daily on Day 4, in a 1:1 ratio. The primary safety endpoints were the proportion of patients with treatment-emergent adverse events (TEAEs), laboratory abnormalities, discontinuations due to

adverse events (AEs), and serious adverse events (SAEs). The efficacy related analyses were secondary. Efficacy endpoints included the mean change from baseline in: Positive and Negative Syndrome Scale (PANSS) total score, positive, negative, and general psychopathology subscale scores; Clinical Global Impressions-Severity scale (CGI-S), Calgary Depression Scale for Schizophrenia (CDSS), Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), and the Schizophrenia Cognition Rating Scale (SCoRS).

Eligible patients were between 18 and 70 years, inclusive, met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for the primary diagnosis of schizophrenia or schizoaffective disorder, and had duration of illness of ≥6 months. Patients were excluded, among other things, if they were in the midst of an acute exacerbation of psychosis, required inpatient treatment within 3 months prior to baseline visit, pregnant, and had clinically significant acute of chronic medical illness of abnormal ECG parameters.

A total of 210 patients (68%) completed the study. The number of patients completing the study in each treatment group was similar; 104 patients (68%) in the lurasidone treatment group and 106 patients (69%) in the ziprasidone treatment group. The most common reasons for discontinuation included clinical adverse events (n=33), loss to follow-up (n=21), and withdrawal of consent (n=16). There were no between-group differences in any baseline characteristics, including scores for the individual tests of the MCCB and for the SCoRS global score as described in Table 98.

Table 98: Baseline Characteristics, Study D1050254, Safety Population

Baseline Characteristic	Lurasidone 120 mg N=150	Ziprasidone 160 mg N=151
Sex, n (%) Male	105 (70)	107 (71)
Age, years, Mean (Range)	43.3 (19-62)	43.5 (18-65)
Race, n (%), White	51 (34)	53 (35)
DSM-IV diagnosis, n (%), Schizophrenia	125 (83)	130 (86.1)
DSM-IV diagnosis, n (%), Schizoaffective disorder	24 (16)	21 (14)
Age at first psychotic episode, years, mean (SD)	22.8 (8.2)	23.4 (8.9)
MCCB, mean (SD)	0.031 (0.972)	-0.038 (1.039)
SCoRS, mean (SD)	4.9 (2.0)	4.9 (2.1)

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, SD = standard deviation, N = number of patients, MCCB = MATRICS Consensus Cognitive Battery, SCoRS = Schizophrenia Cognition Rating Scale

A total of 184 patients (61%) reported one or more TEAEs. The proportion of patients reporting one or more TEAEs was 56.7% in the lurasidone treatment group compared with 65.5% in the ziprasidone treatment group. The number of patients who discontinued treatment due to a TEAE was similar for the two treatment groups with 16 patients (10%) in the lurasidone treatment group and 17 patients (11%) in the ziprasidone treatment group. No study medication-related serious TEAEs were reported in either treatment group. One death from cardiac arrest, not related to study medication, was reported in the ziprasidone treatment group. The most frequently reported TEAE was insomnia, which was similar for the two treatment groups (10.7% in the lurasidone treatment group versus 9.3% in the ziprasidone treatment group). Somnolence, sedation, akathisia, and

dizziness, all tended to be more frequent (≥3% point difference) in the ziprasidone treatment group. The incidence of TEAEs reported in ≥5% of lurasidone and ziprasidone-treated patients are listed in Table 99.

Table 99: Incidence of TEAEs in ≥5% of Patients, Safety Population

TEAEs, N (%)	Lurasidone 120 mg N = 150	Ziprasidone 160 mg N = 151
Patients with at least one AE	**85 (56.7)**	**99 (65.6)**
Proportion of AEs rated as severe	**10 (6.7)**	**11 (7.3)**
Insomnia	16 (10.7)	14 (9.3)
Vomiting	12 (8.0)	6 (4.0)
Nausea	11 (7.3)	7 (4.6)
Headache	10 (6.7)	7 (4.6)
Somnolence	10 (6.7)	15 (9.9)
Sedation	7 (4.7)	17 (11.3)
Akathisia	5 (3.3)	10 (6.6)
Dizziness	4 (2.7)	10 (6.6)

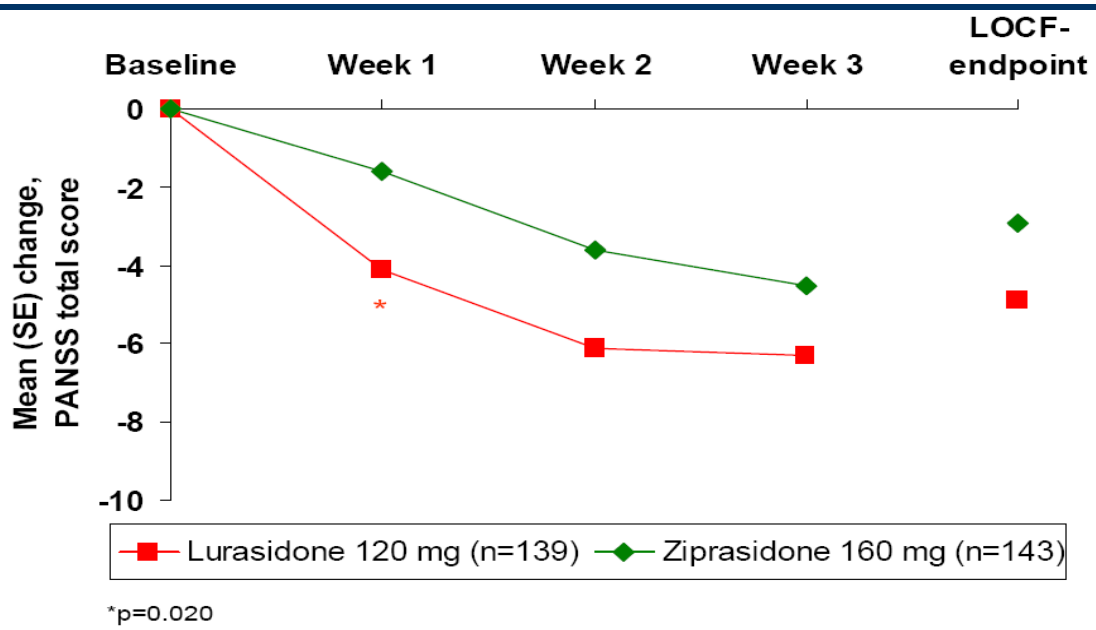
Percentages have been rounded to the nearest whole number.

Abbreviations: N = number of patients; TEAE = treatment-emergent adverse event; AE = adverse event.

Treatment with lurasidone and ziprasidone was associated with a small endpoint reduction in median weight (-0.65 kg vs. -0.35 kg) and median total cholesterol (-6.4 vs. -4.4 mg/dL), with no endpoint change observed in median triglycerides. The median increase in prolactin was 3.0 ng/mL for lurasidone and 2.0 ng/mL for ziprasidone, with a higher incidence of "marked" (defined as >36 ng/mL for males and >58 ng/mL for females) prolactin elevations in the lurasidone group compared with the ziprasidone group (n=41, 29% vs. n=21, 14%). Treatment with either lurasidone or ziprasidone had no clinically significant effects on blood glucose or HbA1c. There were no treatment-emergent abnormalities in ECG or QTc parameters among lurasidone or ziprasidone treated patients.

On a mixed model repeated measures (MMRM) analysis of the PANSS total score, improvement was observed for lurasidone and ziprasidone at Week 1 (-4.1 vs. -1.6; p=0.020), Week 2 (-6.1 vs. 3.6; p=0.074), and Week 3 (-6.3 vs. -4.5; p=0.229) [Figure 13].

Figure 13: Mean Change from Baseline in PANSS Total Score (MMRM Analysis Weeks 1-3; LOCF endpoint Change Based on ANCOVA)



Mixed model repeated measures (MMRM) analysis was used with fixed effects for pooled center, visit as a categorical variable, and treatment by visit interaction, assuming an unstructured covariance matrix. The statistical test of treatment effect on a particular time-point was based on a 1-degree of freedom contrast for the treatment-by-visit interaction effect with adjustment for the baseline score.
ANCOVA model, used to calculate LOCF-endpoint, included treatment and pooled center as fixed factors and Baseline PANSS total score as a covariate.
Abbreviations: LOCF = Last Observation Carried Forward; SE = standard error; PANSS = Postive and Negative Syndrome Scale; N = number of patients; ANCOVA = Analysis of Covariance.

A summary of other efficacy endpoint results are included in Table 100.

Patients in the lurasidone treatment group demonstrated significant within-group improvement from baseline on the MATRICS Concensus Cognitive Battery (MCCB) composite score (p=0.026) and on the SCoRS (p<0.001) compared to ziprasidone treated patients who did not improve on either the MCCB composite (p=0.254) or the SCoRS (p=0.185). There was a statistical trend (p=0.058) for lurasidone to demonstrate greater improvement from baseline to endpoint than ziprasidone in SCoRS ratings.

Table 100: LS Mean Change at LOCF-endpoint from Baseline to Week 3 (ANCOVA Analysis)

Endpoint[a]	Lurasidone 120 mg N=150	Ziprasidone 160 mg N=151
PANSS Total Score	**N = 139**	**N = 143**
Change from baseline to week 3 LOCF	-4.9	-2.9
p-value	0.145	
PANSS Positive Symptoms	**N = 139**	**N = 143**
Change from baseline to week 3 LOCF	-1.5	-1.2
p-value	0.464	
PANSS Negative Symptoms	**N = 139**	**N = 143**
Change from baseline to week 3 LOCF	-1.3	-0.6
p-value	0.046	
CGI-S	**N = 139**	**N = 144**
Change from baseline to week 3 LOCF	-0.1	-0.1
p-value	0.905	
CDSS	**N = 128**	**N = 134**
Change from baseline to week 3 LOCF	-0.4	-0.7
p-value	0.261	
MATRICS	**N = 118**	**N = 121**
Change from baseline to week 3 LOCF	0.162	0.117
p-value	0.538	
SCoRS	**N = 116**	**N = 121**
Change from baseline to week 3 LOCF	-0.5	-0.2
p-value	0.161	

[a] Baseline is defined as the last measurement collected prior to or on the date of randomization; LOCF Endpoint is defined as the last post-Baseline measurement collected within 7 days after the last dose of study medication.

P–value is based on an ANCOVA model with treatment and pooled center as fixed factors and baseline as covariate.

Abbreviations: ANCOVA = Analysis of Covariance; CDSS = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impressions Severity Scale; ITT = intent–to-treat; LOCF = Last Observation Carried Forward; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; PANSS = Positive and Negative Syndrome Scale; SCoRS = Schizophrenia Cognition Rating Scale; SD = standard deviation; SE = standard error.

5.2. Humanistic Benefits (Post-Hoc/Secondary Analyses)

5.2.1. Cognition

Cognitive performance in patients with acute schizophrenia treated with lurasidone: a double-blind, placebo-controlled trial.[120]

Study D1050233 was a 6 week, multicenter, randomized, double-blind, placebo- and active controlled study to evaluate the efficacy and safety of lurasidone (80 mg/day and 160 mg/day) in patients with an acute exacerbation of schizophrenia. Quetiapine XR 600 mg/day was included as an active control to confirm assay sensitivity. For additional description of the study, please refer to Section 3.1.2. Cognitive performance was examined at baseline and after 6 weeks of treatment with the computerized CogState system, which has 7 cognitive tests, including the domains of episodic memory, processing speed, and social cognition. Cognitive improvement was assessed by the standardized CogState composite Z-score and domain test Z-scores. The CogState composite score was derived as average performance across all 7 primary domain task Z-scores (excluding their recall components). Both composite score and individual task scores were standardized to the Z-score scale with mean 0 and SD=1 based upon the normative data provided by CogState. Functional outcome was assessed by University of California San Diego (UCSD) Performance-Based Skills Assessment Brief Version (UPSA-B total score).

At Week 6, within group analysis showed a significant increase (LS mean ± SE) in composite scores in the lurasidone 80 mg group (0.18 ± 0.07, p=0.018), the lurasidone 160 mg group (0.14 ± 0.07, p=0.050), and the placebo group (0.17 ± 0.08, p = 0.031), indicating an overall improvement in cognitive function. There was no significant change in the quetiapine XR group (0.08 ± 0.07, p=0.279). There were no significant treatment differences comparing the lurasidone 80 mg group, the lurasidone 160 mg group, or the quetiapine XR group with the placebo group. There were no significant treatment differences comparing the lurasidone 80 mg group or the lurasidone 160 mg group with the quetiapine XR group. The only exception was a significant treatment difference (LS mean ± SE) observed for the verbal learning domain score: lurasidone 160 mg compared with placebo at LOCF Endpoint (0.31 ± 0.15, p=0.035), indicating an improvement in verbal learning. Treatment differences in UPSA-B total score were significant for Lurasidone 160 mg/d (p=0.011) and lurasidone 80 mg/d (p=0.036) compared to placebo. Quetiapine XR effect on UPSA-B total score was significant when comparing to placebo (p<0.001).

Task completion rates averaged 94%, but data integrity failures, based on pre-planned criteria, were noted in 899 tests out of a total of 7753 (481 patients) test assessments, resulting in a total of 215 patients (45%) with non-evaluable or incomplete CogState tests. When the entire intent-to-treat (ITT) sample was examined, there were no statistically significant differences in the CogState composite score between lurasidone dose groups, the active control and the placebo group. When patients whose data failed the pre-specified integrity checks were excluded, lurasidone at 160 mg was superior on the composite cognitive functioning measure to both placebo (p=0.05, d=0.25) and quetiapine XR (p<0.01, d=0.28), while quetiapine XR, lurasidone 80 mg, and placebo did not differ from each other.

5.2.2. Quality-of-Life

Effect of short-term treatment with lurasidone on quality of life in schizophrenia: results from the PEARL 3 (D1050233) trial.[121]

Study D1050233 was a 6 week, multicenter, randomized, double-blind, placebo- and active controlled study to evaluate the efficacy and safety of lurasidone (80 mg/day and 160 mg/day) in patients with an acute exacerbation of schizophrenia. Quetiapine XR 600 mg/day was included as an active control to confirm assay sensitivity. Patients who met DSM-IV criteria for schizophrenia were tapered off prior psychotropic medication and after a 3-7-day placebo washout period, were randomized to 6 weeks of double-blind treatment with lurasidone 80 mg (n=125), lurasidone 160 mg (n=121), quetiapine XR 600 mg (n=119), or placebo (n=121), administered once-daily. Quality of life was measured using the Quality of Well-Being scale, Self-Administered version (QWB-SA), assessing community mobility, physical activity, social activity, and subjective symptoms which include somatic, cognitive, and emotional symptoms. The QWB-SA is a preference-weighted questionnaire with a combined score ranging from 0 to 1.0 (death to optimal functioning). The objective of quality of life assessment was to evaluate the effect of lurasidone (80 mg/day and 160 mg/day) on well-being in patients with an acute exacerbation of schizophrenia.

At baseline, QWB-SA scores were similar for patients randomized to lurasidone 80 mg (0.572), lurasidone 160 mg (0.562), quetiapine XR (0.583), and placebo (0.581). On an endpoint ANCOVA analysis, there was significant improvement in the LS mean QWB-SA score compared to placebo (0.631) in the lurasidone 80 mg group (0.672; p=0.049), the lurasidone 160 mg group (0.710; p<0.001), and the quetiapine XR group (0.711; p<0.001). Results indicate that treatment with lurasidone, in once-daily doses of 80 mg and 160 mg, was associated with improvements in health-related quality of life in patients with an acute exacerbation of schizophrenia.

5.2.3. Epworth Sleepiness Scale (ESS)

Short-term treatment of acute schizophrenia with lurasidone vs. quetipiapine XR: effect on daytime sleepiness.[122]

A post-hoc evaluation of the study D1050233 evaluated the effect on daytime sleepiness of treatment with lurasidone 80 mg/day and 160 mg/day compared to quetiapine XR 600 mg/day in patients with an acute exacerbation of schizophrenia. Patients who met DSM-IV criteria for schizophrenia were randomized to 6-weeks of double-blind treatment with lurasidone 80 mg (N=125), lurasidone 160 mg (N=121), quetiapine XR (N=120), or placebo (N=122), administered once-daily in the evening. Study D1050233 is described further in Section 3.1. The effect of study medication on daytime sleepiness was measured using the patient-rated Epworth Sleepiness Scale (ESS); an 8-item self-rated questionnaire that assesses the level of daytime sleepiness on a 4-point scale, with higher scores indicated greater sedation. Scores on the ESS can range from 0 to 24; clinically significant levels of sleepiness are most commonly defined as a score of either ≥10 or ≥11.

At baseline, mean ESS scores were comparable for patients treated with lurasidone 80 mg (6.0), lurasidone 160 mg (6.0), quetiapine XR (6.0), and placebo (6.2). A reduction in ESS scores (less sedation) was observed at LOCF-endpoint among patients treated with lurasidone 80 mg (-1.1), lurasidone 160 mg (-0.7) and placebo (-0.9). In contrast, treatment with quetiapine XR was associated with a significant increase in ESS scores (increased sedation) compared to placebo (+0.6 vs. -0.9; p=0.001). There was no significant treatment difference in the lurasidone 80 mg group (-0.6; p=0.276) or the lurasidone 160 mg group (0.1; p = 0.784) compared with placebo. There was a

significant treatment difference in the quetiapine XR group (1.2; p=0.022) compared with the placebo group, indicating increased daytime sleepiness in the quetiapine XR group compared with placebo. The proportion of patients reporting somnolence and sedation, respectively, as an adverse event was 4.0% and 1.6% for the lurasidone 80 mg group, 6.6% and 1.7% for the lurasidone 160 mg group, 13.4% and 4.2% for the quetiapine XR group, and 0.8% and 9% for placebo.

6. APPENDIX 1 PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information for LATUDA.

LATUDA (lurasidone hydrochloride) tablets, for oral use
Initial U.S. Approval: 2010

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis (5.1).

RECENT MAJOR CHANGES

Dosage and Administration, Schizophrenia (2.1)	04/2012
Dosage and Administration, Dose Modifications in Special Populations (2.3)	04/2012

INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic indicated for the treatment of patients with schizophrenia (1). Efficacy was established in five 6-week controlled studies of adult patients with schizophrenia (14.1).

DOSAGE AND ADMINISTRATION

- The recommended starting dose of LATUDA is 40 mg once daily (2.1).
- The maximum recommended dose is 160 mg once daily (2.1).
- LATUDA should be taken with food (2.2).
- Moderate and severe renal impairment: Recommended starting dose is 20 mg and the maximum recommended dose is 80 mg (2.3).
- Moderate and severe hepatic Impairment: Recommended starting dose is 20 mg. The maximum recommended dose is 80 mg in moderate hepatic impairment and 40 mg in severe hepatic impairment (2.3).
- Concomitant use with a moderate CYP3A4 inhibitor (e.g., diltiazem): Recommended starting dose is 20 mg and the maximum recommended dose is 80 mg (2.4, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, 40 mg, 80 mg and 120 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to LATUDA or any components in the formulation (4).
- Concomitant use with a strong CYP3A4 inhibitor (e.g., ketoconazole) (4, 7.1)
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (4, 7.1).

WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions: An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs. (5.2).
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.3).
- Tardive Dyskinesia: Discontinue if clinically appropriate (5.4).
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.5).
  - *Hyperglycemia and Diabetes Mellitus:* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
  - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics.
  - *Weight Gain:* Gain in body weight has been observed; clinical monitoring of weight is recommended.
- Hyperprolactinemia: Prolactin elevations may occur (5.6).
- Leukopenia, Neutropenia, and Agranulocytosis: have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia: Monitor complete blood count (CBC) frequently during the first few months of therapy and discontinue LATUDA at the first sign of a decline in WBC in the absence of other causative factors (5.7).
- Orthostatic Hypotension and Syncope: Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients (5.8).

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) included somnolence, akathisia, nausea and parkinsonism (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use LATUDA during pregnancy only if the potential benefit justifies the potential risk (8.1).
- Nursing Mothers: Discontinue drug or nursing, considering risk of drug discontinuation to the mother (8.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING:
INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Schizophrenia
2.2 Administration Instructions
2.3 Dose Modifications in Special Populations
2.4 Dose Modification due to Drug Interactions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis
5.3 Neuroleptic Malignant Syndrome
5.4 Tardive Dyskinesia
5.5 Metabolic Changes
5.6 Hyperprolactinemia
5.7 Leukopenia, Neutropenia and Agranulocytosis
5.8 Orthostatic Hypotension and Syncope
5.9 Seizures
5.10 Potential for Cognitive and Motor Impairment
5.11 Body Temperature Regulation
5.12 Suicide
5.13 Dysphagia
5.14 Use in Patients With Concomitant Illness
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Potential for Other Drugs to Affect LATUDA
7.2 Potential for LATUDA to Affect Other Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Other Patient Factors
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
10 OVERDOSAGE
10.1 Human Experience
10.2 Management of Overdosage
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Schizophrenia
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
17.2 Neuroleptic Malignant Syndrome
17.3 Hyperglycemia and Diabetes Mellitus
17.4 Orthostatic Hypotension
17.5 Leukopenia/Neutropenia
17.6 Interference with Cognitive and Motor Performance
17.7 Pregnancy and Nursing
17.8 Concomitant Medication and Alcohol
17.9 Heat Exposure and Dehydration

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death *[See Warning and Precautions (5.1)]*.**
- **LATUDA is not approved for use in patients with dementia-related psychosis *[See Warning and Precautions 5.1)]*.**

1 INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies (14.1)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 160 mg/day [*see Clinical Studies (14.1)*]. The maximum recommended dose is 160 mg/day.

2.2 Administration Instructions

LATUDA should be taken with food (at least 350 calories) [*see Clinical Pharmacology (12)*].

2.3 Dose Modifications in Special Populations

Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg. The dose in these patients should not exceed 80 mg/day *[see Use in Specific Populations (8)]*.

Hepatic Impairment

Dose adjustment is recommended in moderate (Child Pugh Score = 7 to 9) and severe hepatic impairment (Child Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg. The dose in moderate hepatic impairment patients should not exceed 80 mg/day and the dose in severe hepatic impairment patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

2.4 Dose Modifications Due to Drug Interactions

Concomitant Use with Potential CYP3A4 Inhibitors

The dose of LATUDA should not exceed 80 mg/day in combination with a moderate CYP3A4 inhibitor such as diltiazem.. LATUDA should not be used in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole) *[see Contraindications (4); Drug Interactions (7.1)]*.

Concomitant Use with Potental CYP3A4 Inducers

LATUDA should not be used in combination with a strong CYP3A4 inducer (e.g., rifampin) *[see Contraindications (4); Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing:

Table 1: LATUDA Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
20 mg	white to off-white round	L20
40 mg	white to off-white round	L40
80 mg	pale green oval	L80
120 mg	white to off-white oval	L120

4 CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [*see Adverse Reactions (6.1)*].
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) *[see Drug Interactions (7.1)]*.
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin) [*see Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%,

compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis [*see Boxed Warning*].

5.2 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential rcintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however,

some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Pooled data from short-term, placebo-controlled studies are presented in Table 2.

Table 2: Change in Fasting Glucose

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
	Mean Change from Baseline (mg/dL)					
	n=680	**n=71**	**n=478**	**n=508**	**n=283**	**n=113**
Serum Glucose	-0.0	-0.6	2.6	-0.4	2.5	2.5
	Proportion of Patients with Shifts to ≥ 126 mg/dL					
Serum Glucose (≥ 126 mg/dL)	8.3% (52/628)	11.7% (7/60)	12.7% (57/449)	6.8% (32/472)	10.0% (26/241)	5.6% (6/108)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 3.

Table 3: Change in Fasting Lipids

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
	Mean Change from Baseline (mg/dL)					
	n=660	**n=71**	**n=466**	**n=499**	**n=268**	**n=115**
Total cholesterol	-5.8	-12.3	-5.7	-6.2	-3.8	-6.9
Triglycerides	-13.4	-29.1	-5.1	-13.0	-3.1	-10.6
	Proportion of Patients with Shifts					
Total cholesterol (≥ 240 mg/dL)	5.3% (30/571)	13.8% (8/58)	6.2% (25/402)	5.3% (23/434)	3.8% (9/238)	4.0% (4/101)
Triglycerides (≥ 200 mg/dL)	10.1% (53/526)	14.3% (7/49)	10.8% (41/379)	6.3% (25/400)	10.5% (22/209)	7.0% (7/100)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled studies are presented in Table 4. The mean weight gain was 0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was 4.15 kg and for quetiapine extended-release was 2.09 kg in Studies 3 and 5 [*see Clinical Studies (*14.1*)*], respectively. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

Table 4: Mean Change in Weight (kg) from Baseline

		LATUDA				
	Placebo (n=696)	**20 mg/day (n=71)**	**40 mg/day (n=484)**	**80 mg/day (n=526)**	**120 mg/day (n=291)**	**160 mg/day (n=114)**
All Patients	-0.02	-0.15	0.22	0.54	0.68	0.60

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

In short-term, placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was 0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 5.

Table 5: Median Change in Prolactin (ng/mL) from Baseline

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	3.3 (n=284)	3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	6.7 (n=70)	7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	3.1 (n=214)	2.4 (n=79)

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of

female patients with prolactin elevations ≥ 5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=307).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology (13)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

5.7 Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < $1000/mm^3$) should discontinue LATUDA and have their WBC followed until recovery.

5.8 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0%]. Assessment of orthostatic hypotension was defined by vital sign changes (≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g. dehydration, hypovolemia, and treatment with antihypertensive medications), and in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), or cerebrovascular disease.

5.9 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

In short-term, placebo-controlled trials, seizures/convulsions occurred in 1.0% (2/1508) of patients treated with LATUDA compared to 0.1% (1/455) placebo-treated patients.

5.10 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with LATUDA, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions (5.8)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from a clinical study database for LATUDA consisting of 2905 patients with schizophrenia exposed to one or more doses with a total experience of 985.3 patient-years. Of these patients, 1508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. A total

of 769 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 6.

Table 6: Adverse Reaction in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class **Dictionary-derived Term**	**Placebo** **(N=708)**	**All LATUDA** **(N=1508)**
Gastrointestinal Disorders		
Nausea	5	10
Vomiting	6	8
Dyspepsia	5	6
Salivary Hypersecretion	<1	2
Musculoskeletal and Connective Tissue Disorders		
Back Pain	2	3
Nervous System Disorders		
Somnolence*	7	17
Akathisia	3	13
Parkinsonism**	5	10
Dizziness	2	4
Dystonia***	<1	5
Psychiatric Disorders		
Insomnia	8	10
Agitation	4	5
Anxiety	4	5
Restlessness	1	2

Note: Figures rounded to the nearest integer

* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

*** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

Dose-Related Adverse Reactions

In pooled data from the short-term, placebo-controlled, fixed-dose studies, there were no dose-related adverse reactions (greater than 5% incidence) in patients treated with LATUDA across the 20 mg/day to 160 mg/day dose range. However, the frequency of akathisia increased with dose up to 120 mg/day (5.6% LATUDA 20 mg, 10.7% LATUDA 40 mg, 12.3% LATUDA 80 mg, 22.0% LATUDA 120 mg); akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo.

Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 7.

Table 7: Incidence of EPS Compared to Placebo

		LATUDA				
Adverse Event Term	**Placebo (N=709) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/Restlessness	**7**	**6**	**14**	**13**	**24**	**14**
Akathisia	3	6	11	12	22	7
Dystonia*	<1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%) and the SAS (LATUDA, 5.0%; placebo, 2.3%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2905 patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 6 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia;*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye Disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis,*

General Disorders and Administrative Site Conditions: ***Rare****: sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolism and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent****: cerebrovascular accident, dysarthria,* *Psychiatric Disorders:* ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;*

Renal and Urinary Disorders: ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

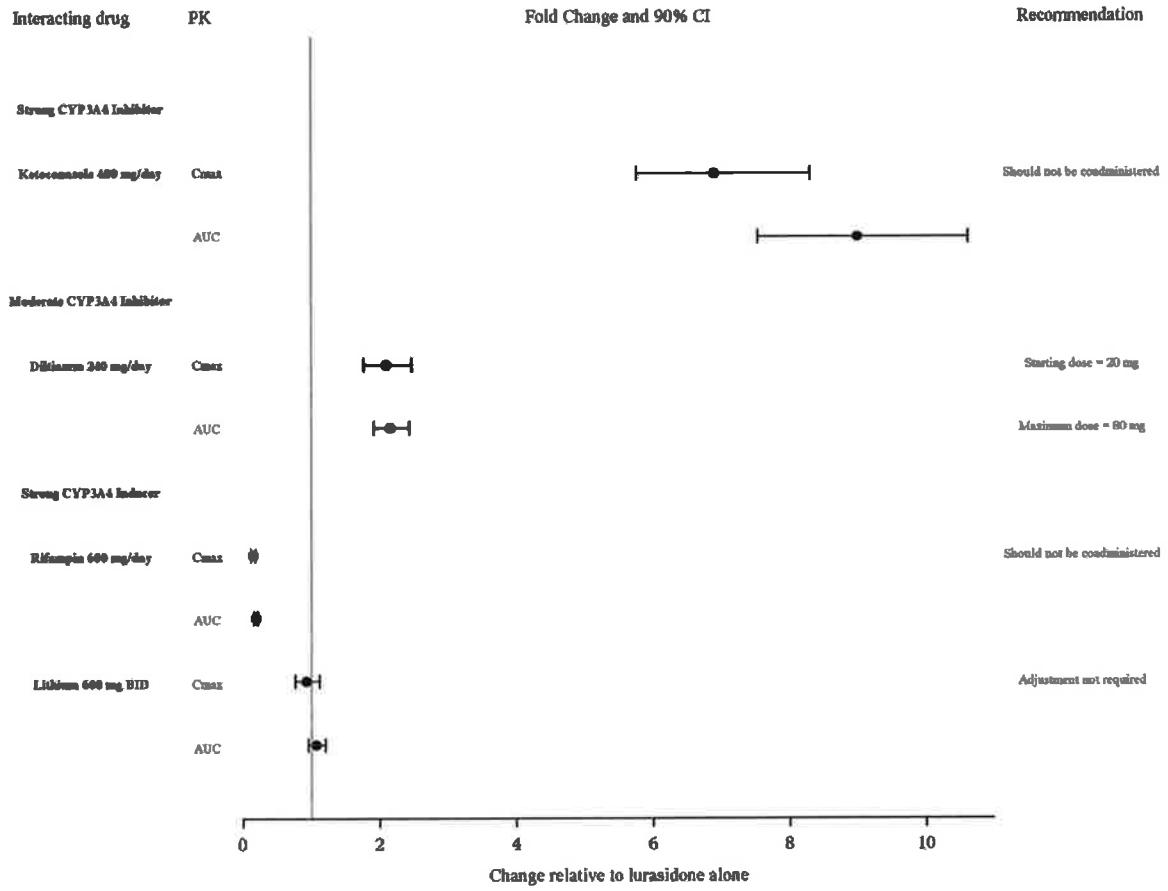
Vascular Disorders: ***Frequent:*** *hypertension;*

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications* (4)*]* and dose should be limited when used in combination with moderate inhibitors of CYP3A4 *[see Dosage and Administration* (2.4)]. No dose adjustment is needed with concomitant use of lithium (see Figure 1*)*.

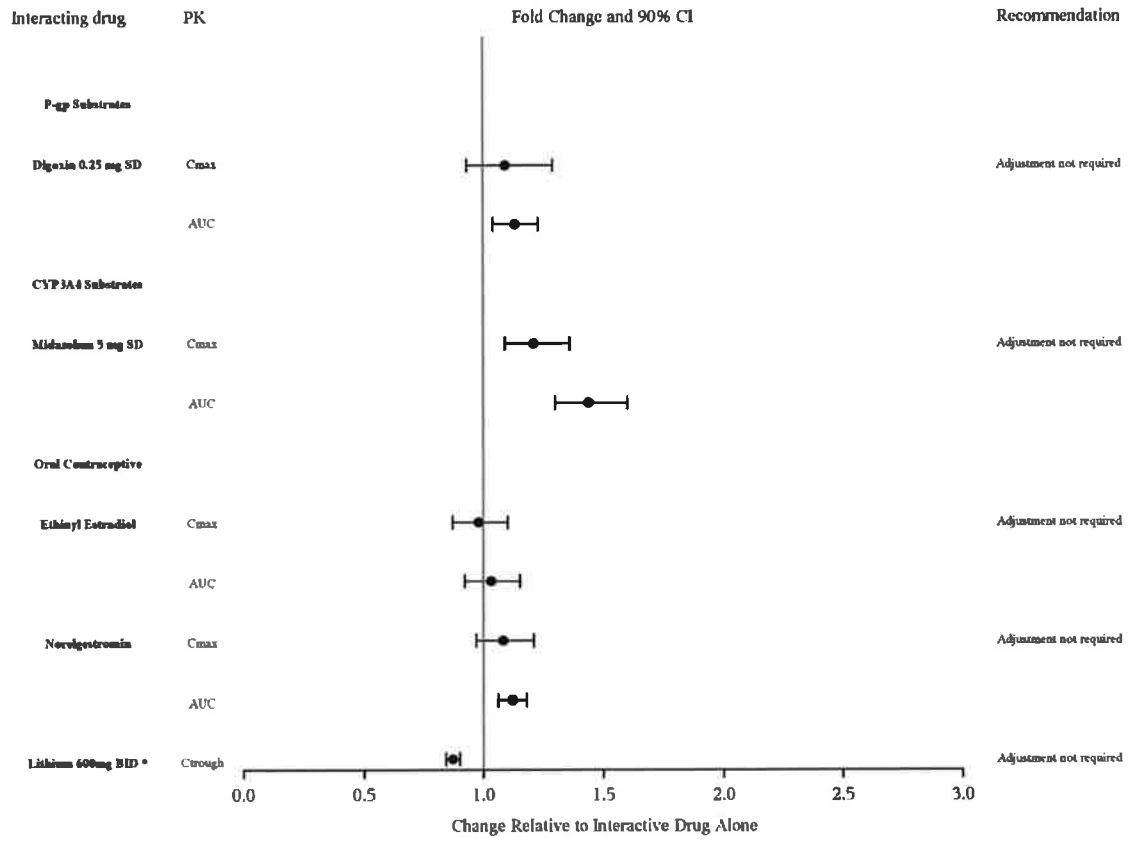
Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed on the dose of lithium, or substrates of P-gp or CYP3A4 when coadministered with LATUDA (Figure 2).

Figure 2: Impact of LATUDA on Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in

these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were seen in a study in which pregnant rats were given LATUDA during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately half of the MRHD based on body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given LATUDA during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5 and 6 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 160 mg/day based on body surface area.

8.3 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

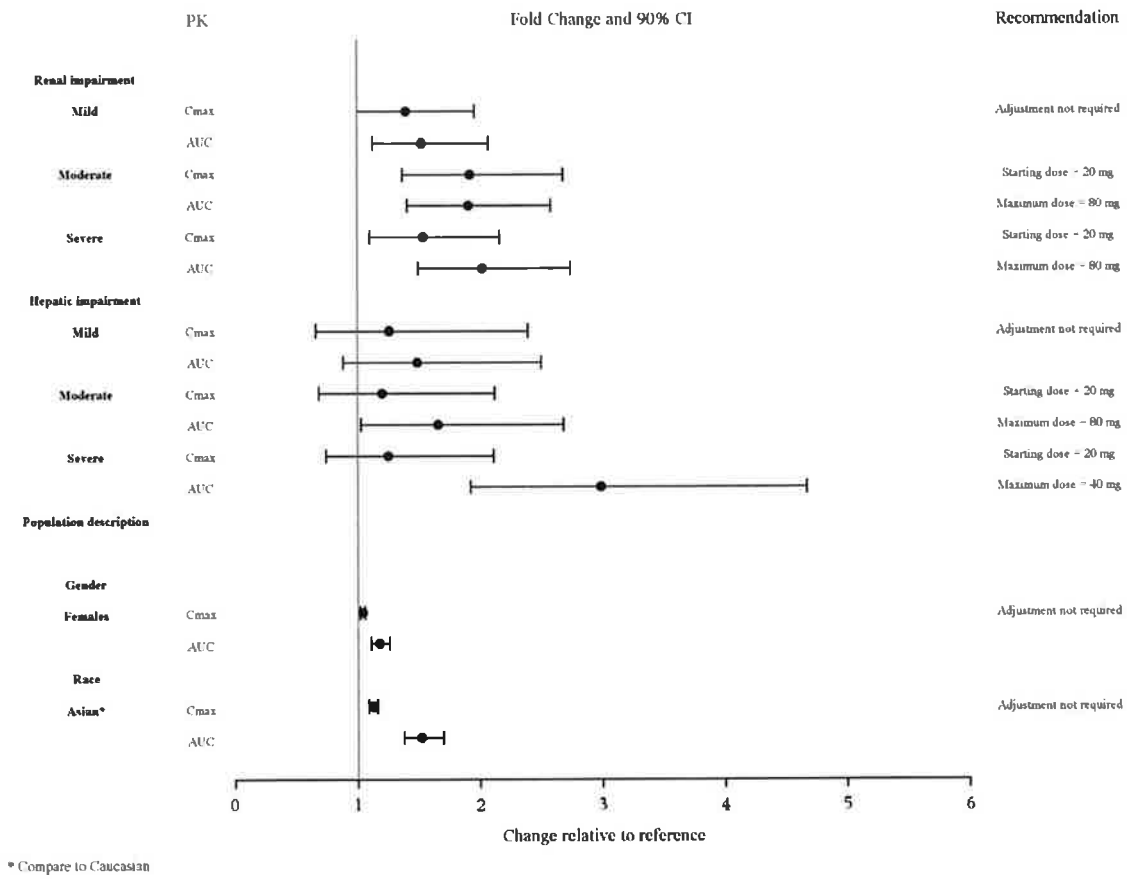
Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology (*12.3*)]*. No dose adjustment is necessary in elderly patients (Figure 2).

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6 Other Patient Factors

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics



9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LATUDA is not a controlled substance.

9.2 Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies involving 2905 patients, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

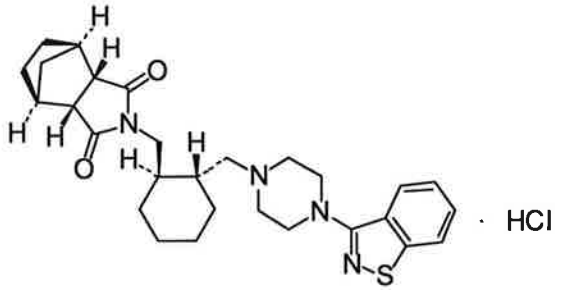
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11 DESCRIPTION

LATUDA is an atypical antipsychotic belonging to the chemical class of benzisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is $C_{28}H_{36}N_4O_2S{\cdot}HCl$ and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, 80 mg, or 120 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No.2 Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the mechanism of action of LATUDA is unknown, the efficacy of LATUDA in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

LATUDA is an antagonist with high affinity binding at the dopamine D_2 receptors (Ki=0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors $5\text{-}HT_{2A}$ (Ki=0.47 nM) and $5\text{-}HT_7$ (Ki=0.495 nM) receptors. It also binds with moderate affinity at the human α_{2C} adrenergic receptors (Ki=10.8 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (Ki=6.38 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (Ki=40.7 nM). LATUDA exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} > 1,000 nM).

ECG Changes

The effects of LATUDA on the QTc interval were evaluated in a randomized, double-blind, multiple-dose, parallel dedicated thorough QT study in 43 patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively, observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship.

In short-term, placebo-controlled studies, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

Changes in Laboratory Tests

There were no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry.

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study [*see Dosage in Special Populations (2.3); Use in Specific Populations (8)]*.

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.6% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.0%, respectively).

12.3 Pharmacokinetics

The activity of LATUDA is primarily due to the parent drug. The pharmacokinetics of LATUDA is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of LATUDA are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

Absorption and Distribution: LATUDA is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed. Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. LATUDA is highly bound (~99%) to serum proteins.

In a food effect study, LATUDA mean C_{max} and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions]. LATUDA exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content [see *Dosage and Administration (2.2)*].

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food [*see Dosage and Administration (2.2)*].

Metabolism and Elimination: LATUDA is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. LATUDA is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220). Based on in vitro studies LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. Because LATUDA is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of LATUDA.

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [^{14}C]-labeled LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: LATUDA increased incidences of malignant mammary gland tumors and pituitary gland adenomas in female mice orally dosed with 30, 100, 300, or 650 mg/kg/day. The lowest dose produced plasma levels (AUC) approximately equal to those in humans receiving the MRHD of 160 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 14 times those in humans receiving the MRHD.

LATUDA increased the incidence of mammary gland carcinomas in females rats orally dosed at 12 and 36 mg/kg/day: the lowest dose; 3 mg/kg/day is the no effect dose which produced plasma levels (AUC) 0.4 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to highest dose tested, which produced plasma levels (AUC) 6 times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents to humans is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis: LATUDA did not cause mutation or chromosomal aberration when tested in vitro and in vivo. LATUDA was negative in the Ames gene mutation test, the Chinese Hamster Lung (CHL) cells, and in the *in vivo* mouse bone marrow micronucleus test up to 2000 mg/kg (61 times the MRHD of 160 mg/day based on body surface area).

Impairment of Fertility: Estrus cycle irregularities were seen in rats orally administered LATUDA at 1.5, 15 and 150mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through day 7 of gestation. The no-effect dose is 0.1 mg/kg which is approximately 0.006 times the MRHD of 160 mg/day based on body surface area. Fertility was reduced only at the highest dose, which was reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is approximately equal to the MRHD based on body surface area.

LATUDA had no effect on fertility in male rats treated orally with LATUDA for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (9 times the MRHD based on body surface area).

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of LATUDA for the treatment of schizophrenia was established in five short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.4 years, range 18-72) who met DSM-IV criteria for schizophrenia. An active control arm (olanzapine or quetiapine extended-release) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a clinician-rated scale that measures the subject's current illness state on a 1 to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. In a 6-week, placebo and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. In a 6-week, placebo and active-controlled trial (N=482) involving two fixed doses of LATUDA (80 or 160 mg/day) and an active control (quetiapine extended-release), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80, 120 and 160 mg/day has been established (Table 8).

Table 8: Summary of Results for Primary Efficacy Endpoints

Study Number	Primary Endpoint	LS Mean (SE)[a] Difference from Placebo in Change from Baseline					
		LATUDA				Olanzapine	Quetiapine Extended-Release
		40 mg/day	80 mg/day	120 mg/day	160 mg/day	15 mg/day	600 mg/day
1	BPRSd	-5.6* (2.1)	-	-6.7* (2.2)	-	-	-
2	BPRSd	-	-4.7* (1.8)	-	-	-	-
3	PANSS	-9.7* (2.9)	-	-7.5* (3.0)	-	-12.6** (2.8)	-
4	PANSS	-2.1 (2.5)	-6.4* (2.5)	-3.5 (2.5)	-	-	-
5	PANSS	-	-11.9* (2.6)	-	-16.2* (2.5)	-	-17.5** (2.6)

* adjusted p-value ≤0.05
** non-adjusted p-value ≤0.05
a Least Squares Mean (Standard Error)

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 mg), pale green, oval (80 mg) or white to off-white, oval (120 mg)and identified with strength-specific one-sided debossing, "L20" (20 mg), "L40" (40 mg), "L80" (80 mg) or "L120" (120 mg). Tablets are supplied in the following strengths and package configurations (Table 9):

Table 9: Package Configuration for LATUDA Tablets

Tablet Strength	Package Configuration	NDC Code
20 mg	Bottles of 30	63402-302-30
	Bottles of 90	63402-302-90
	Bottles of 500	63402-302-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-302-10 Carton 63402-302-01 Blister
40 mg	Bottles of 30	63402-304-30
	Bottles of 90	63402-304-90
	Bottles of 500	63402-304-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 Blister
80 mg	Bottles of 30	63402-308-30
	Bottles of 90	63402-308-90
	Bottles of 500	63402-308-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-308-10 Carton 63402-308-01 Blister
120 mg	Bottles of 30	63402-312-30
	Bottles of 90	63402-312-90
	Bottles of 500	63402-312-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-312-10 Carton 63402-312-01 Blister

Storage

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) *[See USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss with patients for whom they prescribe LATUDA all relevant safety information including, but not limited to, the following:

17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. LATUDA is not approved for elderly patients with dementia-related psychosis [*see Boxed Warning; Warnings and Precautions* (5.1)].

17.2 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

17.3 Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [*see Warnings and Precautions* (5.5)].

17.4 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.8)]*.

17.5 Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking LATUDA [*see Warnings and Precautions* (5.7)].

17.6 Interference with Cognitive and Motor Performance

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely *[see Warnings and Precautions (5.10)]*.

17.7 Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA *[see Use in Specific Populations (8.1)]*.

17.8 Concomitant Medication and Alcohol

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be advised to avoid alcohol while taking LATUDA *[see Drug Interactions (7)]*.

17.9 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (*5.11*)]*.

Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

Revised: April 2012

901456R04

LATUDA is a registered trademark of Dainippon Sumitomo Pharma Co. Ltd.
Sunovion Pharmaceuticals Inc. is a U.S. subsidiary of Dainippon Sumitomo Pharma Co. Ltd.

© 2012 Sunovion Pharmaceuticals Inc.

7. APPENDIX 2 MELTZER 2011 REPRINT

Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry*. 2011;168:957-967.

The attached document is provided for your use by Sunovion Pharmaceuticals Inc. Rights to this document have been secured for your sole use. A single copy, print or electronic, may be saved for your personal use. Please do not forward, send, or in any other way redistribute the attached document.

Do Not Copy or Distribute

Lurasidone in the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study

Herbert Y. Meltzer, M.D.

Josephine Cucchiaro, Ph.D.

Robert Silva, Ph.D.

Masaaki Ogasa, M.S.

Debra Phillips

Jane Xu, Ph.D.

Amir H. Kalali, M.D.

Edward Schweizer, M.D.

Andrei Pikalov, M.D., Ph.D.

Antony Loebel, M.D.

Objective: The study was designed to evaluate the short-term efficacy and safety of lurasidone in the treatment of acute schizophrenia.

Method: Participants, who were recently admitted inpatients with schizophrenia with an acute exacerbation of psychotic symptoms, were randomly assigned to 6 weeks of double-blind treatment with 40 mg of lurasidone, 120 mg of lurasidone, 15 mg of olanzapine (included to test for assay sensitivity), or placebo, dosed once daily. Efficacy was evaluated using a mixed-model repeated-measures analysis of the change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score (as the primary efficacy measure) and Clinical Global Impressions severity (CGI-S) score (as the key secondary efficacy measure).

Results: Treatment with both doses of lurasidone or with olanzapine was associated with significantly greater improvement at week 6 on PANSS total score, PANSS positive and negative subscale scores, and CGI-S score compared with placebo. There was no statistically significant difference in mean PANSS total or CGI-S change scores for the lurasidone groups compared with the olanzapine group. With responders defined as those with an improvement of at least 20% on the PANSS, endpoint responder rates were significant compared with placebo for olanzapine only. The incidence of akathisia was higher with 120 mg of lurasidone (22.9%) than with 40 mg of lurasidone (11.8%), olanzapine (7.4%), or placebo (0.9%). The proportion of patients experiencing ≥7% weight gain was 5.9% for the lurasidone groups combined, 34.4% for the olanzapine group, and 7.0% for the placebo group.

Conclusions: Lurasidone was an effective treatment for patients with acute schizophrenia. Safety assessments indicated a higher frequency of adverse events associated with 120 mg/day of lurasidone compared with 40 mg/day.

(Am J Psychiatry 2011; 168:957–967)

Do Not Copy or Distribute

Atypical antipsychotic drugs generally share more potent antagonism for 5-HT_{2A} than dopamine D_2 receptors (1, 2). However, there are significant differences among these agents in their relative affinities for 5-HT_{1A}, 5-HT_{2C}, 5-HT_7, alpha-adrenergic, histamine H_1, muscarinic, and other receptors that may affect their efficacy and tolerability (2). Genetic polymorphisms in receptor proteins, as well as in cytochrome P450 isoenzymes, contribute additional between-drug variability in clinical effect (3). Thus, atypical antipsychotics do not produce uniform clinical responses in all patients, and it remains important to have multiple antipsychotic drug treatment choices to address unmet therapeutic needs in patients with schizophrenia and other psychotic disorders (4, 5).

Lurasidone is a novel psychotropic agent that has been shown in studies of cloned human receptors to be an antagonist at the 5-HT_{2A} receptor, with a binding affinity (Ki; the dissociation constant of the inhibitor) of 0.47, and a Ki of 0.99 at the D2 receptor. It also has a very high affinity for the 5-HT_7 receptor (Ki, 0.49), which is nearly identical to its affinity for the 5-HT_{2A} receptor. In addition, lurasidone has moderate partial agonist effects at the 5-HT_{1A} receptor (Ki, 6.4) and moderately potent antagonist effects at α_{2c} receptor subtypes (Ki, 10.8) (6).

In a double-blind, placebo-controlled phase 2 clinical trial (7), lurasidone demonstrated efficacy in schizophrenia at a fixed daily dose of 80 mg.

The primary objective of this phase 3 study was to evaluate the efficacy of two dosages of lurasidone (40 and 120 mg/day) compared with placebo in the treatment of patients suffering from an acute exacerbation of chronic schizophrenia. The key secondary objective was to evaluate the efficacy of lurasidone compared with placebo in improving the Clinical Global Impressions severity (CGI-S) score. Another major secondary objective was to evaluate the safety and tolerability of the 40 mg and 120 mg doses of lurasidone during 6 weeks of treatment.

Method

This was a prospective, multicenter, parallel-group study in which recently admitted acutely ill inpatients with schizophrenia with an acute exacerbation of psychotic symptoms were

This article provides **Clinical Guidance** (p. 967)

randomly assigned to receive 6 weeks of double-blind treatment with once-daily doses of 40 mg or 120 mg of lurasidone, 15 mg of olanzapine (included to establish assay sensitivity), or placebo. The study was conducted between January 31, 2008, and June 16, 2009, enrolling a total of 478 patients at 25 sites in the United States (N=286), five in Colombia (N=48), four in Lithuania (N=29), and 18 in Asia (India, 14 sites [N=89]; Philippines, four sites [N=26]).

All patients who entered the trial reviewed and signed an informed consent document explaining study procedures and potential risks before study entry. The study protocol and all related forms and amendments were approved by an independent ethics committee associated with each study center. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practices guidelines and with the ethical principles of the Declaration of Helsinki. An independent data and safety monitoring board reviewed unblinded safety and clinical outcome data.

Entry Criteria

Hospitalized male and female patients 18–75 years of age who met DSM-IV criteria for a primary diagnosis of schizophrenia as determined by the Mini International Neuropsychiatric Interview (8) were enrolled. Patients were also required to have an illness duration of at least 1 year and to have been hospitalized for ≤2 weeks for an acute exacerbation of psychotic symptoms and, at the screening and baseline visits, to have a CGI-S score ≥4 (moderate or greater) and a Positive and Negative Syndrome Scale (PANSS) total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness.

Study Medication

All study medication was identically overencapsulated to preserve the double-blind. A unique participant number was assigned by interactive voice response system when a patient entered the screening phase. At baseline (day 0), patients who continued to meet all study inclusion criteria were randomly assigned via interactive voice response system (in a 1:1:1:1 ratio) to one of four treatment arms: lurasidone, 40 mg; lurasidone, 120 mg; olanzapine, 15 mg; or placebo. Study medication was administered in the morning with a meal or within 30 minutes after eating. Participants assigned to receive lurasidone started treatment at their target dose; patients assigned to olanzapine treatment received 10 mg on days 1–7 and 15 mg thereafter. The olanzapine dosage of 15 mg/day was selected because it is widely used and because there is substantial evidence that it is an effective dosage in patients with schizophrenia, with little evidence that higher dosages offer additional efficacy advantages (9, 10). This dosage is also consistent with the olanzapine package insert (http://pi.lilly.com/us/zyprexa-pi.pdf), which states that efficacy in schizophrenia has been demonstrated in a dosage range of 10–15 mg/day, with higher doses not demonstrated to be more efficacious.

Limited use of benzodiazepines was permitted for severe anxiety, agitation, or insomnia. Participants were eligible for hospital discharge to a stable residence after 21 days of treatment if they had a CGI-S score ≤3.

Assessments

The screening evaluation consisted of the Mini International Neuropsychiatric Interview, medical and psychiatric histories, a physical examination, measurement of vital signs, ECG, and laboratory tests.

Efficacy was assessed using the PANSS total and subscale scores (including a post hoc analysis of a modified version of the cognitive subscale, consisting of items P2, N5, N7, G10, G11) (11, 12), the CGI-S, and the Montgomery-Åsberg Depression Rating Scale (MADRS; 13). PANSS and CGI-S evaluations were performed at the screening and baseline visits and, during treatment, on day 4 and at each of weeks 1 through 6. The MADRS was administered at the screening and baseline visits and at weeks 3 and 6.

Extrapyramidal symptoms were assessed with the Simpson-Angus Rating Scale (14), the Barnes Rating Scale for Drug-Induced Akathisia (15), and the Abnormal Involuntary Movement Scale (16). Safety evaluations included vital signs, weight, laboratory tests (including fasting lipids, glucose, glycosylated hemoglobin [HbA_{1c}], and insulin), 12-lead ECG, and reported adverse events. Insulin resistance and beta-cell function were measured using the homeostasis model assessment for insulin resistance (HOMA-IR) method (17).

Statistical Methods

A power calculation was performed that incorporated Bonferroni's procedure for controlling pairwise differences with placebo and was obtained via computer simulations. Assuming that lurasidone differed from placebo in the change from baseline in PANSS total score by 6.8 and 10.0 for the 40 and 120 mg/day dosages, respectively, and further assuming a standard deviation of 19.1, we calculated that 120 patients per group would provide 97% power (at an alpha level of 0.05, two-sided test) to reject the null hypothesis of no difference between placebo and at least one of the lurasidone dosage groups.

The primary efficacy analysis was performed on the intent-to-treat sample, which consisted of all participants assigned to a treatment group who received at least one dose of study medication, had a baseline PANSS assessment, and had at least one postbaseline PANSS assessment during the 6-week study. The primary efficacy measure was the change from baseline in PANSS total score at week 6, and the key secondary efficacy measure was the change from baseline in CGI-S score at week 6. Both measures were evaluated by a mixed-model repeated-measures analysis with an unstructured covariance matrix. The model included factors for pooled center, time (including all scheduled postbaseline assessment visits as a categorical variable), baseline PANSS total score or CGI-S score, treatment, and treatment-by-time interaction. The p values for the comparison of each lurasidone group with the placebo group at week 6 on change from baseline in PANSS total score and CGI-S score were adjusted for multiple comparisons using the Hommel-based tree-gatekeeping procedure to control the family-wise type I error rate (18). The olanzapine treatment group, which was included to confirm the assay sensitivity of the study, was compared with placebo using the same mixed-model repeated-measures model, without the multiple comparison adjustment. A post hoc mixed-model repeated-measures analysis of the PANSS total score and CGI-S score was also performed comparing the 40 mg and 120 mg lurasidone treatment groups to the olanzapine treatment group.

A prespecified secondary analysis was conducted for change in PANSS total score and CGI-S score, using an analysis of covariance (ANCOVA) model.

Secondary efficacy measures, including PANSS subscale scores (positive, negative, and general psychopathology) and MADRS total score, were evaluated using similar mixed-model repeated-measures models. A post hoc analysis of the modified PANSS cognitive subscale was also performed. Participants who had an improvement of at least 20% from baseline in PANSS total score at week 6 endpoint (last observation carried forward) were defined as "responders." A logistic regression was performed using the responder outcome as the dependent variable, treatment as a categorical factor, and baseline PANSS total score as a covariate.

The Cohen's d effect size was calculated for week 6 efficacy measures as the between-treatment difference score divided by the pooled standard deviation. For adverse events, number need-

Do Not Copy or Distribute

TABLE 1. Baseline Characteristics of Patients With Schizophrenia in a 6-Week Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone

Characteristic[a]	Treatment Group							
	Lurasidone, 40 mg (N=119)		Lurasidone, 120 mg (N=118)		Olanzapine, 15 mg (N=122)		Placebo (N=114)	
	N	%	N	%	N	%	N	%
Male	93	78	93	79	95	78	88	77
Race								
White	44	37	48	41	41	34	36	32
Black	39	33	36	31	44	36	41	36
Asian	31	26	27	23	30	25	27	24
Other	5	4	7	6	7	6	10	9
Hispanic/Latino ethnicity	23	19	19	16	17	14	16	14
≥4 previous hospitalizations	51	43	64	54	58	48	53	46
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	37.7	11.0	37.9	11.2	38.3	10.2	37.0	11.3
Age at onset of illness (years)	23.9	8.3	22.7	8.8	24.7	7.8	23.9	8.0
Duration of illness (years)	13.3	9.9	14.7	11.0	13.2	10.9	12.6	9.6
Duration of current episode (days)	33.9	15.3	33.0	12.9	33.5	14.5	35.6	16.8
PANSS total score	96.6	10.7	97.9	11.3	96.3	12.2	95.8	10.8
CGI severity score	5.0	0.7	5.0	0.6	4.9	0.7	4.9	0.7
MADRS total score	10.8	7.0	11.4	7.2	10.8	6.2	10.6	6.1

[a] PANSS=Positive and Negative Syndrome Scale; CGI=Clinical Global Impressions scale; MADRS=Montgomery-Åsberg Depression Rating Scale.

Do Not Copy or Distribute

ed to harm was calculated as 1 divided by the difference in the risk of an adverse event for active drug compared with placebo.

Significance testing of selected safety parameters was performed based on a nonparametric rank ANCOVA with baseline value as a covariate, not adjusted for multiple comparisons.

Results

Of a total of 781 patients who were screened and entered the washout period, 478 were randomly assigned to 6 weeks of double-blind treatment (Figure 1). Baseline demographic and clinical characteristics were comparable among the four treatment groups (Table 1). The proportion of patients in the lurasidone 40 mg group who completed the study treatment (64.2%) was similar to the proportions who completed treatment in the placebo group (61.2%) and the olanzapine group (68.3%); a somewhat lower proportion of patients in the lurasidone 120 mg group completed the study treatment (55.5%) (Figure 1).

Efficacy

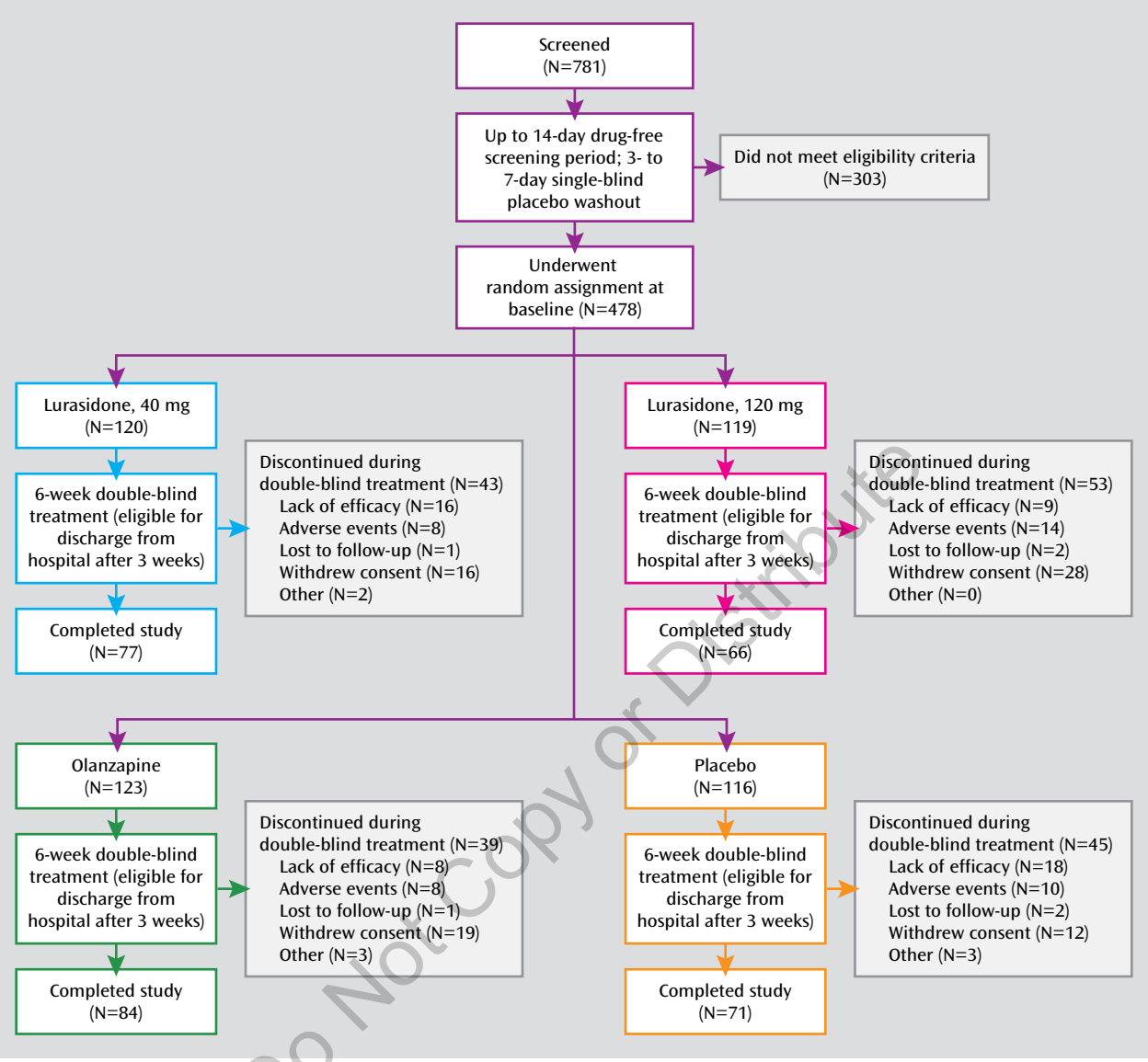
Based on the mixed-model repeated-measures analysis, the change from baseline to week 6 in PANSS total score was significantly greater for the lurasidone 40 mg (–25.7; adjusted p=0.002) and 120 mg (–23.6; adjusted p=0.022) groups compared with the placebo group (–16.0) (Table 2). The change in PANSS total score was also significantly greater for the olanzapine group (–28.7, p<0.001), thus confirming the assay sensitivity of the study. Statistically significant separation from placebo on the PANSS total score was observed from week 1 onward for the lurasidone 40 mg and olanzapine groups, and from week 3 onward for the lurasidone 120 mg group (Figure 2; see also Table S1 in the online data supplement). Treatment with both dosages of lurasidone and with olanzapine was also associated with significantly greater improvement at week 6 compared with placebo on the PANSS positive, negative, and general psychopathology subscale scores (Table 2; see also Table S1 in the online data supplement). Based on a post hoc analysis, treatment with both dosages of lurasidone, as well as with olanzapine, was also associated with significantly greater improvement at week 6 on the modified PANSS cognitive subscale score (see Table 2).

For the CGI-S score, the change from baseline to week 6 was also significantly greater for the lurasidone 40 mg (–1.5; adjusted p=0.011) and 120 mg (–1.4; adjusted p=0.040) groups compared with the placebo group (–1.1; see Table 2). The change in CGI-S score was also significantly greater for the olanzapine group (–1.5; p<0.001). Statistically significant separation from placebo on the CGI-S was observed from week 1 onward for the lurasidone 120 mg group, and from week 2 onward for the lurasidone 40 mg group and the olanzapine group compared with the placebo group (see Table S1 and Figure S1 in the online data supplement).

In a post hoc mixed-model repeated-measures analysis of PANSS total score and CGI-S score, there was no statistically significant difference in least-squares mean change scores at week 6 for the olanzapine group compared with either lurasidone group.

In a secondary analysis, an ANCOVA was performed on change from baseline to week 6 (last observation carried forward) for PANSS total score and CGI-S score. In this analysis, the least-squares mean change in PANSS total score was significantly greater for the lurasidone 40 mg (–23.1, p=0.001; effect size, 0.43) and 120 mg (–20.0, p=0.049; effect size, 0.26) groups compared with the place-

FIGURE 1. Flow of Patients With Schizophrenia in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone



Do Not Copy or Distribute

bo group (–15.2). Similarly, the least-squares mean change in PANSS total score was also significantly greater for the olanzapine group (–26.7, p<0.001). In an ANCOVA analysis of CGI-S score, least-squares mean change at week 6 (last observation carried forward) was significantly greater for the lurasidone 40 mg group compared with the placebo group (–1.2, p=0.012), but the comparison with the placebo group was not significant for the lurasidone 120 mg group. The least-squares mean change in CGI-S score was significant for the olanzapine group (–1.4, p<0.001). The results of these sensitivity analyses for PANSS total score and CGI-S score were similar to, and support, the results of the primary mixed-model repeated-measures analysis. Furthermore, on a pairwise comparison, there were no significant differences in endpoint change between the two lurasidone groups on PANSS total score or CGI-S score.

In a logistic regression analysis, responder rates (compared with placebo) and associated odds ratios at 6 weeks (last observation carried forward) were not significant for either of the lurasidone groups, but the comparison was significant for the olanzapine group (a responder rate of 74%, compared with a rate of 49% for placebo; odds ratio=2.9, p<0.001).

Improvement on the MADRS at week 6 was not significantly different between either of the lurasidone groups and the placebo group, whereas the olanzapine group showed significantly greater improvement compared with the placebo group (Table 2; see also Figure S2 in the online data supplement).

The ANCOVA subgroup analyses showed no significant treatment interactions by gender, race, ethnicity, region, or age for either the PANSS total score or the CGI-S score.

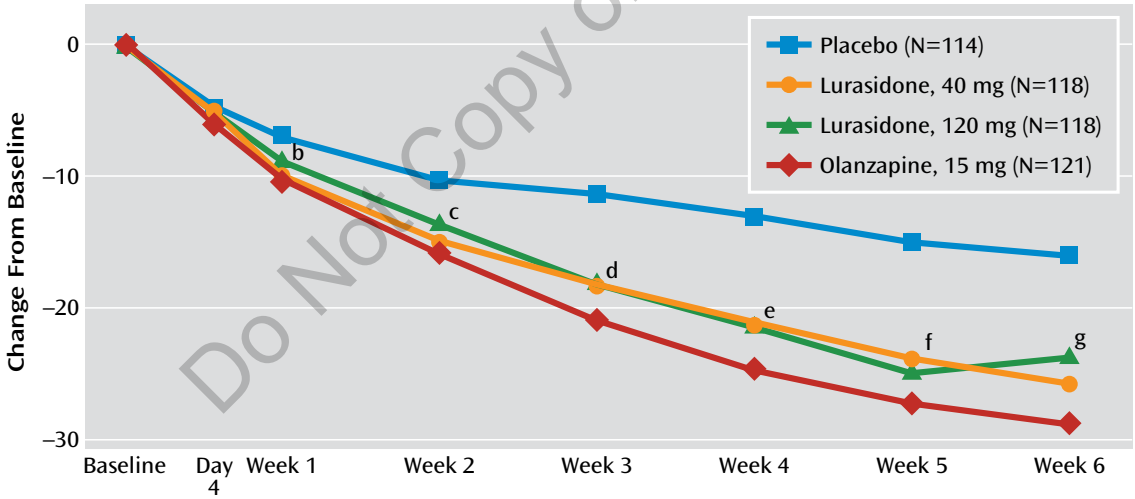
TABLE 2. Change From Baseline to Week 6 on Efficacy Measures for Patients With Schizophrenia in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone[a]

	Treatment Group										
	Lurasidone, 40 mg (N=118)			Lurasidone, 120 mg (N=118)			Olanzapine, 15 mg (N=121)			Placebo (N=114)	
Measure[b]	Estimate	SE	p[c]	Estimate	SE	p[c]	Estimate	SE	p[c]	Estimate	SE
PANSS											
Total score change[d]	–25.7	2.0	<0.001	–23.6	2.1	0.011	–28.7	1.9	<0.001	–16.0	2.1
Positive subscale score change	–7.7	0.7	0.018	–7.5	0.7	0.035	–9.3	0.7	<0.001	–5.4	0.7
Negative subscale score change	–6.0	0.5	0.002	–5.2	0.6	0.045	–6.2	0.5	<0.001	–3.6	0.5
General psychopathology score change	–12.4	1.0	0.001	–11.1	1.0	0.022	–13.3	0.9	<0.001	–7.8	1.0
Cognitive subscale (modified) score change	–4.2	0.3	0.005	–4.0	0.4	0.012	–4.6	0.3	<0.001	–2.7	0.4
CGI severity score change[e]	–1.5	0.1	0.006	–1.4	0.1	0.040	–1.5	0.1	<0.001	–1.1	0.1
MADRS total score change	–3.5	0.5	0.324	–3.2	0.6	0.571	–5.0	0.5	0.003	–2.8	0.6

[a] Change was assessed using a mixed-model repeated-measures analysis.
[b] PANSS=Positive and Negative Syndrome Scale; CGI=Clinical Global Impressions scale; MADRS=Montgomery-Åsberg Depression Rating Scale.
[c] Compared with placebo group; p values are unadjusted and are based on a repeated-measures linear regression model of the change from baseline score, with fixed effects for pooled center, assessment visit as a categorical variable, baseline score, treatment, and treatment-by-assessment visit interaction, assuming an unstructured covariance matrix.
[d] For total score change on the PANSS, the adjusted p values (using the Hommel-based tree-gatekeeping procedure) for the lurasidone 40 mg and 120 mg groups compared with the placebo group were 0.002 and 0.022, respectively. For each of the lurasidone groups compared with the olanzapine group, unadjusted p values were nonsignificant.
[e] For CGI severity score change, the adjusted p values (using the Hommel-based tree-gatekeeping procedure) for the lurasidone 40 mg and 120 mg groups compared with the placebo group, were 0.011 and 0.040, respectively. For each of the lurasidone groups compared with the olanzapine group, unadjusted p values were nonsignificant.

Do Not Copy or Distribute

FIGURE 2. Change From Baseline in PANSS Total Score in a Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study of Lurasidone[a]



[a] Statistical significance was computed on the basis of a repeated-measures linear regression model of the change from baseline score, with fixed effects for pooled site, assessment visit as a categorical variable, baseline score, treatment, and treatment-by-assessment visit interaction, assuming an unstructured covariance matrix; p values are unadjusted, and only significant p values are noted.
[b] Week 1 comparison with placebo: p=0.022 for lurasidone 40 mg; p=0.008 for olanzapine.
[c] Week 2 comparison with placebo: p=0.008 for lurasidone 40 mg; p=0.002 for olanzapine.
[d] Week 3 comparison with placebo: p=0.002 for lurasidone 40 mg; p=0.004 for lurasidone 120 mg; p<0.001 for olanzapine.
[e] Week 4 comparison with placebo: p<0.001 for lurasidone 40 mg; p<0.001 for lurasidone 120 mg; p<0.001 for olanzapine.
[f] Week 5 comparison with placebo: p=0.001 for lurasidone 40 mg; p<0.001 for lurasidone 120 mg; p<0.001 for olanzapine.
[g] Week 6 comparison with placebo: p<0.001 for lurasidone 40 mg; p=0.011 for lurasidone 120 mg; p<0.001 for olanzapine.

Safety

Adverse events. A comparable proportion of patients in the lurasidone 40 mg group and in the placebo group reported experiencing at least one adverse event (Table 3); the incidence was somewhat higher in the lurasidone 120 mg group and the olanzapine group. The majority of adverse events in all treatment groups were rated as mild to moderate. Rates of discontinuations due to adverse

TABLE 3. Effect of 6 Weeks of Treatment With Lurasidone, Olanzapine, or Placebo on the Incidence of Adverse Events Reported in 5% or More of Participants

	Treatment Group							
	Lurasidone, 40 mg (N=119)		Lurasidone, 120 mg (N=118)		Olanzapine, 15 mg (N=122)		Placebo (N=116)	
Event	N	%	N	%	N	%	N	%
At least one adverse event	90	75.6	97	82.2	100	82.0	84	72.4
Headache	26	21.8	21	17.8	17	13.9	25	21.6
Akathisia	14	11.8	27	22.9	9	7.4	1	0.9
Somnolence	12	10.1	18	15.3	11	9.0	5	4.3
Insomnia	15	12.6	14	11.9	13	10.7	13	11.2
Sedation	11	9.2	16	13.6	18	14.8	4	3.4
Anxiety	12	10.1	12	10.2	7	5.7	8	6.9
Nausea	13	10.9	9	7.6	6	4.9	5	4.3
Agitation	14	11.8	7	5.9	8	6.6	6	5.2
Dyspepsia	9	7.6	9	7.6	6	4.9	7	6.0
Constipation	6	5.0	9	7.6	8	6.6	6	5.2
Vomiting	5	4.2	10	8.5	3	2.5	8	6.9
Back pain	6	5.0	6	5.1	7	5.7	5	4.3
Dizziness	5	4.2	6	5.1	3	2.5	2	1.7
Restlessness	7	5.9	4	3.4	4	3.3	3	2.6
Salivary hypersecretion	2	1.7	8	6.8	1	0.8	0	0.0
Musculoskeletal stiffness	3	2.5	6	5.1	3	2.5	2	1.7
Appetite decreased	6	5.0	1	0.8	2	1.6	2	1.7
Appetite increased	1	0.8	3	2.5	7	5.7	4	3.4
Weight increased	2	1.7	2	1.7	25	20.5	6	5.2
Toothache	4	3.4	3	2.5	12	9.8	6	5.2
Dry mouth	2	1.7	3	2.5	12	9.8	1	0.9
Psychotic disorder	2	1.7	4	3.4	4	3.3	8	6.9
Extrapyramidal adverse events								
Parkinsonism	11	9.2	13	11.0	6	4.9	2	1.7
Tremor	2	1.7	9	7.6	7	5.7	5	4.3
Dystonia	4	3.4	9	7.6	1	0.8	1	0.9

Do Not Copy or Distribute

events were relatively low in the lurasidone 40 mg group (6.7%), the lurasidone 120 mg group (11.8%), and the olanzapine group (6.5%) and were comparable to those in the placebo group (8.6%). The four adverse events with the highest incidence relative to placebo (that is, the largest drug-versus-placebo difference; see Table 3) were, for the lurasidone 40 mg group, akathisia (11.8%), agitation (11.8%), nausea (10.9%), and parkinsonism (9.2%); for the lurasidone 120 mg group, akathisia (22.9%), somnolence (15.3%), sedation (13.6%), and parkinsonism (11.0%); and for the olanzapine group, increased weight (20.5%), sedation (14.8%), dry mouth (9.8%), and akathisia (7.4%).

Physical examination and vital signs. There were no clinically significant treatment-emergent changes in either of the lurasidone groups or the olanzapine group compared with the placebo group in pulse rate, systolic or diastolic blood pressure, or body temperature.

Extrapyramidal symptoms. The proportion of patients treated with an anticholinergic medication was similar in the lurasidone 40 mg group (20%) and the olanzapine group (18%) but higher in the lurasidone 120 mg group (41%). A smaller proportion of patients in the placebo group (9%) used anticholinergic agents. Benztropine was the most frequently prescribed medication for parkinsonism-related adverse effects (see Table S2 in the online data supplement), followed by trihexyphenidyl, propranolol, and biperiden. The proportions of patients reporting the extrapyramidal symptom-related adverse events of parkinsonism, tremor, dystonia, and akathisia during study treatment are listed in Table 3. No episodes of opisthotonos were reported in any treatment group. Two patients (1.7%) in the lurasidone 120 mg group discontinued the drug because of extrapyramidal adverse events, whereas none in the other three treatment groups did. The mean endpoint changes in Simpson-Angus Rating Scale score and in the Barnes Rating Scale for Drug-Induced Akathisia global clinical assessment scores were small and not clinically significant in the majority of patients. In the lurasidone 40 mg group and the olanzapine group, change from baseline in the least-squares mean Simpson-Angus and Barnes scale scores was not significantly different from that of the placebo group (see Figures S3 and S4 in the online data supplement). In contrast, the lurasidone 120 mg group had significantly greater Simpson-Angus and Barnes change scores compared with the placebo group. Consistent with these data, the proportions of patients reporting categorical worsening on the Barnes scale, the

TABLE 4. Effect of 6 Weeks of Treatment With Lurasidone, Olanzapine, or Placebo on Weight, Body Mass Index, Waist Circumference, and Laboratory Test Results[a]

	Treatment Group							
	Lurasidone, 40 mg (N=119)		Lurasidone, 120 mg (N=118)		Olanzapine, 15 mg (N=122)		Placebo (N=116)	
Measure	Mean or Median	SD	Mean or Median	SD	Mean or Median	SD	Mean or Median	SD
Weight (kg)								
Baseline	76.4	19.3	75.4	18.6	76.0	20.1	75.2	18.6
Mean change	+1.0	2.9	+1.0	2.2	+4.1	4.3	+0.6	2.7
Median change	+0.9		+0.5		+3.1***		0.0	
Body mass index								
Baseline	26.3	5.9	25.5	5.0	26.0	6.1	25.8	5.4
Mean change	+0.3	1.0	+0.4	0.7	+1.4	1.4	+0.2	0.9
Median change	+0.3		0.2		+1.1***		0.0	
Waist circumference (cm)								
Baseline	91.2	15.9	90.4	13.7	91.1	15.2	89.1	14.0
Mean change	+1.4	8.2	+1.0	4.2	+3.4	4.9	+0.6	5.4
Median change	0.0		+0.5		+2.0***		0.0	
Total cholesterol (mg/dl)								
Baseline	197.8	43.4	191.9	42.6	193.8	44.9	195.7	46.2
Mean change	–8.6	29.8	–7.3	25.3	+9.6	31.2	–6.8	28.7
Median change	–8.0		–5.0		+9.0***		–5.0	
LDL cholesterol (mg/dl)								
Baseline	116.1	34.9	112.6	33.3	113.8	34.7	113.8	35.7
Mean change	–4.9	23.3	–4.6	20.9	+4.3	25.9	–1.8	24.8
Median change	–4.0		–5.0		+7.0*		–4.0	
HDL cholesterol (mg/dl)								
Baseline	48.0	13.5	46.2	12.4	48.4	13.2	48.9	14.0
Mean change	–0.9	9.3	–0.4	8.5	–2.1	9.3	–1.2	8.1
Median change	–1.0		0.0		–2.0		–1.0	
Triglycerides (mg/dl)								
Baseline	143.7	88.3	144.9	96.6	133.6	74.9	131.5	85.8
Mean change	–8.3	76.2	–5.0	85.5	+50.0	115.0	+0.1	64.8
Median change	–3.0		+4.5		+24.0***		–1.0	
Glucose (mg/dl)								
Baseline	96.1	20.0	95.7	19.9	94.2	17.1	93.9	20.1
Mean change	0.0	19.2	+0.5	20.9	+10.3	34.8	+0.4	24.6
Median change	–1.0		–0.5		+4.0*		+1.0	
HbA_{1c} (%)								
Baseline	5.65	0.43	5.57	0.46	5.58	0.48	5.47	0.43
Mean change	–0.04	0.24	+0.06	0.29	+0.18	0.57	–0.05	0.25
Median change	–0.10		0.00**		+0.05***		0.00	
Insulin (mU/liter)								
Baseline	19.1	28.1	15.9	24.5	13.2	13.9	20.3	41.6
Mean change	–3.1	31.5	–1.3	24.3	+5.9	30.8	–2.4	46.3
Median change	–0.6		–0.4		+1.5		–0.1	
HOMA-IR (U)								
Baseline	5.52	10.94	4.10	7.27	3.27	4.00	6.03	16.48
Mean change	–1.30	11.57	–0.28	7.72	+2.61	11.97	–1.32	18.25
Median change	–0.12		–0.09		+0.55*		–0.01	
Prolactin (ng/ml)								
Baseline	10.2	9.8	10.6	12.2	11.1	13.7	13.0	16.2
Mean change	+2.1	13.9	+10.9	28.1	+5.0	12.2	–2.5	+16.9
Median change	+0.7		+4.5***		+3.8***		–0.7	

[a] Sample sizes may vary somewhat because of missing values for individual laboratory tests. HbA_{1c}=glycosylated hemoglobin; HOMA-IR=homeostatic model assessment of insulin resistance (analyzed post hoc); LDL=low-density lipoprotein; HDL=high-density lipoprotein. Indicated p values are for comparison with placebo.
*p<0.05. **p<0.01. ***p<0.001.

Do Not Copy or Distribute

TABLE 5. Proportion of Patients Treated for 6 Weeks With Lurasidone, Olanzapine, or Placebo Whose Laboratory Values Shifted From Normal to Outside the Normal Range at Endpoint

	Treatment Group							
	Lurasidone, 40 mg		Lurasidone, 120 mg		Olanzapine, 15 mg		Placebo	
Measure[a]	N	%	N	%	N	%	N	%
Glucose (shift to high: ≥100 mg/dl)	18/118	15.3	11/114	9.6	27/121	22.3	20/113	17.7
HbA_{1c} (shift to high: >6 mg/dl)	8/113	7.1	5/101	5.0	7/112	6.3	5/107	4.7
Total cholesterol (shift to high: >200 mg/dl)	4/115	3.5	9/102	8.8	17/115	14.8	5/107	4.7
LDL (shift to high: >129 mg/dl)	4/115	3.5	9/102	8.8	15/115	13.0	9/107	8.4
HDL (shift to low: ≤35 mg/dl)	12/115	10.4	5/102	4.9	10/115	8.7	11/107	10.3
Triglycerides (shift to high: >203 mg/dl)	10/115	8.7	7/102	6.9	19/115	16.5	7/107	6.5
Prolactin (shift to high: male, >17.7 ng/ml; female, >29.2 ng/ml)	12/119	10.1	21/115	18.3	16/121	13.2	8/114	7.0

[a] HbA_{1c}=glycosylated hemoglobin; LDL=low-density lipoprotein; HDL=high-density lipoprotein.

Abnormal Involuntary Movement Scale, and the Simpson-Angus scale were higher in the lurasidone 120 mg group compared with the lurasidone 40 mg, olanzapine, and placebo groups (see Tables S3–S5 in the online data supplement).

Body weight, body mass index (BMI), and waist circumference. The mean endpoint changes in weight, BMI, and waist circumference (last observation carried forward) were similar for both lurasidone groups and the placebo group (Table 4). In contrast, there was a significant mean increase in the olanzapine group compared with the placebo group in both weight (4.1 kg compared with 0.6 kg, p<0.001; see Figure S5 in the online data supplement) and BMI (1.4 units compared with 0.2 units, p<0.001). The proportion of patients with a clinically significant weight gain (≥7% over baseline at last-observation-carried-forward endpoint) was also similar in the lurasidone 40 mg (7.6%) and 120 mg groups (4.2%) compared with the placebo group (7.0%), while the proportion in the olanzapine group was higher (34.4%).

Metabolic parameters. Endpoint changes in levels of cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) (last observation carried forward) were comparable for both lurasidone groups and the placebo group, while the olanzapine group showed a significant mean increase compared with the placebo group in levels of cholesterol (+9.6 mg/dl compared with –6.8 mg/dl, p<0.001), LDL (+4.3 mg/dl compared with –1.8 mg/dl, p=0.010), and triglycerides (+50.0 mg/dl compared with +0.1 mg/dl, p<0.001) (see Table 4; see also Figure S6 in the online data supplement). Endpoint changes in glucose, HbA_{1c}, insulin, and HOMA-IR levels were also comparable for both lurasidone groups and the placebo group, while the olanzapine group showed a significantly higher mean increase compared with the placebo group in glucose level (+10.3 mg/dl compared with +0.4 mg/dl, p=0.036) and numerically higher mean increases in levels of HbA_{1c} (+0.18% compared with –0.05%) (see Table 4; see also Figure S7 in the online data supplement), insulin (+5.9 mU/liter compared with –2.4 mU/liter), and HOMA-IR (+2.61 U compared with –1.32 U; see Figure S8 in the online data supplement).

Prolactin and other laboratory values. The median change in prolactin level at endpoint (last observation carried forward) was comparable in the lurasidone 40 mg and placebo groups (+0.7 ng/ml and –0.7 ng/ml, respectively) but was significantly higher compared with the placebo group in the lurasidone 120 mg group (+4.5 ng/ml, p<0.001) and the olanzapine group (+3.8 ng/ml, p<0.001) (see Table 5). A treatment-emergent shift from normal to high (abnormal) prolactin levels occurred in 23/183 male patients (12.6%; criterion for high value, >17.7 ng/ml) and 10/51 female patients (19.6%; criterion for high value, >29.2 ng/ml) in the combined lurasidone groups, in 8/94 males (8.5%) and 8/27 females (29.6%) in the olanzapine group, and in 6/89 males (6.7%) and 2/25 females (8.0%) in the placebo group. No patient in any treatment group discontinued study medication because of an elevated prolactin level, and treatment with lurasidone had no reported effect on menstrual cyclicity.

ECG. Treatment with lurasidone was not associated with any treatment-emergent ECG abnormalities compared with placebo. The mean endpoint change in the QTcF interval (last observation carried forward) was similar for the lurasidone 40 mg and 120 mg groups (+5.1 msec and +4.5 msec, respectively), the olanzapine group (+4.4 msec), and the placebo group (+3.8 msec). With the exception of one patient in the lurasidone 40 mg group who had a QTcF >450 msec at baseline that persisted at study endpoint, no QTcF intervals >450 msec were observed in any patient in any of the treatment groups. No patient in any treatment group had an increase ≥60 msec in QTcF interval or a QTcF interval >500 msec.

Discussion

The results of this multicenter, double-blind, placebo-controlled phase 3 trial indicate that lurasidone, at fixed dosages of 40 and 120 mg/day, was an effective and well-tolerated treatment for patients experiencing an acute

Do Not Copy or Distribute

exacerbation of chronic schizophrenia. Both dosages produced significant improvement on PANSS total score (the primary outcome measure) and CGI-S score (the key secondary outcome measure). There were no significant differences in the efficacy of lurasidone by gender, race, ethnicity, or age. Significant improvement was also observed on the PANSS positive, negative, and general psychopathology subscales and on the modified PANSS cognitive subscale (in a post hoc analysis). The validity of the modified PANSS cognitive subscale is not well established, but our results here are consistent with those from a previous 6-week clinical trial of lurasidone (7). In addition, in a double-blind trial (19), treatment with lurasidone was associated with improvement on the Schizophrenia Cognition Rating Scale, an interview-based assessment of cognition-related functioning.

No apparent dose-response relationship was observed in PANSS total score at week 6 in the ANCOVA analysis of the two lurasidone dosages. In fact, the effect size of the change in PANSS total score at week 6 (last observation carried forward) was smaller for the lurasidone 120 mg group than for the 40 mg group (Cohen's d, 0.26 and 0.43, respectively). The reason for the smaller effect size is uncertain, but an inspection of baseline variables (Table 1) suggests that there were small, but possibly clinically relevant in aggregate, differences in illness severity between the 120 mg and 40 mg groups, namely, a lower age at illness onset (22.7 years and 23.9 years, respectively), a longer duration of illness (14.7 years and 13.3 years, respectively), a higher proportion of patients with ≥4 previous hospitalizations (54% and 43%, respectively), and a higher mean PANSS total score (97.9 and 96.6, respectively). The only previously published trial (7) that used a fixed dose of lurasidone (80 mg) found an effect size of 0.44, which is comparable to that observed with the 40 mg dose in the present study.

Treatment with the active comparator, olanzapine, was associated with significant endpoint improvement on PANSS total score, CGI-S score, and other secondary measures, including the modified PANSS cognitive subscale. Olanzapine was included to confirm the assay sensitivity of the study; thus, no between-group efficacy testing was planned. However, based on a post hoc mixed-model repeated-measures analysis, no statistically significant difference was observed for change in PANSS total score between either of the lurasidone groups and the olanzapine group. These exploratory findings need to be confirmed in further comparative studies.

The onset of significant improvement in PANSS total score occurred by week 1 in the lurasidone 40 mg group and the olanzapine group, but not until week 3 in the lurasidone 120 mg group. In contrast, significant improvement on the CGI-S occurred by week 1 in the lurasidone 120 mg group, but not until week 2 in the lurasidone 40 mg and olanzapine groups. The reason for this discrepancy is unclear; however, the CGI-S measure reflects more than psychopathology, possibly including functional effects of cognitive improvement or a greater impact on negative symptoms.

The lurasidone 40 mg group had a lower rate of adverse events and fewer discontinuations due to adverse events than the 120 mg group. Based on number-needed-to-harm (NNH) analysis, the highest-risk adverse events (relative to placebo) in the lurasidone 40 mg group were akathisia (NNH=9.2), parkinsonism (NNH=13.3), agitation (NNH=15.2), and nausea (NNH=15.1); the highest-risk events in the lurasidone 120 mg group were somnolence (NNH=9.1), sedation (NNH=9.8), akathisia (NNH=4.5), and parkinsonism (NNH=10.8); and the highest-risk events in the olanzapine group were increased weight (NNH=6.5), sedation (NNH=8.8), dry mouth (NNH=11.1), and akathisia (NNH=15.4). These findings indicate that a higher frequency of akathisia and somnolence or sedation may be associated with the 120 mg/day dosage of lurasidone. Consistent with this, treatment with 120 mg/day of lurasidone was associated with greater treatment-emergent increases in scores on the Simpson-Angus Rating Scale and the Barnes Rating Scale for Drug-Induced Akathisia and more frequent use of medications for parkinsonism.

Our results suggest that lurasidone has a low potential for causing adverse weight and metabolic effects. There were no clinically meaningful differences between the lurasidone groups and the placebo group on levels of total cholesterol, LDL, HDL, triglycerides, insulin, glucose, or HbA_{1c} or on change in weight or BMI. These findings are consistent with the results from a previous placebo-controlled trial of lurasidone (7). The pharmacological and preclinical profile of lurasidone (20, 21) may provide a rationale for the minimal weight and metabolic effects observed in the present study. Lurasidone has no clinically relevant affinity for the receptors that have been reported to be correlated with short-term weight gain: H_1-histamine (Ki, >1000) or 5-HT_{2C} (Ki, 415) (20, 22). The low rates of weight gain and metabolic disruption associated with lurasidone treatment may be particularly important given the increased prevalence of these problems in patients treated with antipsychotics (23–25).

When compared with placebo, treatment with olanzapine was associated with a high proportion (34.4%) of patients with clinically meaningful weight gain as well as significant increases in levels of glucose, total cholesterol, LDL, and especially triglycerides, for which a mean increase of 50.0 mg/dl was observed. It should be noted that while all participants were required to fast per protocol, over 75% of these laboratory values were confirmed to have been obtained in a fasting state. Elevated fasting triglyceride levels are correlated with insulin resistance, since insulin-dependent lipases are typically inhibited by insulin. However, as insulin resistance worsens, increased lipolysis results in increases in free fatty acids that are hepatically transformed into triglycerides (26). Adverse ef-

Do Not Copy or Distribute

fects of olanzapine on insulin resistance and other cardiometabolic parameters have been previously documented (24, 25). Treatment with lurasidone in this study was not associated with QTc interval prolongation >500 msec in any patient. The incidences of categorical QTc interval change ≥30 msec and ≥60 msec for patients treated with lurasidone were comparable to those for patients in the placebo group.

Treatment with lurasidone was associated with a modest dose-related increase in prolactin levels, with the 40 mg daily dose and placebo showing comparable effects, while the 120 mg daily dose resulted in greater increases than placebo at endpoint. However, the mean increase in prolactin levels on the 120 mg dose of lurasidone was less than that previously reported for risperidone, paliperidone, and conventional antipsychotics (27).

A recent meta-analysis of atypical antipsychotics (28) suggests that within-class differences in efficacy are relatively small, while there are large between-drug differences in safety and tolerability. The results of the present study are consistent with those findings.

Our results did not demonstrate an additional efficacy advantage for the 120 mg/day dosage of lurasidone compared with the 40 mg/day dosage. However, there was a dose-related increase in sedation/somnolence, akathisia, and use of medication for parkinsonism, as well as a modest dose-related increase in prolactin levels. The lack of an apparent dose-response relationship in this study is consistent with findings for other atypical antipsychotics (10). The observation of comparable efficacy but an increase in some adverse effects at 120 mg is consistent with results from other clinical trials of lurasidone (29). These findings provide support for the daily dose range of 40–80 mg for lurasidone recommended by the U.S. Food and Drug Administration. Since clinically optimal dosages of antipsychotics may change over time as medications move from investigational settings into clinical practice (30), it remains to be seen whether wider use will alter the current clinical trial-based judgment regarding the appropriate dosage range for lurasidone.

Presented in part at the annual meeting of the American College of Neuropharmacology, Hollywood, Fla., Dec 6–10, 2009, and the 163rd annual meeting of the American Psychiatric Association, New Orleans, May 22–26, 2010. Received June 2010; revisions received Nov. 3, 2010, and Feb. 20, 2011; accepted March 21, 2011 (doi: 10.1176/appi.ajp.2011.10060907). From the Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn.; Sunovion Pharmaceuticals, Inc., Fort Lee, N.J.; Kanazawa University, Ishikawa, Japan; Quintiles, Inc., San Diego; the Department of Psychiatry, University of California, San Diego; and the Paladin Consulting Group, Hoboken, N.J. Address correspondence to Dr. Meltzer (herbert.meltzer@vanderbilt.edu).

Dr. Meltzer has received grant support from or served as a consultant to Amgen, Astellas, Azur, Cypress, Dainippon Sumitomo, Envivo, Forest, Janssen, Merck, Novartis, Roche, and Sunovion and holds stock in Acadia Pharmaceuticals. Dr. Cucchiaro, Dr. Silva, Mr. Ogasa, Ms. Phillips, Dr. Xu, Dr. Pikalov, and Dr. Loebel are employees of Sunovion Pharmaceuticals. Dr. Kalali is an employee of Quintiles, Inc. Dr. Schweizer has received payment for consulting or medical writing services from Alkermes, Orexigen Therapeutics, Pfizer, Sunovion Pharmaceuticals, and Titan Pharmaceuticals and owns stock in Pfizer.

The authors thank the participants of this study, as well as the members of the Lurasidone Study Group: in Colombia, Drs. M.M. Alzate, A. Arrieta, D. Cardona, L. Giraldo, and R. Cordoba; in India, Drs. V. Barhale, H.A. Ghandi, N.N. Raju, R. Sathianathan, Y.K. Krishanamurthy, S. Phadke, A.P. Chauhan, V. Indla, Sateesh Rao, Sathyanarayana Rao, S. Shah, H. Chandrashekhar, K. Pai, and P.S.V.N. Sharma; in Lithuania, Drs. V. Matoniene, S. Grigorjeva, V. Maciulis, and E. Mikaliunas; in the Philippines, Drs. A. Padilla, E. Reyes, E. Rondain, and J. Sy; and in the United States, Drs. G. Kaczenski, M. Lerman, R. Riesenberg, G. Brannon, R. Brenner, D. Brown, D. Feifel, J. Gilmore, S. Glass, A. Goenjian, R. Knapp, J. Kwentus, H. Meltzer, R. Mofsen, D. Nguyen, S. Potkin, S. Segal, J. Sonnenberg, T. Tran-Johnson, M. Valencerina, M. Bussel, J. Kunovac, G. Mattingly, M. Lesem, and C. Verghese.

References

1. Meltzer HY, Matsubara S, Lee JC: Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin$_2$ pK_i values. J Pharmacol Exp Ther 1989; 251:238–246
2. Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, De Loore K, Leysen JE: Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl) 1996; 124:57–73
3. Arranz MJ, de Leon J: Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Mol Psychiatry 2007; 12:707–747
4. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
5. Vandel P, Talon JM, Haffen E, Sechter D: Pharmacogenetics and drug therapy in psychiatry: the role of the CYP2D6 polymorphism. Curr Pharm Des 2007; 13:241–250
6. Ishiyama T, Loebel A, Cucchiaro J, Horisawa T, Tokuda K, Maasaki O, Ishibashi T, Stahl SM: Comparative receptor binding profile of lurasidone and other first and second generation antipsychotics, in Research Abstracts to the 2010 Annual Meeting. Washington, DC, American Psychiatric Association, 2010, p 213
7. Nakamura M, Ogasa M, Guarino J, Phillips D, Severs J, Cucchiaro J, Loebel A: Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry 2009; 70:829–836
8. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(suppl 20):22–33
9. Duggan L, Fenton M, Rathbone J, Dardennes R, El-Dosoky A, Indran S: Olanzapine for schizophrenia. Cochrane Database Syst Rev 2005; 2:CD001359
10. Davis JM, Chen N: Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004; 24:192–208
11. Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276
12. Marder SR, Davis JM, Chouinard G: The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997; 58:538–546
13. Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382–389

Do Not Copy or Distribute

14. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 212:11–19
15. Barnes TRE: A rating scale for drug-induced akathisia. Br J Psychiatry 1989; 154:672–676
16. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 534–537
17. Mather KJ, Hunt AE, Steinberg HO, Paradisi G, Hook G, Katz A, Quon MJ, Baron AD: Repeatability characteristics of simple indices of insulin resistance: implications for research applications. J Clin Endocrinol Metab 2001; 86:5457–5464
18. Brechenmacher T, Xu J, Dmitrienko A, Tamhane AC: A mixture gatekeeping procedure based on the Hommel test for clinical trial applications. J Biopharm Stat 2011; 21:748–767
19. Harvey PD, Ogasa M, Cucchiaro J, Loebel A, Keefe RSE: Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs ziprasidone. Schizophr Res 2011; 127:188–194
20. Ishibashi T, Horisawa T, Tokuda K, Ishiyama T, Ogasa M, Tagashira R, Matsumoto K, Nishikawa H, Ueda Y, Toma S, Ohki H, Tanno N, Saji I, Ito A, Ohno Y, Nakamura M: Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-HT_7 and 5-HT_{1A} receptor activity. J Pharmacol Exp Ther 2010; 334:171–181
21. Meyer JM, Loebel AD, Schweizer E: Lurasidone: a new drug in development for schizophrenia. Expert Opin Investig Drugs 2009; 18:1715–1726
22. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL: H_1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003; 28:519–526
23. Correll CU, Druss BG, Lombardo I, O'Gorman C, Harnett JP, Sanders KN, Alvir JM, Cuffel BJ: Findings of a US national cardiometabolic screening program among 10,084 psychiatric outpatients. Psychiatr Serv 2010; 61:892–898
24. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity: Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004; 65:267–272
25. Newcomer JW: Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry 2007; 68(suppl 4):8–13
26. Raz I, Eldor R, Cernea S, Shafrir E: Diabetes: insulin resistance and derangements in lipid metabolism: cure through intervention in fat transport and storage. Diabetes Metab Res Rev 2005; 21:3–14
27. Bostwick JR, Guthrie SK, Ellingrod VL: Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 2009; 29:64–73
28. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Asenjo Lobos C, Schwarz S, Davis JM: A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009; 166:152–163
29. Citrome L: Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. Int J Clin Pract 2011; 65:189–210
30. Citrome L, Reist C, Palmer L, Montejano L, Lenhart G, Cuffel B, Harnett J, Sanders KN: Dose trends for second-generation antipsychotic treatment of schizophrenia and bipolar disorder. Schizophr Res 2009; 108:238–244

Do Not Copy or Distribute

Clinical Guidance: Treatment of Schizophrenia With Lurasidone

Lurasidone is a recently approved antipsychotic drug for schizophrenia, with daily doses up to 80 mg. Doses above that level were associated with increased levels of akathisia in the 6-week study by Silva et al. At recommended doses, lurasidone is efficacious for both positive and negative symptoms with no effect on metabolic parameters. Olanzapine was associated with greater significant improvement on some measures but also had increased metabolic effects.

8. APPENDIX 3 NAKAMURA 2009 REPRINT

Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009; 70(6):829-836.

The attached document is provided for your use by Sunovion Pharmaceuticals Inc. Rights to this document have been secured for your sole use. A single copy, print or electronic, may be saved for your personal use. Please do not forward, send, or in any other way redistribute the attached document.

Do Not Copy or Distribute

Lurasidone in the Treatment of Acute Schizophrenia: A Double-Blind, Placebo-Controlled Trial

Mitsutaka Nakamura, Ph.D.; Masaaki Ogasa, M.S.; John Guarino, Ph.D.; Debra Phillips, A.S.; Joseph Severs, M.S.; Josephine Cucchiaro, Ph.D.; and Antony Loebel, M.D.

Objective: Lurasidone is a novel psychotropic agent with high affinity for D_2 and 5-HT_{2A} receptors, as well as for receptors implicated in the enhancement of cognition and mood and the reduction of negative symptoms (5-HT_7, 5-HT_{1A}, and α_{2c}). The objective of the study was to evaluate the safety and efficacy of lurasidone in patients hospitalized for an acute exacerbation of DSM-IV–defined schizophrenia.

Method: Patients were randomly assigned to 6 weeks of double-blind treatment with a fixed dose of lurasidone 80 mg (N = 90, 75.6% male, mean age = 39.7 years, mean baseline score on the Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale [BPRSd] = 55.1) or placebo (N = 90, 77.8% male, mean age = 41.9 years, mean BPRSd score = 56.1). The primary efficacy measure was the BPRSd. The study was conducted from May to December 2004.

Results: At day 42, last-observation-carried-forward endpoint, treatment with lurasidone was associated with significant improvement compared to placebo on the BPRSd (least squares mean ± SE = –8.9 ± 1.3 vs. –4.2 ± 1.4; p = .012), as well as on all secondary efficacy measures, including the PANSS total score (–14.1 ± 2.1 vs. –5.5 ± 2.2; p = .004) and the PANSS positive (–4.3 ± 0.7 vs. –1.7 ± 0.7; p = .006), negative (–2.9 ± 0.5 vs. –1.3 ± 0.5; p = .025), and general psychopathology (–7.0 ± 1.1 vs. –2.7 ± 1.2; p = .0061) subscales. Significant improvement was seen as early as day 3, based on BPRSd, PANSS, and Clinical Global Impressions-Severity of Illness assessments. Treatment with lurasidone was generally well tolerated and was not associated with adverse changes in metabolic or electrocardiogram parameters. There were no clinically significant differences between lurasidone and placebo in objective measures of extrapyramidal symptoms.

Conclusions: The results of this study suggest that the novel psychotropic agent lurasidone is a safe and effective treatment for patients with an acute exacerbation of schizophrenia.

Trial Registration: clinicaltrials.gov Identifier: NCT00088634

J Clin Psychiatry 2009;70(6):829–836

© Copyright 2009 Physicians Postgraduate Press, Inc.

Received November 27, 2008; accepted March 23, 2009.

From Dainippon Sumitomo Pharma America, Inc, Fort Lee, NJ. (Dr. Nakamura); and Dainippon Sumitomo Pharma Co, Ltd, Osaka, Japan (Messrs. Ogasa and Severs; Drs. Guarino, Cucchiaro, and Loebel; and Ms. Phillips).

Dr. Nakamura is currently employed at Setsunan University, Osaka, Japan.

This study was funded by Dainippon Sumitomo Pharma America, Inc, Fort Lee, NJ.

The data reported in the current manuscript were previously presented, in part, at the International Congress on Schizophrenia Research; March 27–28, 2007; Colorado Springs, Colo.

Acknowledgments are listed at the end of the article.

Messrs. Ogasa and Severs; Drs. Guarino, Cucchiaro, and Loebel; and Ms. Phillips are full-time employees of Dainippon Sumitomo Pharma America, Inc. Dr. Nakamura was an employee of Dainippon Sumitomo Pharma Co, Ltd, at the time the study was conducted.

Corresponding author and reprints: Masaaki Ogasa, M.S., Dainippon Sumitomo Pharma America, Inc, One Bridge Plaza, Suite 510, Fort Lee, NJ 07024 (e-mail: mogasa@dsp-a.com).

Do Not Copy or Distribute

Lurasidone (SM-13496, (3a*R*,4*S*,7*R*,7a*S*)- 2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4, 7-methano-2*H*-isoindole-1,3-dione hydrochloride) is a novel psychotropic agent discovered by Dainippon Sumitomo Pharma research laboratories in Japan. Lurasidone has a high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors. However, despite its potent D_2-antagonist activity, treatment with lurasidone is associated with minimal extrapyramidal side effects in animal models.[1]

Compared with other atypical antipsychotic agents, lurasidone has similar binding affinities for D_2 and 5-HT_{2A} receptor subtypes, but greater affinity for serotonin 5-HT_7, 5-HT_{1A}, and norepinephrine α_{2c} receptor subtypes.[1] Lurasidone has little affinity for norepinephrine α_1 and no affinity for histamine H_1 or cholinergic M_1 receptors.[1]

The pharmacologic and preclinical profile of lurasidone suggests that it may be an effective antipsychotic drug in humans, with a reduced potential for histamine H_1– and 5-HT_{2C}–mediated weight gain, histamine H_1– and cholinergic M_1–mediated central nervous system (CNS) depression, and α_1 adrenergic–mediated orthostatic hypotension.

The primary objective of the current study was to evaluate the efficacy of lurasidone in the treatment of patients suffering from an acute exacerbation of schizophrenia. The secondary objectives were to assess the safety and

tolerability of lurasidone and to evaluate the ability of lurasidone to improve secondary measures such as negative symptoms and depressive symptoms.

METHOD

Patients

Men and women between 18 and 64 years of age, inclusive, who were hospitalized for an acute exacerbation of schizophrenia meeting DSM-IV criteria[2] (disorganized, paranoid, or undifferentiated subtypes) based on the Structured Clinical Interview for DSM-IV Disorders-Clinician's Version (SCID-CV)[3] were enrolled. Patients were also required to have (1) a minimum illness duration of at least 1 year; (2) a Brief Psychiatric Rating Scale (BPRSd)[4] total score, extracted from the Positive and Negative Syndrome Scale (PANSS),[5] of at least 42, with a score of at least 4 on 2 or more positive symptom items; (3) a Clinical Global Impressions-Severity of Illness scale (CGI-S)[4] score ≥ 4 (illness of at least moderate severity); (4) a Simpson-Angus Scale (SAS)[6] score of < 2; and (5) an Abnormal Involuntary Movement Scale (AIMS)[7] score of < 3. Women were required to be at least 1 year postmenopausal, surgically sterilized, or using a medically reliable form of birth control. Patients were also excluded if their baseline BPRSd score was < 42, or if they had a ≥ 20% decrease from screen to baseline in their BPRSd score.

Key exclusion criteria included (1) DSM-IV diagnosis of schizophreniform disorder, schizoaffective disorder, or the catatonic or residual subtypes of schizophrenia; (2) no hospitalizations in the month prior to screening (the current hospitalization must have begun < 3 weeks prior to screening); (3) failure to respond to adequate trials of 2 or more antipsychotic agents from 2 different classes; (4) evidence of chronic neurologic disease, organic mental disorder, clinically significant medical illness, and/or laboratory or electrocardiogram (ECG) abnormality, or any condition that might interfere with the absorption, metabolism, or excretion of study medication; (5) prolactin level ≥ 200 ng/mL at screen or baseline; (6) use of depot neuroleptics within 1 standard treatment cycle, or use of antidepressants (including reversible monoamine oxidase inhibitors [MAOIs]) within 1 week of entry into washout (1 month for fluoxetine or irreversible MAOIs); or (7) positive urine drug screen or a history in the past 3 months of alcohol or substance abuse.

The protocol was approved by institutional review boards (ethics committees) at each of the 22 U.S. sites and conducted from May to December 2004. Study conduct was consistent with the Declaration of Helsinki. The study was explained to prospective participants, and written informed consent was obtained prior to study entry from either the patient or the patient's legal guardian.

Study Design and Treatment

This was a multicenter, parallel-group trial in which eligible patients completed a 7- to 14-day screening period. Patients who continued to meet study entry criteria were hospitalized for a single-blind, 3- to 7-day placebo washout period before being randomly assigned, in a 1:1 ratio, to 6 weeks of double-blind treatment with a once-daily morning dose of lurasidone 80 mg or placebo taken with or immediately following breakfast. Patients remained in the hospital until the day 28 assessment time point. After day 28, patients could be discharged to the outpatient setting or could remain in the hospital at the discretion of the investigator.

During the placebo washout period, patients were not permitted to take any CNS medication other than benztropine mesylate, lorazepam, zolpidem, or temazepam on an as-needed basis until 8 hours prior to baseline efficacy assessments. As-needed use of these concomitant medications was also permitted during the double-blind phase, until 8 hours prior to any efficacy assessment.

Assessments

Efficacy. The primary efficacy measure was the BPRSd extracted from the PANSS. The secondary efficacy measures included the PANSS total and positive, negative, general psychopathology, and cognitive subscales[8]; the CGI-S; and the 10-item, clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS).[9] The PANSS was completed at screen, baseline, and double-blind treatment days 3, 7, 14, 21, 28, 35, and 42 (or on early termination). The CGI-S was omitted at the screening visit, but otherwise was completed at the same time points. The MADRS was completed at baseline and day 42 (or on early termination). Patients were evaluated in the inpatient setting from the screen assessment to the day 28 assessment. Weekly evaluations were conducted on an outpatient basis after day 28 for those patients released from the hospital. After release from the hospital, compliance with study treatment was assessed by weekly pill counts.

Investigators received expert training, prior to the start of the study and again at the midpoint in the study, in the use of the SCID-CV and the PANSS and in the assessment of extrapyramidal symptoms.

Safety and tolerability. All adverse events volunteered or observed during the study were recorded, together with their severity, duration, and the investigator's assessment of the possible causative relationship to study drug. Movement disorders were assessed using the 10-item SAS to measure extrapyramidal symptoms (0 = normal to 4 = most severe),[6] the Barnes Akathisia Scale to evaluate akathisia (0 = normal to 5 = most severe),[10] and the AIMS to evaluate tardive dyskinesia (0 = normal to 4 = most severe).[7] These 3 scales were assessed at screen, baseline, and days 3, 7, 14, 21, 28, 35, and 42 (or on early termination). A 12-lead ECG was done at screen, baseline, day 1

Do Not Copy or Distribute

(predose and 1.5 hours postdose), and days 7, 14, and 42 at approximately 1.5 hours postdose. Supine and standing vital signs and weight were obtained at every assessment visit. Clinical laboratory tests (blood chemistry, hematology, prolactin, urine pregnancy) were obtained at screen, baseline, and days 21 and 42 (or on early termination). A physical examination was performed at screen, baseline, and day 42 (or on early termination). Urine pregnancy and drug screening was performed at each assessment visit after discharge from the hospital.

Statistical Analysis

The intent-to-treat population consisted of all randomly assigned patients who received at least 1 dose of study medication and had at least 1 postrandomization efficacy assessment during the double-blind treatment phase.

Allowing for a 10% attrition rate prior to the first on-drug assessment, and assuming a BPRSd change score standard deviation of 10.5, it was estimated that 80 patients per dosage group would provide at least 90% power to detect a 6-point difference between lurasidone and placebo on a 2-sided t test at an α level of .050.

Descriptive statistics were calculated for baseline demographic and clinical characteristics of each treatment group.

For efficacy measures, descriptive statistics were calculated for the actual value and the change from baseline value. Efficacy analyses were performed using a 2-way analysis of covariance model with the baseline to day 42 last-observation-carried-forward (LOCF) endpoint change score for each efficacy measure as the dependent variable and with treatment group and study center as main effects and baseline score on each efficacy measure as a covariate. No evidence of treatment-by-center or treatment-by-baseline interaction was found on an exploratory analysis. Day 42 LOCF endpoint analyses were performed, as well as an observed case analysis of patients available at each study visit. Analyses of covariance of change scores were performed on the BPRSd and PANSS total scores, the PANSS subscales (positive and negative symptom, general psychopathology, and cognitive [consisting of the following 5 items: P2, N5, G5, G10, and G11]), the MADRS total score, and the CGI-S score. The Cohen d effect size was calculated for day 42 efficacy measures as the between-treatment difference score divided by the pooled standard deviation.

Patients achieving a $\geq 20\%$ reduction from baseline in PANSS score were classified as responders, and the proportion was compared using the Cochran-Mantel-Haenszel test, controlling for center.

For adverse events, number needed to harm (NNH) was calculated as 1 divided by the difference in the risk of an event for lurasidone versus placebo. From a clinical standpoint, NNH represents the number of patients who need to be given the experimental treatment for 1 more patient to experience the event than would be expected to experience the event with placebo.

The NNH is the number of patients who need to be treated with the first treatment rather than with the second treatment of the given treatment contrast in order for 1 additional patient to be harmed. The NNH was calculated as $NNH = 1/(Pt - Pc)$. Pt is the probability risk of the study treatment, and Pc is the probability risk of the comparator (placebo).

RESULTS

A total of 180 patients (79.6%), out of 226 screened, met study entry criteria at the end of the single-blind placebo washout and were randomly assigned to double-blind treatment (Figure 1). At pretreatment baseline, the 2 treatment groups were similar across key demographic and clinical characteristics (Table 1). Patients were predominantly male and between the ages of 30 and 50 years. Paranoid was the most common schizophrenia subtype.

Study Treatment

The mean ± SD duration of study treatment was similar among patients randomly assigned to lurasidone 80 mg (30.1 ± 15.3 days) and placebo (32.3 ± 12.9 days). During the 4 weeks of inpatient treatment, compliance rates were > 99% for both lurasidone and placebo. Mean medication compliance among outpatients in the study was similar for both lurasidone and placebo (92.3% vs. 88.2%).

The overall discontinuation rate was slightly higher in the placebo group (47.8%) compared with the lurasidone group (42.2%; Figure 1). Discontinuation due to lack of efficacy was significantly higher in the placebo group compared to the lurasidone group (32.2% vs. 10.0%; 2-sided Fisher exact test; $p < .001$). Discontinuation due to withdrawal of consent (20.0% vs. 10.0%; 2-sided Fisher exact test; $p = .094$) and adverse events (6.7% vs. 1.1%; 2-sided Fisher exact test; $p = .118$) were both marginally higher in the lurasidone compared to the placebo group.

Efficacy

Treatment with lurasidone 80 mg was associated with statistically significantly greater improvement than placebo on the primary efficacy measure, day 42 LOCF endpoint change in BPRSd (Table 2). The onset of improvement on lurasidone was rapid, achieving statistical significance compared to placebo by day 3, and continued at a significant level throughout the 6 weeks of study treatment (Figure 2A). The PANSS total score and CGI-S showed a similar pattern of statistically significant early and sustained improvement with lurasidone (Figure 2B, Figure 2C).

Do not copy or distribute

Figure 1. Flow Diagram for a 6-Week Study of Lurasidone Versus Placebo in Acute Schizophrenia

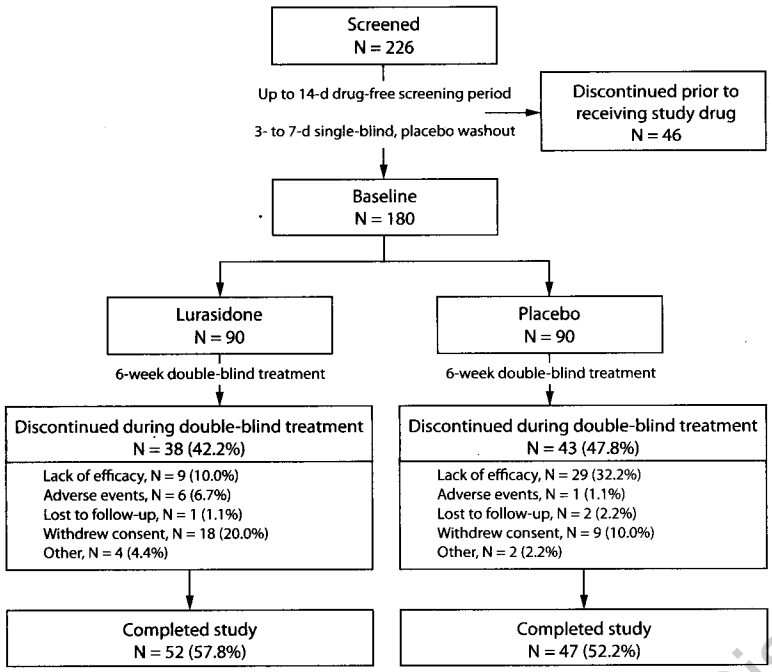


Table 1. Patient Characteristics at Baseline, Safety Sample

Parameter	Lurasidone (N = 90)	Placebo (N = 90)
Sex, male, N (%)	68 (75.6)	70 (77.8)
Race, N (%)		
White	35 (38.9)	26 (28.9)
Black	47 (52.2)	56 (62.2)
Other	8 (8.9)	8 (8.9)
Age, y		
Mean (SD)	39.7 (9.9)	41.9 (9.8)
Range	22–62	21–63
BMI, kg/m^2, mean (SD)	30.7 (8.5)	31.2 (7.7)
Tobacco use, yes, N (%)	73 (81.1)	68 (75.6)
DSM-IV schizophrenia subtype, N (%)		
Paranoid	73 (81.1)	72 (80.0)
Undifferentiated	13 (14.4)	14 (15.6)
Disorganized	4 (4.4)	4 (4.4)
Prior medications, N (%)		
Antipsychotics		
Atypical	68 (75.6)	71 (78.9)
Typical	6 (6.7)	12 (13.3)
Benzodiazepines	24 (26.7)	25 (27.8)
Antidepressants	24 (26.7)	24 (26.7)
BPRSd score, mean (SD)	55.1 (6.0)	56.1 (6.8)
PANSS score, mean (SD)		
Total score	94.4 (10.9)	96.0 (11.6)
Positive symptoms	24.0 (3.8)	25.0 (4.2)
Negative symptoms	23.4 (4.8)	23.5 (4.4)
General psychopathology	47.0 (6.3)	47.5 (6.3)
Cognitive	14.5 (3.5)	15.2 (4.1)
MADRS score, mean (SD)	14.2 (8.0)	14.5 (8.3)
CGI-S score, mean (SD)	4.8 (0.7)	4.8 (0.7)

Abbreviations: BMI = body mass index, BPRSd = Brief Psychiatric Rating Scale (extracted from PANSS), CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

Treatment with lurasidone also demonstrated significant efficacy compared to placebo on all other secondary measures (Table 2), including the PANSS positive (least squares mean ± SE = –4.3 ± 0.7 vs. –1.7 ± 0.7; p = .006), negative (–2.9 ± 0.5 vs. –1.3 ± 0.5; p = .025), cognitive (–2.1 ± 0.4 vs. –0.5 ± 0.4; p = .0015), and general psychopathology (–7.0 ± 1.1 vs. –2.7 ± 1.2; p = .0061) subscales.

The Cohen d effect sizes were 0.39, 0.44, and 0.41 for the BPRSd, PANSS total score, and CGI-S score, respectively. Cohen d effect sizes were 0.42, 0.34, and 0.49 for the PANSS positive, negative, and cognitive subscales, respectively.

With ≥ 20% improvement in PANSS score used as the criterion to define treatment response, the proportion of responders was significantly higher with lurasidone compared to placebo on the day 42 LOCF endpoint analysis (44.4% vs. 26.7%; p = .007).

Despite relatively low baseline MADRS scores (mean score of 14), lurasidone also demonstrated significant efficacy compared to placebo on the MADRS (LS mean ± SE = –2.9 ± 0.8 vs. –0.1 ± 0.9; p = .019; Cohen d effect size, 0.37). In a post hoc analysis of the subgroup of patients (combined subgroup N = 113; 62.8% of total intent-to-treat population) with elevated levels of depressive symptomatology (baseline MADRS ≥ 12; mean = 18.7), the effect size was 0.44 (LS mean ± SE MADRS change at day 42 LOCF endpoint, –6.1 ± 1.2 vs. –2.7 ± 1.2; p = .033).

Safety and Tolerability

The incidence of at least 1 adverse event was nonsignificantly higher with lurasidone compared to placebo (76.7% vs. 68.9%; Table 3). The most frequent adverse events were gastrointestinal (nausea, constipation, vomiting, dyspepsia; Table 3). However, only nausea was significantly more frequent in the lurasidone group compared to placebo (16.7% vs. 3.3%; p = .005; NNH = 7.5). The incidence of adverse events rated as severe was low in both the lurasidone group and the placebo group (N = 7 vs. N = 5). Among adverse events in the lurasidone group with an incidence ≥ 5%, 4 were rated as severe: insomnia (N = 2) and anxiety and akathisia (1 event each).

Treatment-emergent adverse events leading to discontinuation of study treatment occurred in 6 patients in the lurasidone group: 1 patient reported nausea, dyskinesia, and akathisia; 1 reported dystonia and akathisia; 1 reported anxiety and insomnia; and 1 each reported facial

Do Not Copy or Distribute

Table 2. Endpoint Change in Primary and Secondary Efficacy Measures[a]

Parameter	N	LS Mean (SE) Change	95% CI	p Value
BPRSd				
Lurasidone	90	–8.9 (1.3)	–11.5 to –6.2	.0118
Placebo	90	–4.2 (1.4)	–6.9 to –1.5	
PANSS total				
Lurasidone	90	–14.1 (2.1)	–18.3 to –9.9	.0040
Placebo	90	–5.5 (2.2)	–9.8 to –1.2	
PANSS positive symptoms				
Lurasidone	90	–4.3 (0.7)	–5.7 to –3.0	.0060
Placebo	90	–1.7 (0.7)	–3.1 to –0.3	
PANSS negative symptoms				
Lurasidone	90	–2.9 (0.5)	–3.9 to –1.8	.0250
Placebo	90	–1.3 (0.5)	–2.3 to –0.2	
PANSS general psychopathology				
Lurasidone	90	–7.0 (1.1)	–9.3 to –4.8	.0061
Placebo	90	–2.7 (1.2)	–5.0 to –0.4	
PANSS cognitive				
Lurasidone	90	–2.1 (0.4)	–2.8 to –1.4	.0015
Placebo	90	–0.5 (0.4)	–1.2 to 0.2	
CGI-S				
Lurasidone	90	–0.6 (0.1)	–0.8 to –0.4	.0072
Placebo	90	–0.2 (0.1)	–0.4 to 0.0	
MADRS				
Lurasidone	86	–2.9 (0.8)	–4.6 to –1.3	.0187
Placebo	83	–0.1 (0.9)	–1.9 to 1.6	

[a]Analysis of covariance model based on LOCF endpoint data including treatment, center, and baseline terms.

Abbreviations: BPRSd = Brief Psychiatric Rating Scale (extracted from PANSS), CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

Do not copy or Distribute

swelling, headache, and increased liver enzymes (alanine aminotransferase and aspartate aminotransferase). Adverse events leading to study discontinuation occurred in 1 placebo-treated patient, who reported psychotic disorder and had an increase in blood creatine phosphokinase levels. None of the patients who discontinued due to withdrawal of consent had a severe adverse event.

Physical examination and vital signs. There were no clinically significant, treatment-emergent changes with either lurasidone or placebo in physical examination findings (including fundoscopy), heart rate, or systolic or diastolic blood pressure.

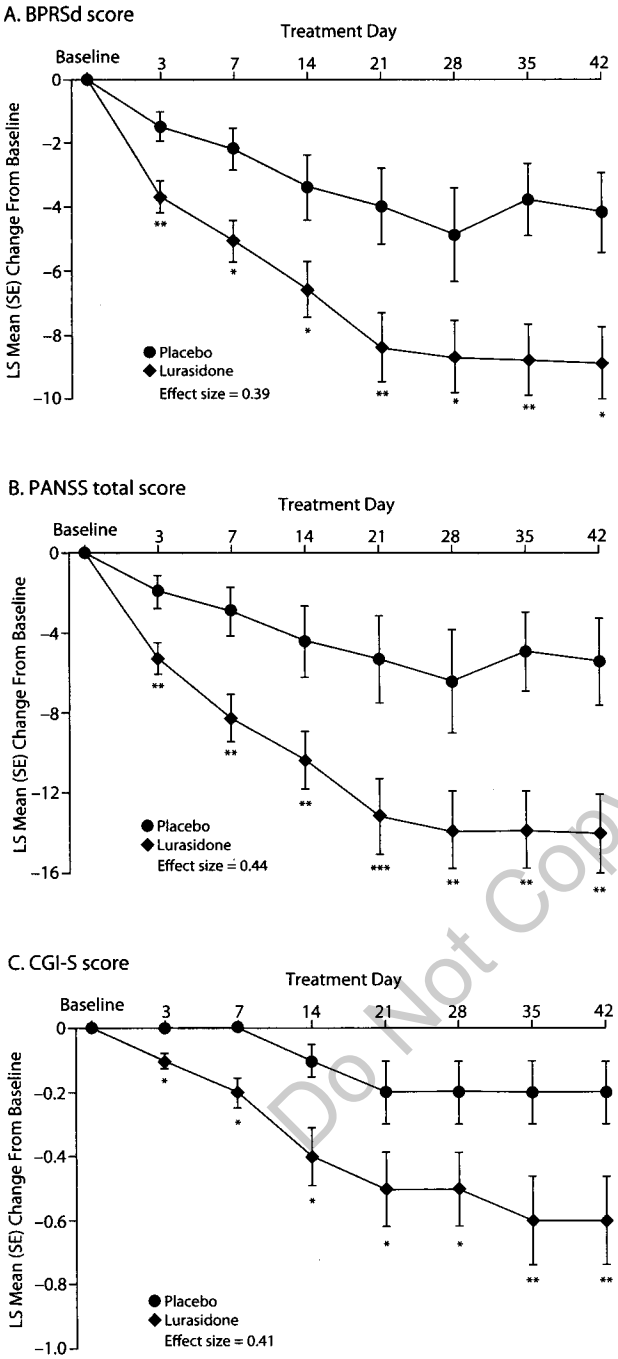
Extrapyramidal symptoms. Mean ± SD endpoint change from baseline was comparable for the lurasidone and placebo groups, respectively, on the AIMS (+0.3 ± 2.1 vs. +0.5 ± 2.5; p = .61) and the SAS (+0.2 ± 1.4 vs. +0.1 ± 1.3; p = .58). However, there was a modest but significant between-group difference at endpoint on the BAS (+0.2 ± 0.9 vs. –0.1 ± 0.7; p = .03). In addition, treatment with lurasidone and placebo was associated with similar rates of use of benztropine (12.2% vs. 8.9%) and β-adrenoceptor antagonists (2.2% vs. 4.4%). Use of as-needed lorazepam and benzodiazepine hypnotics was also similar for both lurasidone and placebo (87.8% vs. 85.6%).

Body weight. Median change from baseline in weight was 0.9 kg for lurasidone (N = 89) and 0.5 kg for placebo (N = 90). The incidence of clinically significant weight gain (≥ 7% increase from baseline) was 6.7% with lurasidone versus 7.8% with placebo. The incidence of clinically significant weight gain was slightly lower among patients treated with lurasidone compared to placebo in all body mass index (BMI) subgroups, including individuals with BMI > 27 (3.8% vs. 4.8%).

Metabolic laboratory tests. There were no significant differences between lurasidone and placebo in endpoint change in cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, or fasting blood glucose (Figure 3). Mean serum cholesterol and triglycerides decreased with lurasidone treatment during the course of the study. There was a statistically significant difference between treatment groups in glycosylated hemoglobin (HbA1c) levels (mean increase of 0.1% with lurasidone vs. a mean change of 0.0% with placebo; p < .05), but this difference was not clinically significant.

Prolactin and other laboratory tests. Treatment with lurasidone was associated with a small but significant median increase in prolactin levels at endpoint compared to placebo (+2.4 vs. –0.3 ng/mL; p < .05). There was a gender difference in the effect of lurasidone on prolactin, with larger median increases observed in the small group of women (N = 19; +9.2 ng/mL) compared to men (N = 57; +1.4 ng/mL). None had any prolactin-related adverse events (i.e., galactorrhea, menstrual disturbances, sexual dysfunction). The Pearson correlation coefficient between serum lurasidone concentrations and prolactin levels was

Figure 2. Efficacy Measures During Treatment With Lurasidone (N = 90) or Placebo (N = 90)[a]



[a]Analysis of covariance with treatment, center, and baseline terms. Analysis sample consists of last-observation-carried-forward data at each assessment timepoint.
*p < .05.
**p < .01.
*** p < .001.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale (extracted from PANSS), CGI-S = Clinical Global Impressions-Severity of Illness scale, LS = least squares, PANSS = Positive and Negative Syndrome Scale.

Table 3. Treatment-Emergent Adverse Events Occurring With an Incidence ≥ 5% (all-causality)[a]

Adverse Event	Lurasidone (N = 90)	Placebo (N = 90)
Nausea	15 (16.7)*	3 (3.3)
Headache	10 (11.1)	9 (10.0)
Constipation	10 (11.1)	5 (5.6)
Vomiting NOS	10 (11.1)	5 (5.6)
Dyspepsia	10 (11.1)	3 (3.3)
Somnolence	10 (11.1)	3 (3.3)
Insomnia	9 (10.0)	3 (3.3)
Sedation	9 (10.0)	4 (4.4)
Akathisia	8 (8.9)	3 (3.3)
Anxiety	6 (6.7)	1 (1.1)
Toothache	5 (5.6)	3 (3.3)
Upper respiratory tract infection NOS	3 (3.3)	6 (6.7)
Back pain	3 (3.3)	5 (5.6)
At least 1 adverse event	69 (76.7)	62 (68.9)
No. of adverse events rated as severe	7	5

[a]Data shown as number (percentage) of patients experiencing events, except in the last row, which shows number of events.
*p = .005.
Abbreviation: NOS = not otherwise specified.

Do Not Copy or Distribute

0.39, suggesting a moderate correlation. Three patients treated with lurasidone (2 male, 1 female) had treatment-emergent prolactin concentrations at day 42 LOCF endpoint between 50 and 100 ng/mL.

There were no clinically significant, treatment-emergent changes in hematology or chemistry results with lurasidone when compared to placebo.

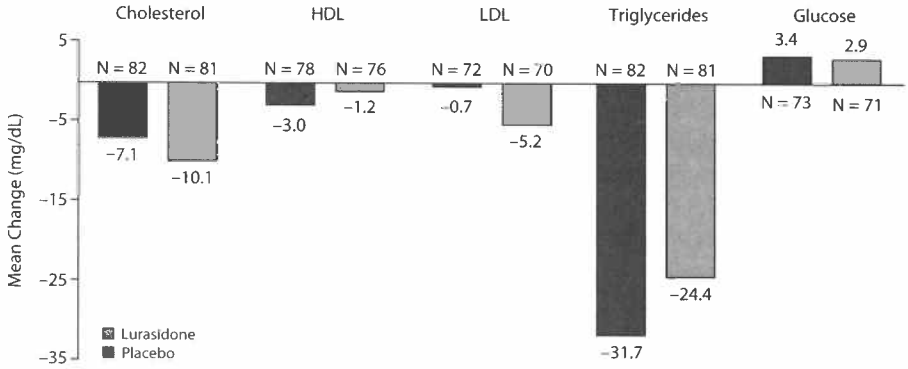
Electrocardiogram. Treatment with lurasidone was not associated with any significant treatment-emergent ECG abnormalities. Mean ± SD QTc (Fridericia) change was −1.2 ± 17.3 and +0.9 ± 16.7 ms for lurasidone and placebo, respectively. No subjects in either group experienced a QTc change > 500 ms during the study.

DISCUSSION

This is the first reported double-blind, placebo-controlled clinical trial evaluating the efficacy of the novel psychotropic lurasidone in the treatment of patients with an acute exacerbation of schizophrenia. The results demonstrate consistent antipsychotic efficacy in all primary and secondary efficacy measures, including the BPRSd, the CGI-S, and the PANSS total and subscale scores, across all study visits through the 6-week primary endpoint.

Notably, significant improvement in BPRSd, PANSS total, and CGI-S scores was observed by day 3 of lurasidone treatment, suggesting an early onset of treatment effect. While antipsychotics have traditionally been thought to have a delayed onset of action, several meta-analyses[11,12] suggest that significant improvement may occur within the first week of treatment. Early onset has not always been measured in previous trials; therefore, the consistency of this finding for individual atypical

Figure 3. Change From Baseline in Metabolic Parameters With Lurasidone or Placebo



Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

drugs remains to be determined. Due to the absence of adverse event–limiting α_1 adrenergic and antihistaminergic effects, treatment with lurasidone can be initiated at a therapeutically effective dose, which may contribute to the potential for rapid onset of efficacy.

Lurasidone's lack of affinity for muscarinic M_1 and histamine H_1 receptors, and high affinity for 5-HT_7, 5-HT_{1A}, α_{2C} receptors,[1] suggests the potential for enhancement of cognitive function.[13] Consistent with this receptor binding profile, lurasidone demonstrated significant improvement in a group of items that comprise a proposed cognition subscale,[14] including conceptual disorganization, poor attention, and difficulty in abstract thinking. This preliminary result is consistent with preclinical findings that lurasidone reverses scopolamine- and MK-801–induced impairment in learning and memory in the passive-avoidance test in rats.[15–17] However, since the PANSS cognitive symptom subscale has not consistently demonstrated good validity as a measure of neurocognitive change,[18] a more definitive characterization of the cognitive effects of lurasidone awaits completion of ongoing clinical trials.

Clinically significant depressive symptoms occur in one quarter or more of patients with schizophrenia[19,20] and have been shown to be more responsive to selected second-generation compared to first-generation antipsychotics, although the number of well-designed, adequately powered clinical trials is limited.[21,22] Treatment with lurasidone significantly improved mean MADRS scores when compared to placebo, with the largest effect observed among the subgroup of patients (62.8%) with clinically significant depressive symptoms (baseline MADRS ≥ 12; mean = 18.7).

Lurasidone was well tolerated in the current study. The percentage of patients reporting at least 1 adverse event was nonsignificantly higher (7.8%) in the lurasidone group compared to the placebo group. Only 1 adverse event (nausea; NNH = 7.5) was significantly more frequent in the lurasidone group. Overall, the most frequent adverse events were gastrointestinal (nausea, constipation, vomiting, dyspepsia). The incidence of adverse events rated as severe was low in both the lurasidone and placebo groups (N = 7 vs. N = 5). Only 3 adverse events were considered serious in the lurasidone group, compared to 4 categorized as serious in the placebo group. All 3 serious adverse events in the lurasidone group were due to exacerbation of preexisting schizophrenia, and none were judged by the investigator to be due to lurasidone. Adverse events leading to discontinuation were more frequent in the lurasidone group, but the absolute frequency was low (6.7%) and in the range reported for short-term trials of other atypical antipsychotics.

No clinically significant differences were seen between lurasidone and placebo in any of the 3 extrapyramidal symptom score scales. Furthermore, use of antiparkinsonian medication was similarly low in both the lurasidone group (12.2%) and the placebo group (8.9%).

Although lurasidone was associated with a small (0.5 kg) placebo-adjusted increase in weight, there were no clinically significant differences between lurasidone and placebo in laboratory parameters, including metabolic assessments (cholesterol, triglycerides, HDL, LDL, fasting blood glucose). A minor observed increase in HbA1c levels (+0.1) was not regarded as clinically significant and may have been due to nonspecific measurement variation.

Several possible study limitations should be noted. First, the use of a single fixed dose of lurasidone did not permit us to evaluate dose-response effects and may have reduced the tolerability of the drug. Second, the absence of an atypical antipsychotic comparator group limits our ability to draw inferences regarding the comparative efficacy and tolerability of lurasidone. Finally, the relatively high discontinuation rate (42%) in the current study, while typical of double-blind, placebo-controlled trials in schizophrenia, nonetheless complicates the analysis of the data.

Do Not Copy or Distribute

In conclusion, the results of this study indicate that lurasidone is an effective treatment for patients with an acute exacerbation of schizophrenia. This study utilized a fixed daily dose of 80 mg. The full dose range of lurasidone will be characterized in further studies. Significant improvement occurred early, by day 3, and was consistent across all primary and secondary efficacy measures, including positive and negative symptoms as well as assessments of depressed mood and cognitive impairment. Treatment with lurasidone was well tolerated and was not associated with adverse changes in metabolic or ECG parameters. Further research is underway to fully characterize the antipsychotic effects of lurasidone in patients with schizophrenia, as well as its potential for enhancement of cognitive deficits and improvement in other schizophrenic psychopathology beyond the core psychotic syndrome.

Drug names: benztropine mesylate (Cogentin and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), temazepam (Restoril and others), zolpidem (Zolpimist, Ambien, and others).

Acknowledgments: Edward Schweizer, M.D., provided paid editorial assistance funded by Dainippon Sumitomo in the preparation of an early draft of the manuscript. The authors thank the patients who participated in this study, as well as the members of the Lurasidone Study Group: David W. Brown, M.D.; Andrew Cutler, M.D.; Donald J. Garcia, M.D.; Steven J. Glass, M.D.; Robert L. Horne, M.D.; Gregory S. Kaczenski, M.D.; Mark N. Lerman, M.D.; Michael D. Lesem, M.D.; Robert E. Litman, M.D.; Harry Edward Logue, M.D.; Adam F. Lowy, M.D.; David M. Marks, M.D.; Mark A. Novitsky, M.D.; Pauline S. Powers, M.D.; Sohail S. Punjwani, M.D.; Robert Riesenberg, M.D.; Murray H. Rosenthal, D.O.; David A. Sack, M.D.; Scott D. Segal, M.D.; Rajinder S. Shiwach, M.D.; Tram K. Tran-Johnson, Pharm.D.; David P. Walling, Ph.D.; Dan L. Zimbroff, M.D. (deceased).

REFERENCES

1. Ishibashi T, Horisawa T, Yabuuchi K, et al. Receptor binding characteristics of SM-13496, a novel atypical antipsychotic agent. Soc Neurosci Abstr 2002;894:7
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
3. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV (SCID). Washington, DC: American Psychiatric Press; 1997
4. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised. US Department of Health, Education, and Welfare (ADM) no. 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
5. Kay SR, Fiszbein A, Opler L. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
6. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
7. Guy WA. Abnormal Involuntary Movement Scale (AIMS). ECDEU Assessment Manual for Psychopharmacology, revised. US Department of Health, Education, and Welfare (ADM) no. 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
8. Lindenmayer J-P, Grochowski S, Hyman RB. Five factor model of schizophrenia: replication across samples. Schizophr Res 1995;14(3): 229–234
9. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
10. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
11. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. Arch Gen Psychiatry 2003;60(12):1228–1235
12. Leucht S, Busch R, Hamann J, et al. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed, and extended. Biol Psychiatry 2005;57(12):1543–1549
13. Terry AV Jr, Buccafusco JJ, Wilson C. Cognitive dysfunction in neuropsychiatric disorders: selected serotonin receptor subtypes as therapeutic targets. Behav Brain Res 2008;195(1):30–38
14. Good KP, Rabinowitz J, Whitehorn D, et al. The relationship of neuropsychological test performance with the PANSS in antipsychotic naïve, first-episode psychosis patients. Schizophr Res 2004;68:11–19
15. Ishiyama T, Matsumoto Y, Tokuda K, et al. Effects of SM-13496, a novel serotonin-dopamine antagonist, and other antipsychotics on cognitive performance in the rat passive avoidance test [poster]. Presented at the 33rd annual meeting of the Society for Neuroscience; November 2003; New Orleans, La
16. Ishiyama T, Tokuda K, Ishibashi T, et al. Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801–induced impairment of learning and memory in the rat passive-avoidance test. Eur J Pharmacol 2007;572(2–3):160–170
17. Enomoto T, Ishibashi T, Tokuda K, et al. Lurasidone reverses MK-801–induced impairment of learning and memory in the Morris water maze and radial-arm maze tests in rats. Behav Brain Res 2008;186(2):197–207
18. Lykouras L, Oulis P, Psarros K, et al. Five-factor model of schizophrenic psychopathology: how valid is it? Eur Arch Psychiatry Clin Neurosci 2000;250(2):93–100
19. Burrows GD, Norman TR. Affective mood disturbance in schizophrenia. In: Ancill R, ed. Schizophrenia: Exploring The Spectrum of Psychosis. West Sussex, England: John Wiley & Sons Ltd; 1994:205–214
20. Siris SG. Depression in schizophrenia: perspective in the era of "atypical" antipsychotic agents. Am J Psychiatry 2000;157(9):1379–1389
21. Whitehead C, Moss S, Cardno A, et al. Antidepressants for the treatment of depression in people with schizophrenia: a systematic review. Psychol Med 2003;33(4):589–599.
22. Möller HJ. Antidepressive effects of traditional and second generation antipsychotics: a review of the clinical data. Eur Arch Psychiatry Clin Neurosci 2005;255(2):83–93

Do Not Copy or Distribute

visit *The Journal of Clinical Psychiatry* @
PSYCHIATRIST.COM