Dyanavel XR® Formulary Submission

Dyanavel XR® (amphetamine)

Extended-Release Oral Suspension, CII

Date of Document: 2/2016

This is a confidential document provided to [name of requestor] in response to an unsolicited request from [name of requestor].

The format of this document follows that of the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions 2.1 but does not contain all of the elements. The information presented in this dossier is focused on attention deficit/hyperactivity disorder (ADHD). Please note: Tris Pharma does not recommend the use of Dyanavel XR® (amphetamine) outside of its FDA-approved product labeling.

Table of Contents

ABBREVIATIONS LIST 4
LIST OF TABLES 7
SECTION 1.0 EXECUTIVE SUMMARY 8
1.1 DESCRIPTION 8
1.3 DIAGNOSIS AND TREATMENT OF ADHD 9
1.4 CLINICAL BENEFITS OF DYANAVEL XR IN CHILDREN WITH ADHD 9
1.6 VALUE PROPOSITION 11
SECTION 2.0 PRODUCT INFORMATION AND DISEASE DESCRIPTION 13
2.1 PRODUCT DESCRIPTION 13
2.1.1 Generic, Brand Name, and Therapeutic Class 13
2.1.2 Dosage Forms 13
2.1.3 National Drug Code (NDC) 13
2.1.5 American Hospital Formulary Service (AHFS) 13
2.1.6 US. Food and Drug Administration (FDA)–Approved Indications; Approval Date .. 13
2.1.7 Boxed Warning 14
2.1.8 Pharmacology 14
2.1.9 Pharmacokinetics/Pharmacodynamics 14
2.1.10 Clinical Efficacy 15
2.1.11 Contraindications, Warning/Precautions, and Adverse Events 16
2.1.12 Drug Interactions 17
2.1.13 Dosing and Administration 18
2.1.14 Comparison with the Primary Comparator Products in the Same Therapeutic Area . 19
2.2 PLACE OF THE PRODUCT IN THERAPY 29
2.2.1 Disease Description 29
2.2.2 Approaches to Treatment 35
2.2.3 Identification of Alternative Medications 38
2.2.4 Relevant Treatment Guidelines and Consensus Statement from National and/or International Bodies 39
2.2.5 Place and Anticipated Uses of Dyanavel XR in Treatment 40

2.3 EVIDENCE FOR PHARMACOGENOMIC TESTS AND DRUGS 40
SECTION 3.0 SUPPORTING CLINICAL EVIDENCE FOR DYANAVEL XR® 41
3.1 SUMMARIZED KEY CLINICAL STUDIES 41
3.1.1 Study TRI102-ADD-001 41
3.2 SUMMARIZED KEY CLINICAL STUDIES SUPPORTING OFF-LABEL INDICATIONS 61
3.3 EVIDENCE TABLE SPREADSHEET OF TRIS PHARMA–CONDUCTED DYANAVEL XR ADHD CLINICAL TRIALS IN CHILDREN (6–12 YEARS OF AGE) 62

4.3 ANTICIPATED UTILIZATION OF DYANAVEL XR 63
4.5 SIZE OF PATIENT POPULATION 64
SECTION 5.0 OTHER SUPPORTING EVIDENCE 65
SECTION 6.0 REFERENCES..... 66
APPENDIX: PRESCRIBING INFORMATION..... 69

ABBREVIATIONS LIST

Abbreviation	Description
AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ADHD	Attention deficit-hyperactivity disorder
ADHD-RS-IV	Attention Deficit-Hyperactivity Disorder-Rating Scale, Version lV
AE	Adverse event
AHFS	American Hospital Formulary Service
AMCP	Academy of Managed Care Pharmacy
APA	American Psychiatric Association
APRS	Academic Performance Rating Scale
AUC	Area under the plasma concentration–time curve
BPRS-C	Brief Psychiatric Rating Scale for Children
BRIEF	Behavior Rating Inventory of Executive Function
C	Carbon
CBCL	Child Behavior Checklist
CBT	Cognitive behavioral therapy
CD	Conduct disorder
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impressions of Improvement Scale
CGI-S	Clinical Global Impressions of Severity Scale
CHADD	Children and Adults with Attention Deficit-Hyperactivity Disorder
CI	Confidence interval
C_{max}	Maximum plasma concentration
CHIP-CE:PRF	Child Health and Illness Profile, Child Edition: Parent Report Form
CNS	Central nervous system
CPRS	Conners' Parent Rating Scale
CTRS-R	Conners’ Teacher Rating Scale—Revised

C-SSRS	Columbia-Suicide Severity Rating Scale
DACON	Daily average consumption
DRQS	Drug Rating Questionnaire-Subject
DSM-IV-TR®	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
GDP	Gross domestic product
H	Hydrogen
HAM-A	Hamilton Anxiety Rating Scale
HIV	Human immunodeficiency virus
HR	Heart rate
HRQoL	Health-related quality of life
HSQ-R	Home Situations Questionnaire-Revised
IOWA	Inattention/Overactivity with Aggression
IQ	Intelligence quotient
ITT	Intent-to-treat
K-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia
LS	Least squares
LSP	Laboratory School Protocol
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MMWR	Morbidity and Mortality Weekly Report
mg	Milligram
mL	Milliliter
N	Nitrogen
(N)	Number of patients
NDC	National Drug Code

NE	Norepinephrine
ODD	Oppositional defiant disorder
PERMP	Permanent Product Measure of Performance
PGA	Parental Global Assessment
PK	Pharmacokinetic
PO	Oral
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SKAMP-C	Swanson, Kotkin, Agler, M-Flynn, and Pelham-Combined scale
SKAMP-D	Swanson, Kotkin, Agler, M-Flynn, and Pelham-Deportment scale
SNAP-IV	Swanson, Nolan, and Pelham rating scale-4
SSQ-R	School Situations Questionnaire-Revised
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
$T_{1/2}$	Elimination half-life
TRF	Teacher Report Form
US	United States
WASI	Wechsler Abbreviated Scale of Intelligence
XR	Extended-release

LIST OF TABLES

Table 2.1: Drug Interactions Associated With Amphetamines

Table 2.2: Therapy Comparison of Prescribing Information Highlights

Table 2.3: Stratification of Diagnosis of ADHD by Age

Table 2.4: Prevalence of Comorbid Disorders for Children With ADHD Versus Those Without

Table 2.5: Three Classes of ADHD Medications

Table 2.6: Behavior Rating Scales Identified in the AACAP Guidelines

Table 2.7: Non–FDA-Approved Medications Used for Treating ADHD

Table 3.1: Trial TRI102-ADD-001 Inclusion and Exclusion Criteria

Table 3.2: Reasons for Discontinuation

Table 3.3: Primary Efficacy Results: Differential in 4 Hour SKAMP-Combined Scores At Visit 8: Intent-to-Treat Population

Table 3.4: Drug Exposure to Dyanavel XR: Enrolled Safety Population

Table 3.5: Treatment-Emergent Adverse Events: Open-Label Phase

Table 3.6: Treatment-Emergent Adverse Events: Double-Blind Phase

Table 3.7: Evidence Table Spreadsheet of Tris Pharma–Conducted Dyanavel XR ADHD Clinical Trials In Children (6–12 Years of Age)

Table 4.3: Dosing for Age Groups 6–17 for Dyanavel XR Based on Adderall XR and Quillivant XR

SECTION 1.0 EXECUTIVE SUMMARY

This dossier presents a scientific portfolio of clinical evidence to support formulary consideration for the use of Dyanavel XR® for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 years and older.

1.1 DESCRIPTION

Dyanavel XR (amphetamine) is the first and only extended-release oral suspension for once-a-day administration. The oral suspension formulation contains a 3.2 to 1 ratio of d- to l-amphetamine. Each 1 mL of Dyanavel XR contains 2.5 mg of amphetamine, the same amount of amphetamine (base equivalent) found in a 4-mg strength amphetamine mixed-salts product (i.e., Adderall XR®). Tris Pharma developed Dyanavel XR using its patented LiquiXR™ technology, a delivery system comprised of both immediate-release and extended-release amphetamine. By utilizing ion exchange polymeric chemistry, continuous release of amphetamine is achieved throughout the day.[1,2] Dyanavel XR is a Schedule II controlled substance.

Dyanavel XR was approved through the 505(b)(2) pathway, and its efficacy in the treatment of ADHD was established on the basis of a controlled, phase 3 trial in children aged 6 to 12 years (FDA approval: October 19, 2015).[1]

Dyanavel XR carries a Boxed Warning that is similar to that for other stimulants, noting that central nervous system (CNS) stimulants (eg, amphetamines and methylphenidate-containing products), including Dyanavel XR, have a high potential for abuse and dependence. Prior to prescribing, the risk of abuse should be assessed, and patients should be monitored for signs of abuse and dependence while on therapy.[2] (Please see the enclosed Full Prescribing Information including Boxed Warning.)

This dossier format follows the Academy of Managed Care Pharmacy (AMCP) Version 3.1 but does not contain all the suggested elements. The information presented in this dossier is focused on ADHD. The data discussed in this dossier regarding Dyanavel XR are exclusively from clinical trials conducted by Tris Pharma. Please note, Tris Pharma does not recommend the use of Dyanavel XR outside of its FDA-approved product labeling.

1.2 ADHD IN CHILDREN AND BURDEN OF ILLNESS

ADHD is a neurobehavioral disorder that involves having difficulty paying attention, hyperactive behavior, and controlling impulsive behavior. The symptoms of ADHD (e.g., inattention, impulsivity, hyperactivity) interfere with a person's ability to conduct normal daily activities at school, home, and work.[3] Individuals with ADHD utilize a greater than average share of healthcare, mental health, social, and special education services.

The number of children in the U.S. diagnosed with ADHD has increased since 2003, with 11% of children 4–17 years of age (6.4 million) having a lifetime prevalence of this diagnosis in 2011.[4] The diagnosis of ADHD in children also varies by race, with non-Hispanic white children having a higher

prevalence than non-Hispanic black children (11.5% vs. 8.9%, respectively). Hispanic children have the lowest prevalence of ADHD (6.3%).[5]

Children with ADHD are at high risk for comorbid conditions, including learning problems, language disorder, disruptive behavior anxiety, mood disorders, tic disorders, seizures, development coordination disorder, or sleep disorders. The presence of additional disease may impact therapy decisions for the patient.[6]

1.3 DIAGNOSIS AND TREATMENT OF ADHD

Diagnosing ADHD is based on meeting criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Formerly, there were three subtypes of ADHD; however, in DSM-5, these are now referred to as presentations that may change over time. The three presentations are: inattention, hyperactivity and impulsivity, and a combined presentation. Diagnosis of ADHD requires the presence of symptoms for at least the previous 6 months whereby the patient's developmental level and social and academic activities are negatively impacted. Impairment must be observed in at least two settings (home, school, or job) to meet the criteria for the disorder.[3]

The treatment of ADHD should incorporate several types of interventions, including behavioral, social, educational, and medical therapies. Guidelines for the treatment of ADHD (American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry) have been in use for many years and are well accepted. Drug therapy is considered first-line therapy in school-age patients with ADHD.[6,9] Drugs used to treat the symptoms of ADHD are broadly segmented into stimulants and non-stimulants. Stimulants (i.e., amphetamine, and methylphenidate-based products) have been used successfully for decades to treat ADHD in children.[9]

Numerous behavior rating scales are utilized to assess ADHD behaviors as well as to assess the patients' response to therapy. Commonly used rating systems to assess ADHD in practice include the Vanderbilt ADHD Parent and Teacher, ADHD-RS, and Conners' Ratings scales, among others.[9] The SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) Scale has proven to be useful in assessing response to stimulant medication prescribed for ADHD in a clinical trial setting.[10] Stimulant medications can be effectively titrated on a 3- to 7-day basis to achieve maximal dosing.[6]

1.4 CLINICAL BENEFITS OF DYANAVEL XR IN CHILDREN WITH ADHD

Dyanavel XR is indicated for the treatment of ADHD in children 6 years and older. The efficacy of Dyanavel XR in the treatment of ADHD was established on the basis of one phase 3, randomized, double-blind, placebo-controlled trial in children ages 6 to 12 years (study TRI102-ADD-01).[2]

This trial had two main objectives: (1) to assess the efficacy of dose-optimized Dyanavel XR in the treatment of ADHD compared with placebo in pediatric subjects aged 6 to 12 years with ADHD and (2) to assess the safety and tolerability of Dyanavel XR in pediatric subjects with ADHD.

Detailed information about this study can be found in **Section 3.**

Dyanavel XR Clinical Trial Evidence in ADHD

Patients enrolled in this trial were diagnosed with ADHD according to the DSM-IV criteria (DSM-5 represents the newest update, which was introduced after the clinical trial was initiated). For ADHD, DSM-5 diagnostic criteria are similar to those in DSM-IV.[3] This trial began with an open-label dose-optimization period (lasting 5 weeks), during which all participants received Dyanavel XR in doses starting at 2.5–5.0 mg/day, titrated at scheduled intervals until an optimal dose was achieved (or a maximum of 20 mg/day was attained). All patients reaching and maintaining a stable dose of 10–20 mg/day were entered into the 1-week double-blind phase of the study, in which the group was randomized to receive either Dyanavel XR at their individual optimal dose or an identical placebo.[2]

The primary endpoint was the change in performance on the SKAMP-Combined rating scale from morning dosing to 4 hours post dose in a school laboratory environment at the end of the 1-week double-blind phase. Secondary study endpoints included change from predose SKAMP-Combined rating scores at 1, 2, 6, 8, 10, 12, and 13 hours postdose. Safety and tolerability of the product were also evaluated.[2] In addition, the secondary study endpoints measured efficacy using the following ADHD assessments (unpublished data, Tris Pharma):

- ADHD-RS (ADHD Rating Scale)
- PERMP (Permanent Product of Performance)
- CPRS (Conners' Parent Rating Scale)
- CCSS (Columbia Suicide Severity Rating Scale)
- CGI-S (Clinical Global Impression of Severity)

Patients were not allowed to receive psychoactive medications like monoamine oxidase inhibitors or atomoxetine within 30 days of the baseline visit or any psychotropic medication other than stimulants for treatment of ADHD for 48 hours prior to baseline. However, patients were allowed to receive acetaminophen and other non-psychoactive medications concomitantly. Other exclusion criteria included diagnosis of a DSM-IV axis 1 disorder other than ADHD, clinically significant cognitive impairment, history of specific chronic medical illnesses (e.g., seizure disorder, thyroid disorders, serious cardiac conditions, severe hypertension, family history of glaucoma, HIV infection, hepatitis B or C infection), abnormal electrocardiogram, or other abnormal cardiac findings, abnormal laboratory test values, and a history of hypersensitivity or lack of response to amphetamine treatment (unpublished data, Tris Pharma).

One hundred eight children with ADHD were enrolled in the trial, with 100 being included in the randomized, double-blind portion of the investigation. Of the eight children who did not participate in the randomized phase, 4 were excluded by the sponsor due to recruiting difficulty at a single site, 2 were withdrawn by their parents, 1 was lost to follow-up, and 1 was excluded due to lack of response to treatment. None of the subjects withdrew from either the dose-optimization portion or the double-blind phase because of treatment-emergent adverse events. None of the subjects experienced any serious treatment-emergent adverse events (unpublished data, Tris Pharma).

Of the remaining 100 patients, 48 were assigned to receive placebo and 52 received Dyanavel XR. One patient from the Dyanavel XR group did not complete the 1-week double-blind phase, owing to an inability to attend the laboratory classroom testing visit (unpublished data, Tris Pharma).

On the primary efficacy outcome, change in SKAMP-Combined score from pre-dose (i.e., just prior to drug dosing) on the laboratory school day to 4 hours postdose, a mean difference of –14.8 ± –1.61 ($P < .0001$) was observed between the two treatment groups.[2]

With regard to secondary efficacy outcomes, SKAMP-Combined scores were significantly improved compared with placebo at all time points tested (from 1 to 13 hours, $P < .0001$ for all time points), demonstrating rapid onset of action (1 hour after dosing) and long duration of effect (13 hours after dosing). Significant improvements were seen on other measures (PERMP, CGI-S, CGI-I, ADHD-RS, CPRS) (unpublished data, Tris Pharma).

Treatment-emergent adverse events (TEAEs) were reported by 64 (59.8%) of the subjects during the open-label dose optimization period; 78% were rated mild and 22% were rated moderate. Twenty-four TEAEs were reported by 15 subjects during the double-blind treatment period (6 [12.5%] receiving placebo, 9 [17.3%] receiving study drug). Two-thirds were deemed mild and one-third were rated moderate; none were considered severe or led to study discontinuation (in either the open-label or the double-blind phase of the trial) (unpublished data, Tris Pharma).

In the open-label phase, the most common TEAEs were decreased appetite (26.2%), insomnia (13.1%), affect lability (9.3%), upper abdominal pain (7.5%), and mood swings (5.6%). All other TEAEs occurred in fewer than 5.0% of subjects. During the double-blind phase, no TEAE occurred in 5.0% or more of the study population (unpublished data, Tris Pharma).

It is important to point out that while the duration of clinical effect was shown to be 13 hours after dosing, the incidence of insomnia seen in the study was similar to that for placebo, and no children discontinued from the study for adverse events, including insomnia. When it occurs, insomnia tends to be transient, decreasing in frequency over time as patients accommodate to the medication (unpublished data, Tris Pharma).

Dyanavel XR appears to be safe and effective for the treatment of ADHD in children ages 6 and older, with a rapid onset of action and duration of effect of up to 13 hours post dosing. The safety analysis revealed that Dyanavel XR was well tolerated across all optimized daily dose levels between 10 and 20 mg. The side effect profile seems to be similar to that for other extended-release amphetamine-based ADHD products.[2]

1.6 VALUE PROPOSITION

Dyanavel XR provides patients, prescribers and payers a safe and effective therapy for children 6 years and older. It offers a number of positive attributes for the first-line treatment of ADHD:

- It is the first and only extended-release oral amphetamine liquid for treatment of ADHD. It contains both immediate-release and extended-release components. Dyanavel XR is a once-daily, oral suspension that offers flexible dosing.[2]
- Treatment of ADHD is individualized and requires precise dose titration to reach an optimal balance between symptom control and side effects.[6] Dyanavel XR is available in a concentration of 2.5 mg/mL, which allows for a low starting dose (2.5–5.0 mg/day).[2]
- Dyanavel XR can be titrated rapidly (in increments of 2.5 mg to 10 mg per day every 4–7 days),[2] giving individualized, precise optimal doses. Based on its available concentration and recommended doses,[2] titration can be performed from a single prescription bottle, reducing the need for additional prescriptions and reducing wasted medication during the titration phase.
- Dyanavel XR has a fast onset of action, with clinical trial evidence that it significantly improves SKAMP-Combined scores in 1 hour after dosing, compared with placebo, and it has demonstrated a duration of clinical effect of 13 hours after dosing.[2] Dyanavel XR delivers statistically significant symptom control versus placebo over its entire duration of action, as shown during a SKAMP laboratory classroom study.[2]
- Dyanavel XR has a safety profile that appears to be similar to that of other extended-release amphetamines, with only mild or moderate treatment-emergent adverse effects observed during clinical study.[2]

SECTION 2.0 PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 PRODUCT DESCRIPTION

Dyanavel XR® (amphetamine) is the first and only extended-release suspension of amphetamine for once-a-day oral administration in children ages 6 years and older with ADHD. The oral suspension formulation contains a 3.2 to 1 ratio of d- to l-amphetamine. The molecular formula is $C_9H_{13}N$, and it has a molecular weight of 135.21 daltons. Each 1 mL of Dyanavel XR contains 2.5 mg of amphetamine, the same amount of amphetamine (base equivalent) found in a 4-mg strength amphetamine mixed-salts product (e.g., Adderall XR). Inactive ingredients in the suspension are anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified food starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, triacetin, and xanthan gum. Dyanavel XR is a Schedule II controlled substance.[2]

Dyanavel XR was developed using patented LiquiXR™ technology, a delivery system comprised of both immediate-release and extended-release amphetamine. By utilizing ion exchange polymeric chemistry, continuous release of amphetamine is achieved throughout the day.[1]

2.1.1 Generic, Brand Name, and Therapeutic Class

Generic name: amphetamine

Brand Name: Dyanavel XR

Therapeutic class: Attention Deficit Hyperactivity Disorder

Drug class: Central nervous system stimulant

2.1.2 Dosage Forms

Dyanavel XR is supplied as an oral suspension containing 2.5 mg amphetamine base per mL. It is a light beige to tan viscous suspension with bubblegum flavor supplied in bottles of 464 mL.[2]

2.1.3 National Drug Code (NDC)

NDC number 27808-102-01

2.1.5 American Hospital Formulary Service (AHFS)

AHFS Class: TBD*

* (Other amphetamine products have been classified as category 282004: Central Nervous System Stimulants)

2.1.6 US. Food and Drug Administration (FDA)–Approved Indications; Approval Date

Dyanavel XR is indicated for the treatment of ADHD in children 6 years and older.

FDA approval through the 505(b)(2) pathway was received October 19, 2015. The approval was based on a Phase III randomized, placebo-controlled, laboratory classroom efficacy study conducted in 108 children (ages 6–12 yr, who met DSM-IV® criteria for ADHD). The study, which included a 5-week, open-label, dose optimization followed by a 1-week, double-blind treatment period, demonstrated a positive outcome by meeting its primary endpoint of change from pre-dose in the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score at 4 hours post-dosing. Dyanavel XR also met key secondary endpoints by demonstrating an onset of clinical effect at one hour that persisted through 13 hours post-dosing.[1]

2.1.7 Boxed Warning

Warning: ABUSE AND DEPENDENCE

CNS stimulants, including Dyanavel XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.[2]

2.1.8 Pharmacology

Mechanism of Action: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known. It is thought that amphetamines block the reuptake of norepinephrine and dopamine in the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.[2]

2.1.9 Pharmacokinetics/Pharmacodynamics

Pediatric Patients

Twelve children with ADHD ages 6-12 years were evaluated under fasting conditions after receiving a single 10 mg oral dose of Dyanavel XR. Peak plasma concentrations for d-amphetamine and l-amphetamine occurred at a median time of 3.9 and 4.5 hours after dosing. The mean (± standard deviation [SD]) plasma terminal elimination half-life of d-amphetamine was 10.43 ± 2.01 hours while the mean plasma terminal half-life for l-amphetamine was 12.14 ± 3.15 hours.[2]

Healthy Adults

A single oral dose of 18.8 mg after fasting was administered to 29 healthy adults. The median (range) times to peak plasma concentration (T_{max}) for both the d- and l-amphetamine components were 4.0 (2–7) hours. The mean peak concentrations (C_{max}) of d- and l-amphetamine were 102% and 106%, respectively, of the C_{max} of immediate-release mixed amphetamine salts tablets. The relative bioavailability of Dyanavel XR compared with an equal dose of mixed amphetamine salts immediate-release is 106% for d-amphetamine and 111% for l-amphetamine.[2]

In these same adults, the mean ± SD plasma terminal elimination half-life of d-amphetamine was 12.36 ± 2.95 hours and 15.12 ± 4.40 hours for l-amphetamine.[2]

The enzymes involved in amphetamine metabolism have not been clearly defined, but CYP2D6 is known to be involved. This enzyme is genetically polymorphic, in that population variations in amphetamine metabolism are a possibility. Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate there may be minor inhibition of CYP2D6, CYP1A2, 2D6, and 3A4 by amphetamine or its metabolites. However, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.[2]

In the presence of normal urine pH, approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine. Another 30-40% of the dose is recoverable as amphetamine. Due to the pKa of amphetamine, urinary recovery is highly dependent on pH and urine flow rates. Alkaline urine pH levels result in reduced renal elimination, whereas acidic pH levels and high flow rates result in increased renal elimination. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH with the remaining amphetamine being metabolized by the liver. Therefore, hepatic and renal dysfunction has the potential to inhibit the elimination of amphetamine and result in prolonged exposures. Drugs impacting the pH of the urine are known to alter the elimination of amphetamine. Additionally, when any drug interactions or genetic polymorphisms are present, it is more likely to be clinically significant when renal elimination is decreased.[2]

Food Effect

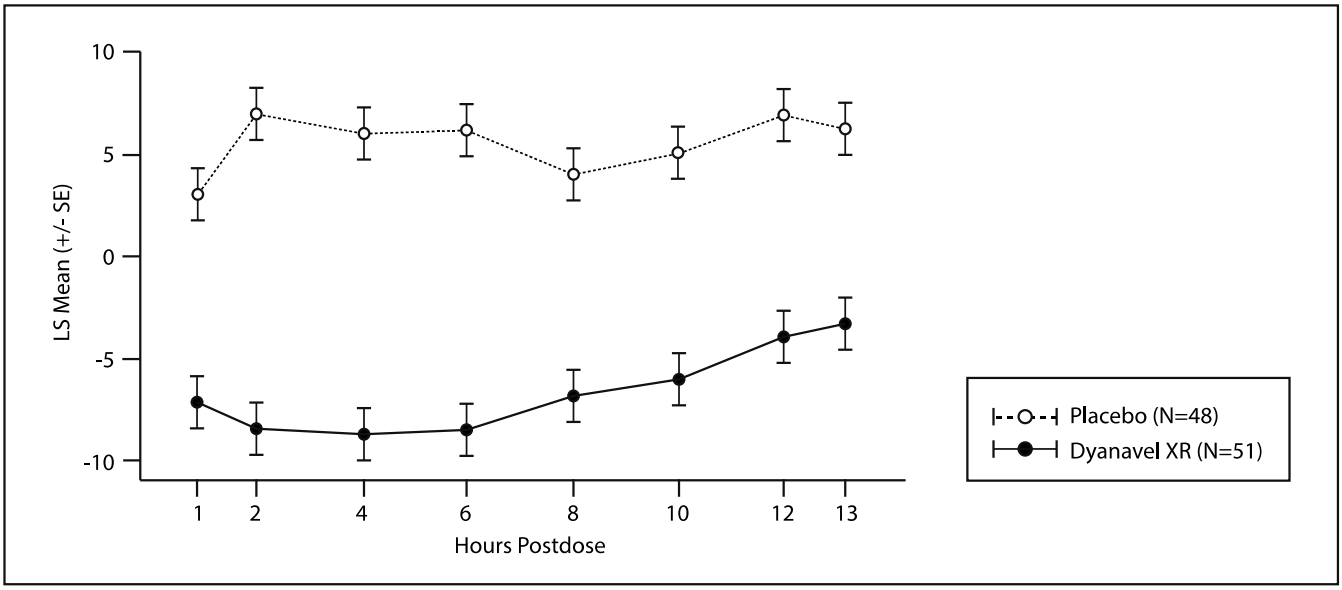
In these same adult patients given a high-fat meal, the presence of food delayed the time-to-peak concentration of both d- and l-amphetamine by approximately 1 hour (fed: median [range] 5 [3–8] hr vs. fasted: 4 [2–7] hr). A high-fat meal increased the average C_{max} of both isomers by about 2% and decreased the AUC by 5-7%, (a decrease of 5.7% and 7.4% for the d- and l-amphetamine, respectively). None of these changes were considered clinically significant.[2]

No *in vivo* studies have been conducted for the effect of alcohol on drug exposure. An *in vitro* study has shown alcohol-induced dose dumping potential (increase in concentration of drug) in the presence of 40% alcohol.[2]

2.1.10 Clinical Efficacy

The efficacy of Dyanavel XR was evaluated in a laboratory classroom study conducted in 108 pediatric patients (aged 6–12 yr) with ADHD (See **Section 3.0—Supporting Clinical Evidence** for a summary of the clinical trial). The primary endpoint was the change in SKAMP-Combined score seen 4 hours after patients were dosed with Dyanavel XR compared with those given placebo. Dyanavel XR was associated with a statistically significant improvement in SKAMP-Combined score at 4 hours and at all other measured time points postdose over the 13-hour duration of the test (Figure 1).[2]

FIGURE 1. Least squares (LS) mean change from pre-dose in SKAMP-Combined Score after treatment with Dyanavel XR or Placebo. All differences significant at $P < .0001$.[2]



2.1.11 Contraindications, Warning/Precautions, and Adverse Events

Contraindications

- Known hypersensitivity to amphetamine products or other ingredients in Dyanavel XR.
- Concurrent use of monoamine oxidase inhibitor (MAOI) or use of Dyanavel XR within 14 days of the last MAOI dose.[2]

Warnings and Precautions

- Serious cardiovascular reactions: sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid using Dyanavel XR in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease.[2]
- Blood pressure and heart rate increases: monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic.[2]
- Psychiatric adverse reactions: may cause psychotic or manic symptoms in patients without a history of psychiatric disorders or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder before prescribing stimulants.[2]

- Long-term suppression of growth: monitor height and weight in pediatric patients during treatment.[2]
- Peripheral vasculopathy, including Raynaud's phenomenon: stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.

Adverse Events

The most common adverse reactions observed with amphetamine products are dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, and tachycardia. [2]

There is limited experience with Dyanavel XR in controlled trials. Based on this limited experience, the adverse reaction profile of Dyanavel XR appears similar to other amphetamine extended-release products. The most common (≥2% in the Dyanavel XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 108 patients with ADHD (aged 6–12 years) were: epistaxis, allergic rhinitis, and upper abdominal pain.[2]

2.1.12 Drug Interactions

Table 2.1 provides information on clinically important drug interactions that have been seen with amphetamine use.[2]

TABLE 2.1: DRUG INTERACTIONS ASSOCIATED WITH AMPHETAMINES[2]

Drug/Drug Category	Clinical Impact	Intervention	Examples
MAO Inhibitors (MAOI)	MAOIs slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.	Do not administer Dyanavel XR during or within 14 days following the administration of MAOIs	Selegiline, isocarboxazid, phenelzine, tranylcypromine
Alkalinizing Agents	Increase blood levels and potentiate the action of amphetamine	Co-administration of Dyanavel XR and gastrointestinal alkalinizing agents should be avoided	Gastrointestinal alkalinizing agents (e.g., sodium bicarbonate) Urinary alkalinizing agents (e.g. acetazolamide,

			some thiazides)
Acidifying Agents	Lower blood levels and efficacy of amphetamines	Increase dose based on clinical response	Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid) Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)
Tricyclic Antidepressants	May enhance the activity of tricyclic or sympathomimetic agents causing stroke and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated	Monitor frequently and adjust or use alternative therapy based on clinical response	Desipramine, protriptyline
Proton Pump Inhibitors	Time to maximum concentration (T_{max}) of amphetamine is increased compared to when administered alone	Monitor patients for changes in clinical effect and adjust therapy based on clinical response	omeprazole

2.1.13 Dosing and Administration

For full information, please refer to the full prescribing information in the Appendix.

Important Information Prior to Initiating Treatment

Prior to treating patients of all ages with CNS stimulants, including Dyanavel XR, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam).

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while therapy continues. Maintain careful prescription records, educate patients/caregivers about abuse, monitor for signs of abuse and overdose and periodically re-evaluate the need for Dyanavel XR.

General Dosing Information

Dyanavel XR should be orally administered once daily in the morning with or without food. The dose should be individualized according to the needs and responses of the patient. Shake the bottle of Dyanavel XR before measuring the exact dose with a dosing device and administering it.

In children ≥ 6 years of age, start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 to 10 mg/day every 4–7 days up to a maximum dose of 20 mg/day.[2] Dyanavel XR is available as a 2.5 mg/mL in liquid dosage form.[2] This concentration and titration schedule should result in rapid titration in small increments, allowing for precise balance between optimal dose and adverse events.

Pharmacological treatment of ADHD may be needed for extended periods. Health care providers should periodically re-evaluate the long-term use of Dyanavel XR and adjust the dosage as needed.

Switching from Other Amphetamine Products

If switching from other amphetamine products, discontinue that treatment, and titrate with Dyanavel XR using the above titration schedule. Do not substitute for other amphetamine products on a milligram-per-milligram basis, because individual amphetamines formulations have different base compositions and differing pharmacokinetic profiles.

2.1.14 Comparison with the Primary Comparator Products in the Same Therapeutic Area

1. The comparators of Dyanavel XR in the treatment of ADHD are included in Table 2.2. The information in the table has been derived primarily from the respective prescribing information.

TABLE 2.2: THERAPY COMPARISON OF PRESCRIBING INFORMATION HIGHLIGHTS[2,11-15]

Drug Name	DYANAVEL XR extended-release oral suspension	VYVANSE capsules	ADDERALL XR extended-release capsules	APTENSIO XR extended-release capsules	QUILLIVANT XR extended-release oral suspension	PROCENTRA oral solution
Highlights of Prescribing Information Disclaimer	**These highlights do not include all the information needed to use these products safely and effectively. See full prescribing information for each product for complete prescribing information.**					
Drug Description and Controlled Substance Schedule	**DYANAVEL® XR** **(amphetamine) extended-release oral suspension, CII** **Initial U.S. Approval: 1960**	**VYVANSE® (lisdexamfetamine dimesylate) capsules, for oral use, CII** **Initial U.S. Approval: 2007**	**ADDERALL XR® (mixed salts of a single-entity amphetamine product) dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate capsules, CII** **Initial U.S. Approval: 2001**	**APTENSIO XR™ (methylphenidate hydrochloride) extended-release capsules for oral use, CII** **Initial U.S. Approval: 1955**	**QUILLIVANT™ XR (methylphenidate hydrochloride) for extended-release oral suspension, CII** **Initial U.S. Approval: 1955**	**PROCENTRA (dextroamphetamine sulfate) oral solution, CII**
Boxed Warnings	**WARNING: ABUSE AND DEPENDENCE** ***See full prescribing information for complete boxed warning*** • CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse	**WARNING: ABUSE AND DEPENDENCE** ***See full prescribing information for complete boxed warning.*** • Central Nervous System (CNS) stimulants (amphetamines and methylphenidate-containing products) have a high potential for abuse and dependence. • Assess the risk of abuse	**WARNING: POTENTIAL FOR ABUSE** ***See full prescribing information for complete boxed warning*** • Amphetamines have a high potential for abuse; prolonged administration may lead to dependence. • Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.	**WARNING: ABUSE AND DEPENDENCE** ***See full prescribing information for complete boxed warning.*** • CNS stimulants, other methylphenidate products, and amphetamines, including APTENSIO XR, have a high potential for abuse and dependence. • Assess the risk of abuse prior to prescribing, and	**WARNING: ABUSE AND DEPENDENCE** ***See full prescribing information for complete boxed warning.*** • CNS stimulants, including QUILLIVANT XR, have a high potential for abuse and dependence. • Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.	**WARNING: ABUSE AND DEPENDENCE** ***See full prescribing information for complete boxed warning*** • Amphetamines have a high potential for abuse; prolonged administration may lead to dependence. • Monitor patients for any non-therapeutic use of drug or distribution to others; prescribe and dispense sparingly. • Misuse of amphetamines

	and dependence while on therapy.	prior to prescribing and monitor for signs of abuse and dependence while on therapy.		monitor for signs of abuse and dependence while on therapy.		may cause sudden death and serious cardiovascular adverse reactions.
Recent Major Changes to Labeling	N/A	Indications and Usage, 1/2015 Dosage and Administration, 1/2015	Warnings and Precautions, 6/2013	N/A	Warnings and Precautions, Priapism, 12/2013 Peripheral Vasculopathy, including Raynaud's Phenomenon, 8/2013	
Indications and Usage	DYANAVEL XR is a CNS stimulant indicated for the treatment of ADHD.	VYVANSE is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and moderate-to-severe binge eating disorder.	ADDERALL XR is a CNS stimulant indicated for the treatment of ADHD. • Children (ages 6-12): Efficacy was established in one 3-week outpatient, controlled trial and one analogue classroom, controlled trial in children with ADHD. • Adolescents (ages 13-17): Efficacy was established in one 4-week controlled trial in adolescents with ADHD. • Adults: Efficacy was established in one 4-week controlled trial in adults with ADHD.	APTENSIO XR is a CNS stimulant indicated for the treatment of ADHD.	QUILLIVANT XR is a CNS stimulant indicated for the treatment of ADHD. • The efficacy of QUILLIVANT XR was established in a 2-week, placebo-controlled trial in children aged 6–12 years with a diagnosis of ADHD. Accumulated efficacy data from other methylphenidate products were also considered.	PROCENTRA is a CNS stimulant indicated for the treatment of ADHD and Narcolepsy.
Dosage and Administration	• Before administering the dose, shake bottle. • May be taken with or without food. • In children 6 years of age and older, recommended starting dose is 2.5 mg or 5 mg	• Recommended starting dose: 30 mg once daily in the morning in patients ages 6 and above. • Increase in increments of 10 mg or 20 mg at weekly intervals if needed. • Recommended dose: 30	• Pediatric patients (ages 6–-17): 10 mg once daily in the morning. The maximum dose for children 6–12 is 30 mg once daily. • Adults: 20 mg once daily in the morning.	• Pediatric patients (ages 6 and above): 10 mg once daily in the morning. • May be taken with or without food. • Dosage may be increased weekly in increments of 10 mg	• Before administering the dose, vigorously shake bottle for at least 10 seconds. • May be taken with or without food. • For patients 6 years and above, recommended starting dose is 20 mg	• In pediatric patients 3–5 years of age start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. • In pediatric patients 6 years of age and older,

	once daily in the morning. • Dosage may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days until optimal response is obtained. • Daily dose above 20 mg is not recommended. • Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine base compositions and differing pharmacokinetic profiles.	mg to 70 mg/day. • Maximum dose: 70 mg/day. • Prior to treatment, assess for presence of cardiac disease.		per day; daily dosages above 60 mg are not recommended. • Capsules may be swallowed whole or opened and their contents sprinkled onto applesauce.	given orally once daily in the morning. Dosage may be increased weekly in increments of 10 mg to 20 mg per day. Daily dosage above 60 mg is not recommended. • Reconstitution instructions for the pharmacist: Tap bottle until powder flows freely. Remove bottle cap, and add specified amount of water for reconstitution. Insert bottle adapter into neck of bottle. Replace bottle cap. Shake with vigorous back and forth motion for at least 10 seconds to prepare suspension. Dispense in original container.	start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. • Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. • Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.
Dosage Forms and Strengths	Extended-release oral suspension containing 2.5 mg amphetamine base per mL	Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	Capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg	Extended-release capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg.	Extended-release oral suspension (after reconstitution with water): 25 mg per 5 mL (5 mg per mL)	Oral solution containing 5 mg per 5 mL
Contraindications	• Known hypersensitivity to amphetamine products or other ingredients in DYANAVEL XR. • Use of MAOI or within 14 days of the last MAOI dose.	• Known hypersensitivity to amphetamine products or other ingredients in VYVANSE. • Use with monoamine oxidase inhibitor (MAOI), or within 14 days of the last MAOI dose.	• Advanced arteriosclerosis • Symptomatic cardiovascular disease • Moderate to severe hypertension • Hyperthyroidism • Known hypersensitivity or idiosyncrasy to the sympathomimetic amines • Glaucoma • Agitated states • History of drug abuse	• Known hypersensitivity to methylphenidate or product components. • Concurrent treatment with an MAOI, or use of an MAOI within the preceding 14 days.	• Known hypersensitivity to methylphenidate or product components • Concurrent treatment with an MAOI, or use of an MAOI within the preceding 14 days.	• Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. • Agitated states. • Patients with a history of drug abuse.

			• During or within 14 days following the administration of monoamine oxidase inhibitors (MAOI)			• During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crisis may result).
Warnings and Precautions	• Serious Cardiovascular Reactions: Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease. • Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic. • Psychiatric Adverse Reactions: May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use.	• Serious Cardiovascular Reactions: Sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease. • Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic. • Psychiatric Adverse Reactions: May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. • Suppression of Growth: Monitor height and weight in pediatric patients during	• Serious Cardiovascular Events: Sudden death has been reported with usual doses of CNS stimulants in children and adolescents with structural cardiac abnormalities or other serious heart problems; sudden death, stroke, and myocardial infarction have been reported in adults taking CNS stimulants at usual doses. Stimulant drugs should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. • Increase in Blood Pressure: Monitor blood pressure and pulse at appropriate intervals. Use with caution in patients for whom blood pressure increases may be problematic. • Psychiatric Adverse Events: Stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to	• Serious Cardiovascular Reactions: Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. • Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. • Psychiatric Adverse Reactions: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to APTENSIO XR use.	• Serious Cardiovascular Reactions: Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. • Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. • Psychiatric Adverse Reactions: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to QUILLIVANT XR use. • Priapism: Cases of	• Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. • Increase in Blood Pressure: Monitor blood pressure and pulse at appropriate intervals. Use with caution in patients for whom blood pressure increases may be problematic. • Psychiatric Adverse Events: Stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to

	• Long-Term Suppression of Growth: Monitor height and weight in pediatric patients during treatment. • Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.	treatment. • Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.	stimulant use. Monitor for aggressive behavior. • Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals • Seizures: May lower the convulsive threshold. Discontinue in the presence of seizures. • Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. • Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. • Tics: May exacerbate tics. Evaluate for tics and Tourette's syndrome prior to stimulant administration.	• Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed • Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. • Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients.	painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. • Peripheral Vasculopathy, including Raynaud's Phenomenon: CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. • Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients.	stimulant use. Monitor for aggressive behavior. • Seizures: May lower the convulsive threshold. Discontinue ADHD stimulant use in the presence of seizures. • Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. • Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients. • Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.
Adverse Reactions	Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, tachycardia. **To report SUSPECTED ADVERSE REACTIONS, contact Tris Pharma, Inc. 1-732-940-0358 and**	Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in children, adolescents, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal	• Children (ages 6 to 12): Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever. • Adolescents (ages 13 to 17): Most common adverse reactions (≥5%	The most common adverse reactions in double-blind clinical trials (> 5% and twice the rate of placebo) in pediatric patients 6–17 years were abdominal pain, decreased appetite, headache, and insomnia. **To report SUSPECTED ADVERSE REACTIONS, contact Rhodes Pharmaceuticals, LP at 1-**	Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and	• Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. • Central Nervous System: Psychotic episodes at recommended doses

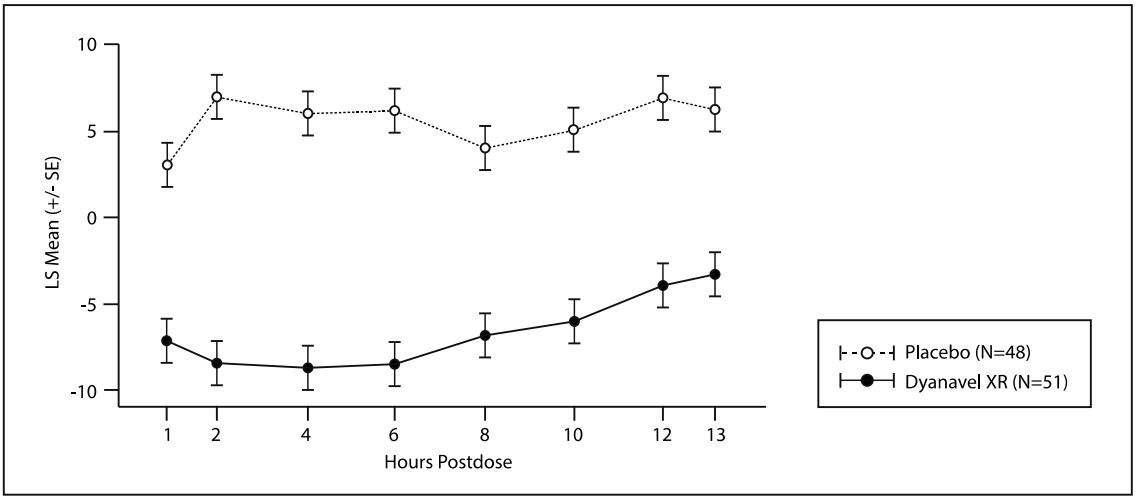
	www.trispharma.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.	pain, and vomiting. **To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**	and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, weight loss, and nervousness. • Adults: Most common adverse reactions ≥5% and with a higher incidence than on placebo were dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, and urinary tract infections. **To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**	**888-827-0616 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.** SEE PATIENT COUNSELING INFORMATION and Medication Guide.	blood pressure increased. **To report SUSPECTED ADVERSE REACTIONS, contact NextWave Pharmaceuticals, Inc. at 1-800-206-8115 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**	(rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. • Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects. • Allergic: Urticaria. • Endocrine: Impotence, changes in libido. • Musculoskeletal: Rhabdomyolysis. **To report SUSPECTED ADVERSE REACTIONS, contact Independence Pharmaceuticals, LLC at 1-855-325-1928, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**
Drug Interactions	Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents can decrease amphetamine blood levels, while alkalinizing agents can increase amphetamine blood levels. Adjust DYANAVEL XR dosage accordingly.	Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust VYVANSE dosage accordingly.	• MAOI antidepressants are contraindicated; MAOIs potentiate the effects of amphetamine. Do not administer ADDERALL XR during or within 14 days after use of MAOI. • Alkalinizing agents (GI antacids and urinary): These agents increase blood levels and potentiate the actions of amphetamines.	Do not administer APTENSIO XR concomitantly or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia,	Do not administer QUILLIVANT XR concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological	• MAOI antidepressants are contraindicated; MAOIs potentiate the effects of amphetamine. Do not administer PROCENTRA during or within 14 days after use of MAOI. • Alkalinizing agents (GI antacids and urinary): These agents increase blood levels and potentiate the actions of amphetamines.

			• Acidifying agents (GI and urinary): These agents reduce blood levels and efficacy of amphetamines. • Adrenergic blockers, antihistamines, antihypertensives, phenobarbital, phenytoin, veratrum alkaloids, and ethosuximide: Effects may be reduced by amphetamines. • Tricyclic antidepressants, norepinephrine, and meperidine: Effects may be potentiated by amphetamines.	pulmonary edema, and renal failure.	complications, eclampsia, pulmonary edema, and renal failure.	• Acidifying agents (GI and urinary): These agents reduce blood levels and efficacy of amphetamines. • Adrenergic blockers, antihistamines, antihypertensives, phenobarbital, phenytoin, veratrum alkaloids, and ethosuximide: Effects may be reduced by amphetamines. • Tricyclic antidepressants, norepinephrine, and meperidine: Effects may be potentiated by amphetamines.
Efficacy in Specific Populations	• Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus. May cause fetal harm. • Nursing Mothers: should refrain from breastfeeding. • Pediatric: Safety and efficacy in pediatric patients younger than 6 years with ADHD have not been established.	• Pregnancy: Based on animal data, may cause fetal harm. • Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. • Pediatric: Safety and efficacy in pediatric patients younger than 6 years with ADHD have not been established.	• Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus. Based on animal data, may cause fetal harm. • Nursing Mothers: should refrain from breastfeeding. • Pediatric Use: has not been studied in children under 6 years of age.	• Pregnancy: Based on animal data, may cause fetal harm. • Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother. • Pediatric Use: has not been studied in children under 6 years of age.	• Pregnancy: Based on animal data, may cause fetal harm. • Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother. Pediatric Use: has not been studied in children under 6 years of age.	• Pregnancy: Based on animal data, may cause fetal harm. • Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother. • Pediatric Use: Amphetamines are not recommended for use in patients under 3 years of age.
Mechanism of Action	**Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Methylphenidate is also a CNS stimulant. Their modes of therapeutic action in ADHD are not known. Amphetamines and methylphenidate are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal spaces.**					
Time to Maximum Concentration (T_{max})	~ 4.0 hr (fasting)	~3.5 hr (fasting)	~ 7.0 hr	~ 2.0 hr	~4.0 hr	No label claim

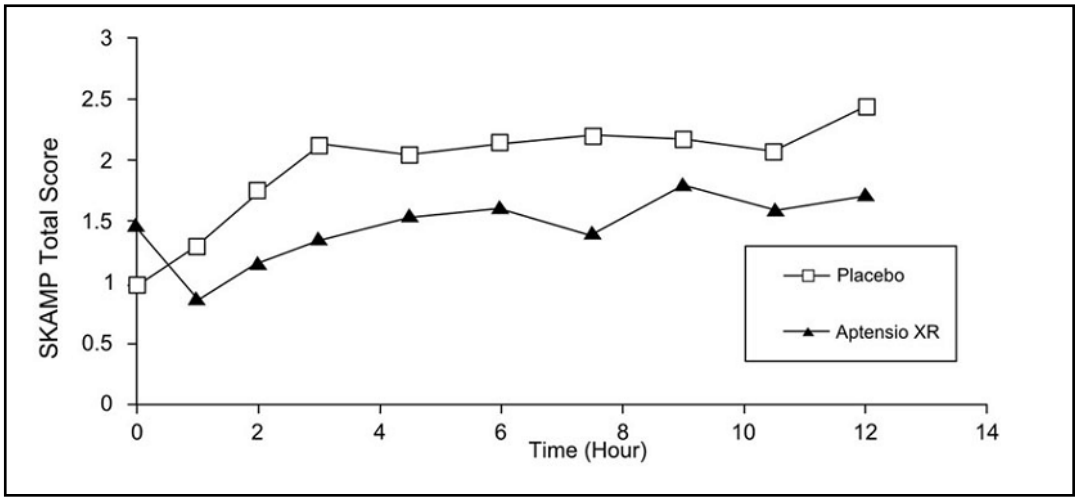
Elimination Half-Life ($T_{1/2}$)	12.36 hr, d-amphetamine; 15.12 hr, l-amphetamine (fasting)	< 1.0 hr	9.0 hr, children, 11.0 hr adolescents	5.09 hr	5.2 hr	11.75 hr
Onset of Action	1.0 hr	1.5 hr	No label claim	1.0 hr	0.75 hr	No label claim
Duration of Action in Children, 6-12 yr	13.0 hr	13.0 hr	No label claim	12.0 hr	12.0 hr	No label claim
Elimination	With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30% to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates.	Following the oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours.	With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30% to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates.	After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.	After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.	The average urinary recovery was 38% in 48 hr.
Dosing Interval	Once daily in the morning with or without food	Once daily in the morning with or without food	Once daily in the morning with or without food	Once daily in the morning with or without food	Once daily in the morning, with or without food	Once or twice daily
Revision Date	Revised 1/2016	Revised: 4/2015	Revised: 04/2015	Revised 05/2015	Revised: 2/2015	Revised 09/2015

2. The following charts depict SKAMP scores by time postdose for each comparator drug for which information is available from their respective prescribing information. These comparisons were based on placebo-controlled trials; they do not represent direct comparisons of active drugs:

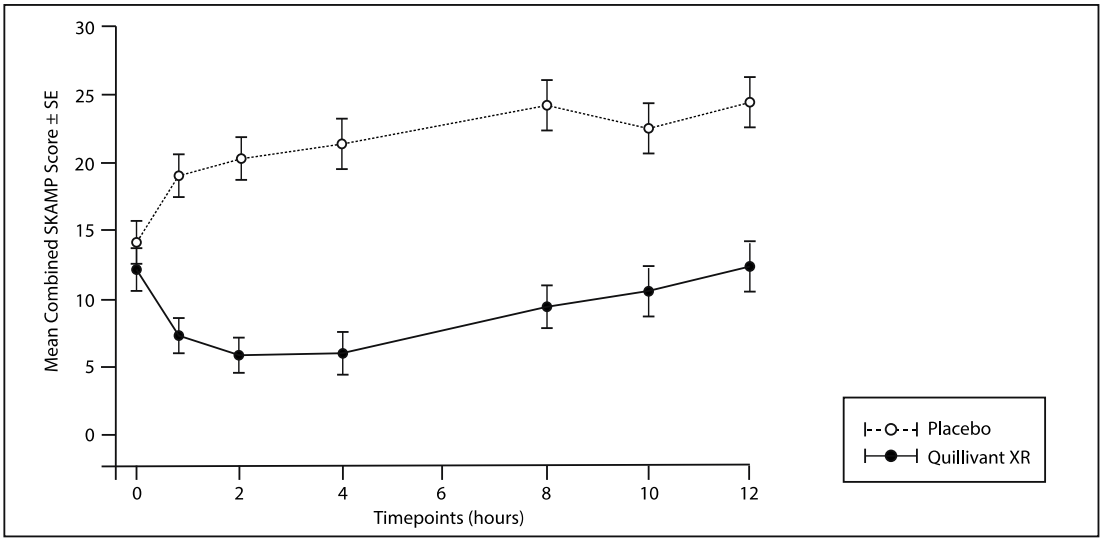
Dyanavel XR (N = 99) SKAMP-Combined Scores (least square mean)[2]



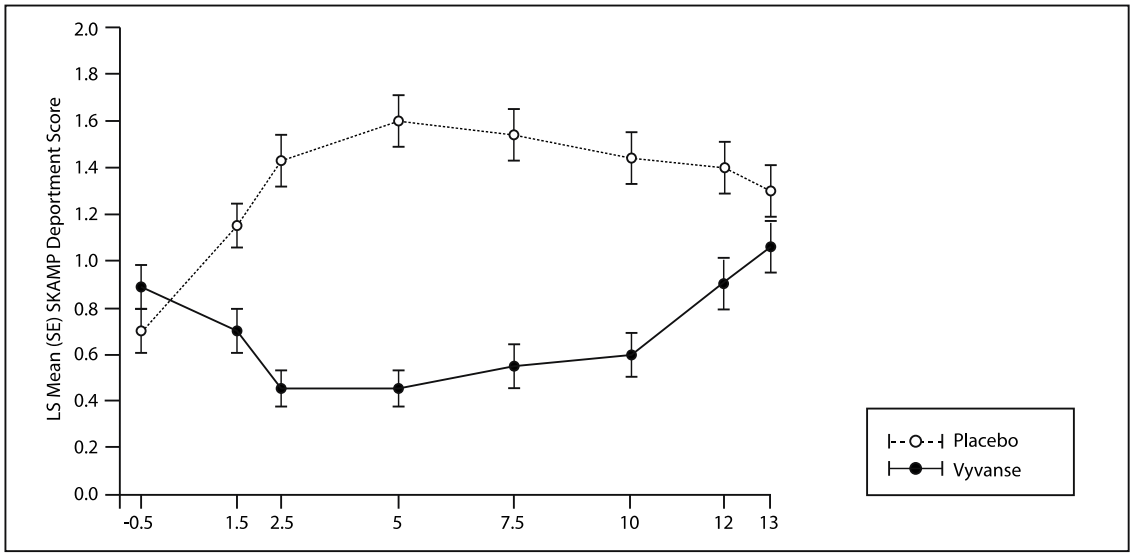
Aptensio XR (N = 26) SKAMP Combined scores (average absolute total scores)[13]



Quillivant XR (N = 45) SKAMP Combined scores (mean total score)[14]



Vyvanse (N = 111) SKAMP-Deportment Subscale Score (least squares mean)[11]



2.2 PLACE OF THE PRODUCT IN THERAPY

2.2.1 Disease Description

ADHD is a neurobehavioral disorder that involves having difficulty paying attention, hyperactive behavior and controlling impulsive behavior. Diagnosing ADHD is based on meeting criteria

outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Formerly, there were three subtypes of ADHD; however, in DSM-5, these are now referred to as presentations that may change over time. The three presentations are: inattention, hyperactivity and impulsivity, and a combined presentation. Diagnosis of ADHD requires the presence of symptoms for at least the previous 6 months whereby the patient's developmental level and social and academic activities are negatively impacted. Impairment must be observed in at least two settings (home, school, or job) to meet the criteria for the disorder.[3]

a. Epidemiology

The number of children in the U.S. diagnosed with ADHD has increased since 2003, with 11% of children 4–17 years of age (6.4 million) having a lifetime prevalence of this diagnosis in 2011.[4]

Table 2.3 categorizes the diagnosis of ADHD by age in 2011.[4]

TABLE 2.3: STRATIFICATION OF DIAGNOSIS OF ADHD BY AGE[4]

Age Category	Ever Been Diagnosed With ADHD (%)	Current Diagnosis of ADHD (%)	Current ADHD and Receiving Medication (%)
4–10 yr	7.7	6.8	4.9
11–14 yr	14.3	11.4	8.0
15–17 yr	14.0	10.2	6.5

The rate of ADHD diagnosis has increased an average of 3% per year from 1997 to 2006 and an average of ~5% per year from 2003 to 2011. Boys are more than twice as likely to be diagnosed with ADHD than girls (13.2% vs 5.6%, respectively). Interestingly, the prevalence varies by geographic location, with Kentucky having the highest prevalence at 18.7% and Nevada having the lowest at 5.6%.[16]

ADHD is not equally represented among ethnicities. Non-Hispanic white children have a higher prevalence than non-Hispanic black children (11.5% vs. 8.9%, respectively). Hispanic children have the lowest prevalence of ADHD (6.3%).[5]

Prevalence of ADHD also appears to be higher in children of low-income families. According to the CDC, in 2011–2013, 11.1% of children aged 6–11 years in families with incomes less than 200% of the federal poverty threshold had ever been diagnosed with ADHD compared with 8.1% of children in families with incomes at 200% or more of the poverty threshold.[17]

The breakdown by presentation indicates that most children have the inattentive presentation (42.8%), whereas 24.8% present with hyperactive-impulsive type and the remainder have a combined presentation (32.4%).[18]

b. Risk Factors and Comorbidities

Risk Factors

There are genetic and environment risk factors for the development of ADHD. No definitive causes have been linked to specific genes so there is no known predictive risk at this time other than the knowledge that family history increases the chances of an ADHD diagnosis. If a child has a first-degree relative who has been diagnosed with ADHD, he or she is two to eight times more likely to also be diagnosed with ADHD. Studies conducted in twins have reinforced the inheritability of ADHD that ranges from 71 to 90%.[19]

Non-genetic investigated risk factors for ADHD include perinatal stress, low birth weight, traumatic brain injury, maternal smoking during pregnancy, institutional rearing, child maltreatment and pre- and post-natal exposure to lead.[9,19]

Comorbidities

All children evaluated for ADHD should also be evaluated for co-existing conditions. Conditions to consider are: learning problems, language disorder, disruptive behavior anxiety, mood disorders, tic disorders, seizures, development coordination disorder, or sleep disorders. The presence of additional disease may impact therapy decisions for the patient.[6]

Common comorbid psychiatric disorders include oppositional defiant disorder (ODD) [54%–84%]; conduct disorder (CD). Mood disorders may also be seen (up to one-third of patients).[9]

Additionally, learning and language problems are seen in 25–35% of patients. As the patients reach adolescence they are at greater risk for smoking, and substance abuse (including alcohol and drugs).[9]

Data from the 2007 National Survey of Children's Health examined patterns of comorbidity in > 60,000 children between the ages of 6 and 17 years (Table 2.4).[19] They found that not only did ADHD carry more risks of individual comorbid conditions like learning disability and conduct disorders, but one-third of children with ADHD had 1 comorbid disorder, 16% had 2, and 18% had at least 3 comorbidities.

TABLE 2.4: PREVALENCE OF COMORBID DISORDERS FOR CHILDREN WITH ADHD VERSUS THOSE WITHOUT (N = 61,779)[20]

Comorbidity	No ADHD	ADHD*	Adjusted Relative Risk (%)†
Learning disability	5.3%	46.1%	7.79%
Conduct disorder	1.8%	27.4%	12.58%
Anxiety	2.1%	17.8%	7.45%
Depression	1.4%	13.9%	8.04%
Speech problems	2.5%	11.8%	4.42%
Autism spectrum disorder	0.6%	6.0%	8.72%
Hearing problems	1.2%	4.2%	2.77%
Epilepsy or seizures	0.6%	2.6%	3.93%
Vision problems	1.4%	2.3%	1.47%
Tourette's syndrome	0.1%	1.3%	10.70%
Any mental health/ neurodevelopmental disorder	11.5%	66.9%	5.12%

*$P < .05$ for chi-squared test.
†Relative risks were adjusted for child age, gender, race/ethnicity, parent education, household income, and family structure.

Source: Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. *Pediatrics*. 2011;127:462-470.

c. Pathophysiology

Both genetic and environmental factors contribute to the diagnosis of ADHD. Neuroimaging has enabled researchers to learn and understand the anatomical abnormalities identified with ADHD.

ADHD involves several areas of the brain responsible for attention, cognitive control, and working memory: specifically the prefrontal cortex, basal ganglia, cerebellum, and parieto-temporal regions. Neuroimaging studies have confirmed that some areas are smaller in patients with ADHD compared with individuals without ADHD; this may explain to some extent abnormal brain activity levels.[21] Additionally the neurotransmitters, dopamine, epinephrine and norepinephrine, play a role in brain functionality.[22] The exact role of the neurotransmitters is not

fully understood, but it is postulated that they may normalize neuroanatomy by acting directly to make brain development more typical or by normalizing brain function.[21]

d. Clinical Presentation

The following DSM-5 diagnostic criteria for ADHD are directly quoted from the manual:[3]

A. Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2) below:

1. **Inattention**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities: **Note**: the symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required:
    a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate)
    b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lecture, conversations, or length reading)
    c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction)
    d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked)
    e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines)
    f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers)
    g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephone)
    h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts)
    i. Is often forgetful in daily activities (e.g. doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
2. **Hyperactivity and Impulsivity**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and negatively impacts directly on social and academic/occupational activity: **Note**: the symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
    a. Often fidgets with hands or feet or squirms in seat
    b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place)
    c. Often runs about or climbs in situations where it is inappropriate (**Note**: in adolescents or adults, may be limited to feeling restless)

d. Often unable to play or engage in leisure activities quietly
e. Is often "on the go" acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless of difficult to keep up with:
f. Often talks excessively
g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation)
h. Often has difficulty waiting his or her turn (e.g., while waiting in line)
i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing)

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

1. **Combined presentation**; If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months (DSM-5 314.01; F90.2).
2. **Predominantly inattentive presentation**; If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months (DSM-5 314.00; F90.0).
3. **Predominantly hyperactive-impulsivity presentation;** If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months (DSM-5 314.01; F90.1).

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are preset, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe: are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.[3]

2.2.2 Approaches to Treatment

Medications for ADHD

The FDA has approved 3 general classes of medications for the treatment of ADHD: amphetamine derivatives, methylphenidate derivatives, and non-stimulants. Within these categories there are short-acting and long-acting products (Table 2.5).[9]

TABLE 2.5: THREE CLASSES OF ADHD MEDICATIONS

Amphetamines	**Methylphenidates**	**Nonstimulants**
Short-Acting	*Short-Acting*	
Adderall (mixed amphetamine salts)	Focalin (dexmethylphenidate)	Intuniv (guanfacine, extended release) [Indicated for monotherapy or in combination with a stimulant medication]
Dextroamphetamine	Methylin	Kapvay (clonidine, extended release) [Indicated for monotherapy or in combination with a stimulant medication]
Procentra	Ritalin	Strattera (atomoxetine)
Long-Acting	*Long-Acting*	
Adderall XR (mixed d- and l-amphetamine salts)	Focalin XR (dexmethylphenidate)	
Dexedrine spansules (d-amphetamine)	Methylin ER	
Dyanavel XR (d- and l-amphetamine base)	Ritalin LA	
Vyvanse (lisdexamfetamine)	Quillivant XR	

Medication Management

Medication should be considered first-line treatment in school-age children, according to the American Academy of Pediatrics as well as the Agency for Healthcare Research Quality.[6,23] The Multimodal Treatment Study of Children with ADHD found that school-age children (7.0–9.9 yr) receiving optimally dosed medication had the best symptom control and positive functioning outcomes versus those receiving behavioral treatment and routine community care that in some cases included medications not dosed at optimal doses.[23]

Behavioral Treatment

Behavioral therapy has also been found to be useful for treating ADHD.[6] This option includes modifying the patient's social and physical environment to promote behavior change. Behavioral therapy usually infers training parents in techniques that help them modify their child's behavior, in an effort to enhance the child's ability to self-regulate his or her behavior. This involves learning methods, like positive reinforcement, that reward the child when desired behavior is elicited. It also involves understanding which behaviors can be curtailed and how this can be accomplished using "planned ignoring," or disciplining the child with appropriate consequences when he or she does not meet expectations.[6]

Pharmacological treatment remains the mainstay of therapy. As stated above, the Multimodal Treatment Study of Children with ADHD found that school-age children receiving optimally dosed medication had the best outcomes versus those receiving behavioral treatment and routine community care that in some cases received non-optimal dosed medications.[24] The guidelines conclude that in patients having a full remission of symptoms and normative function, behavioral therapy is not mandatory; however, parenteral preferences need to be considered.[9] A benefit of combining therapy is that lower dosages of medications may be required to achieve the desired outcomes, which in turn may reduce the risk for adverse events.[6]

In those patients with ADHD and a comorbid condition, adding behavioral therapy to medication therapy did improve outcomes.[6,9]

The age of the child weighs heavily in the decision to use behavioral therapy. For pre–school-age children (4–5 yr), the American Academy of Pediatrics recommends behavioral therapy (parent- and/or teacher administered) be considered first-line treatment, with medication being recommended if the patient does not have significant improvement.[6]

Children diagnosed with ADHD and a comorbid disorder seem to benefit from behavioral therapy added to pharmacological therapy.[9,24] Individualized therapy whether pharmacological therapy or behavioral therapy should be prescribed for patients to achieve the best outcomes.[9]

Assessing ADHD and Monitoring Treatment

There are no blood tests or objective measures to definitively diagnose ADHD or to evaluate the outcomes of medication therapy. Numerous behavior rating scales are utilized to assess ADHD behaviors as well as to assess the patients' response to therapy in clinical practice (Table 2.6).[9] The SKAMP Scale is used only in research, not in clinical practice. It has the advantage of sensitivity allowing for the reliable determination of onset and duration of clinical effect of stimulants used in the treatment of patients with ADHD.[25, 26]

TABLE 2.6: COMMONLY USED BEHAVIOR RATING SCALES

Scale	Comment/Reference
Academic Performance Rating Scale (APRS)	A 19-point scale for determining a child's academic productivity and accuracy in grades 1–6[27]
ADHD Rating Scale-IV	A standard validated, 18-item rating scale modeled after the DSM-IV used to determine the severity of the ADHD symptoms at screening and baseline[28]
Brown ADD Rating Scales for Children, Adolescents, and Adults	Measures six clusters of executive functioning across lifespan of patients with ADHD[29]
Clinical Global Impression of Severity (CGI-S)	An investigator rating scale that determines the severity of the illness[30]
Child Behavior Checklist (CBCL)	Commonly used parent-report measures of youth emotional and behavioral problems in both clinical and research settings[31]
Columbia Suicide Severity Rating Scale (C-SSRS)	A rating scale commonly used in research to check for emergence of suicidal thoughts or behaviors[32]
Conners' Parent Rating Scale—Revised (CPRS-R)	A system designed to provide a complete overview of child and adolescent concerns and disorders[33]
Conners' Teacher Rating Scale—Revised (CTRS-R)	A system designed to provide a complete overview of child and adolescent concerns and disorders[33]
Conners' Wells Adolescent Self-Report Scale	A system designed to provide a complete overview of child and adolescent concerns and disorders[33]
Home Situations Questionnaire—Revised (HSQ-R), School Situations Questionnaire—Revised (SSQ-R)	A 16-item scale designed to assess specific problems with attention and concentration across a variety of home and public situations[34]

Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS)	A semi-structured interview used to confirm the diagnosis of ADHD according to DSM-IV criteria[35]
Swanson, Nolan, and Pelham (SNAP-IV) and Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)	SNAP-IV is a 26-item scale that is widely used in a variety of settings as an instrument for evaluating the efficacy of ADHD treatment and symptom improvement over time[36]; SKAMP is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting[24]
Vanderbilt ADHD Diagnostic Parent and Teacher Scales	Teachers rate 35 symptoms and 8 performance items that measure ADHD symptoms and common comorbid conditions. The parent version contains all ADHD symptoms, with items assessing comorbid conditions and performance[37]
Compiled from multiple sources, including the AACAP Guidelines.[9]	

2.2.3 Identification of Alternative Medications

Not all medications utilized to treat ADHD are approved by the Food and Drug Administration (Table 2.7). Most patients respond to medications approved for the treatment of ADHD. If a patient does not respond, clinicians are advised to reevaluate patients. If the reevaluation is being conducted by a primary care physician, the guidelines suggest that the child be referred to a child and adolescent psychiatrist.[9] Medications not FDA approved for the treatment are referred to as second-line agents, and their evidence for use is not supported as strongly based on fewer clinical trials or a lesser response to therapy.[9]

TABLE 2.7: NON–FDA-APPROVED MEDICATIONS USED FOR TREATING ADHD[9]

Generic Drug Name	Typical Starting Dose	Maximum Daily Dose	Comments
Bupropion	Lesser of 3 mg/kg/day or 150 mg/day	Less of 6 mg/kg or 300 mg with no single dose > 150 mg	Lowers seizure threshold; contraindicated if has current seizure disorder
Imipramine	1 mg/kg/day	Lesser of 4 mg/kg or 200 mg	Baseline ECG is needed
Nortriptyline	0.5 mg/kg/day	Lesser of 2 mg/kg or 100 mg	Baseline ECG is needed

Source: AACAP Guidelines

2.2.4 Relevant Treatment Guidelines and Consensus Statement from National and/or International Bodies

Currently, two national guidelines are widely used: (1) the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines, published in 2007[9] and (2) the American Academy of Pediatrics (AAP) clinical practice guidelines, published in 2011.[6]

The AACAP guidelines include 13 recommendations about screening, evaluation, and treatment for various age categories (e.g., 3–5, 6–12, and 13–17 yr). Screening and evaluation include observations from parents, clinicians, and a review of academic records. The recommendations for medication in the guideline are that pharmacological treatment should begin with a stimulant medication approved by the FDA. If stimulants do not result in satisfactory treatment, behavioral therapy and/or treatments not approved by the FDA for the treatment of ADHD should be considered.[9]

The AAP guideline contains key action statements encompassing six specific areas: (1) evaluation, (2) diagnosis of ADHD, (3) evaluating for coexisting conditions, (4) managing ADHD as a chronic condition, (5) treatment recommendations, and (6) maximizing medication doses to achieve maximum benefits while minimizing adverse events (according to the AAP guidelines, stimulant medications can be effectively titrated on a 3- to 7-day basis, because of their rapid onset of action.[6] Each recommendation is qualified by the strength of the evidence to support the recommendation. The recommended treatments included in the guideline vary by age:

- For preschool children, first-line treatment should be evidence-based parent and/or teacher-administered behavioral therapy.
- For elementary school–aged children, FDA approved medications for ADHD has the strongest effectiveness evidence. Then with lesser evidence, medication and/or evidence-based parent- and/or teacher-administered behavior therapy, preferably both, should be initiated. The guidelines indicate that the utilization of stimulant medication for first-line use is particularly strong.
- For adolescents, FDA approved medication for ADHD should be prescribed. There is lesser evidence for behavioral therapy or a combination of medication and behavioral therapy.[9]

The decision may be made to switch from one therapy to another, for example, because of inadequate coverage or the appearance of adverse events; however, little information in the literature is available about the equivalence of dosages of amphetamine and methylphenidate or the technical aspects of moving patients from one ADHD treatment to another.

2.2.5 Place and Anticipated Uses of Dyanavel XR in Treatment

Dyanavel XR is a first-line therapy for the treatment of children 6 years of age and older diagnosed with ADHD. The extended-release oral suspension was studied for efficacy in 108 children who met DSM-4 criteria for the diagnosis of ADHD. After a dose-optimization period (5 weeks), 1 week of placebo or active treatment was given in a double-blind manner. At the end of 1-week, medication efficacy was measured via the SKAMP rating scale by comparing the score predose to the score at 4 hours postdose. There was a statistically significant improvement in SKAMP scores not only 4 hours postdose but also at 1, 2, 4, 6, 8, 10, 12, and 13 hours postdose.[1,2]

Dyanavel XR offers a number of positive attributes for the first-line treatment of ADHD.

- It is the first and only extended-release oral amphetamine liquid for treatment of ADHD.[1,2,11–15] Dyanavel XR is a simply administered, once-daily, oral suspension that offers flexible dosing.[2]
- Treatment of ADHD is individualized and requires precise dose titration to reach an optimal balance between symptom control and side effects.[6] Dyanavel XR is available in a concentration of 2.5 mg/mL, which allows for a low starting dose (2.5–5.0 mg/day).[2]
- Dyanavel XR can be titrated rapidly (in increments of 2.5–10 mg/day every 4–7 days),[2] giving individualized, precise optimal doses. Based on its available concentration and recommended doses,[2] titration can be performed from a single prescription bottle, reducing the need for additional prescriptions and eliminating wasted medication when the dosage is adjusted.
- Dyanavel XR has a fast onset of action, with clinical trial evidence that it significantly improves SKAMP-Combined scores in 1 hour, compared with placebo, and it has demonstrated a duration of clinical effect of 13 hours after dosing.[2] This is the longest tested duration of effect in pediatric patients in the stimulant category and the fastest onset of action for extended-release amphetamines, based on approved labeling of the competitor products.[2,11–15] Dyanavel XR delivers statistically significant symptom control vs placebo over its entire duration of action, as shown during a SKAMP laboratory classroom study.[2]
- Dyanavel XR has a safety profile that is similar to that of other extended-release amphetamines, with only mild or moderate treatment-emergent adverse effects observed during a clinical study (unpublished data, Tris Pharma).[2]

2.3 EVIDENCE FOR PHARMACOGENOMIC TESTS AND DRUGS

Although pharmacogenomics testing has advanced significantly in some disease areas, this is not the case for ADHD. Studies have not yet yielded evidence to ascertain the type of individualized medicine approach needed in order to treat patients based on their respective genetic make-up.[38]

SECTION 3.0 SUPPORTING CLINICAL EVIDENCE FOR DYANAVEL XR®

3.1 SUMMARIZED KEY CLINICAL STUDIES

3.1.1 Study TRI102-ADD-001

*Berry S. Amphetamine extended-release oral suspension in the treatment of children with ADHD: A laboratory school study. Monmouth Junction, NJ: Tris Pharma Inc., 2014.**

**This clinical study summary references in great part Study TRI102-ADD-001, which is on file with Tris Pharma. The primary study findings described in this section are published in Dyanavel XR®'s prescribing information.*[2]

The principal clinical study supporting the use of Dyanavel XR (formerly known as TRI102) was a dose-optimized, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Dyanavel XR in reducing signs and symptoms of ADHD in patients between the ages of 6 and 12 years.[2] This study was not designed as a comparative trial between active treatments of ADHD.

Objectives:

This phase 3 trial had two principal objectives:[2]

(1) to assess the efficacy of dose-optimized Dyanavel XR in the treatment of ADHD compared with placebo in pediatric subjects aged 6 to 12 years with ADHD, and

(2) to assess the safety and tolerability of Dyanavel XR in pediatric subjects with ADHD.

Study Design and Subject Population:

This was a phase 3, multicenter, randomized, double-blind study with an open-label dose optimization period, conducted in a school laboratory environment. The study was designed to evaluate the efficacy and safety of dose-optimized Dyanavel XR (10–20 mL/day) compared with placebo in pediatric subjects ages 6 to 12 years with ADHD.

Patients who passed the baseline screening (Table 3.1), and for whom informed consent were obtained, were enrolled in a 5-week dose optimization period. Several ADHD diagnostic tests and cognitive assessments,† in addition to physical and laboratory tests, were performed at screening and baseline visits (prior to the dose-optimization period):

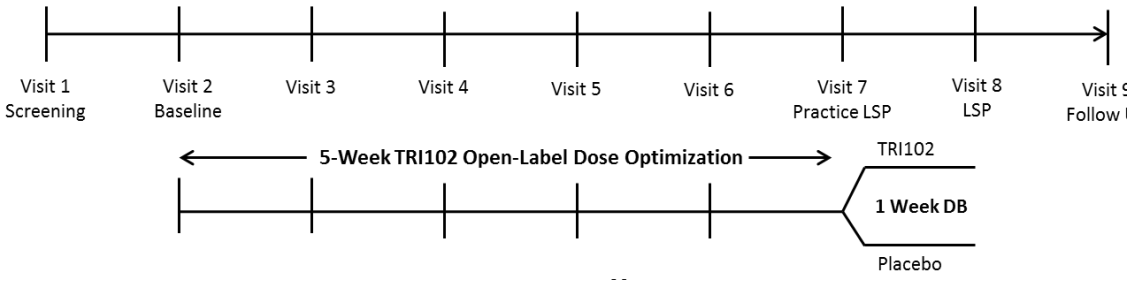
- ADHD-RS (ADHD Rating Scale
- CPRS (Conners' Parent Rating Scale)
- C-SSRS (Columbia Suicide Severity Rating Scale
- CGI-S (Clinical Global Impression of Severity)

†See Section 2.2.2 (**Approaches to Treatment**) for brief descriptions of these rating scales.

Parents and patients were educated about proper drug administration, and patient adherence to taking the study medication was assessed by evaluating drug quantities in medicine bottles at each office visit.

Figure 1 illustrates graphically the timeline from screening to study completion.

FIGURE 1. Study Design and Dosing Schedule. Visit 7 was an abbreviated practice laboratory school day compared with the laboratory school protocol (LSP) day on visit 8 (LSP 1). DB = double blind. (Source: data on file, Tris Pharma).



Once preliminary testing was completed, the open-label dose optimization period commenced. Treatment was initiated with a starting dose of either 2.5 mg/day or 5 mg/day of TRI102. Medication was given before 10 AM each day. Investigators could dose titrate in 2.5- or 5-mg/day increments during the first 2 weeks and 5- to 10-mg/day at weekly increments for the rest of the dose optimization period until an optimal dose or the maximum dose of 20 mg/day was reached. Dose titrations occurred at the investigator's discretion at each visit during the open-label period to achieve efficacy and tolerability based on assessments of the subject's ADHD signs and symptoms and observations of drug-induced side effects.

Patients were required to maintain a stable dose between 10 and 20 mg/day through the end of the dose-optimization period to advance to the next phase of the study. Those who could not maintain this dosage level were discontinued from the study. All children who completed the dose-optimization phase were asked to take part in a practice laboratory classroom setting to familiarize them with the testing to follow.

Subjects must have met the following randomization criteria to enter the double-blind treatment phase: (1) attained a stable dose of Dyanavel XR (defined as no change in dose between Study visits 6 and 7) of 10–20 mg/day, (2) had no change in their medical condition that would exclude them from receiving blinded study medication, and (3) completed pre- and postdose laboratory classroom assessments during visit 7. If they met these criteria, patients were randomized to receive either Dyanavel XR or an identically appearing placebo once daily by mouth for 1 week. Patients entering the randomized trial received the optimized dose they attained during the prior phase.

At the end of 1 week of double-blind treatment at the optimized dose, subjects were evaluated for ADHD symptoms in a laboratory classroom setting utilizing the SKAMP Rating Scale and PERMP assessments. The SKAMP Rating Scale is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. Each item is rated on a 7-point impairment scale. Permanent Product Measure of Performance (PERMP) is a skill-adjusted math test that measures attention in ADHD.

A patient's participation in the study was discontinued if any of the following occurred:

- Signs and symptoms of intolerance to the study drug were observed
- A treatment-related, serious adverse event (SAE) was observed
- Pregnancy
- The subject or parent/guardian was grossly noncompliant, as determined by the investigator
- Continued participation, in the opinion of the investigator, was no longer in the best interest of the subject
- The subject or parent/guardian wished to withdraw for any reason
- Unblinding of an investigator, site personnel performing assessments, or subject/parent to a subject's treatment assignment during the double-blind study phase

No psychoactive medications other than the study medication were permitted prior to the baseline. However, patients were allowed to receive acetaminophen and other non-psychoactive medications concomitantly. All such medications were recorded. Patients were advised to avoid grapefruit juice and caffeine-containing products for the duration of the study.

Target enrollment was 80 to 108 subjects with ADHD, which would accommodate suitable cohorts at six investigational sites in the United States. Patients entering the double-blind treatment phase were randomized on a 1:1 basis to receive active drug or placebo, respectively.

Primary Efficacy Outcome:

The primary efficacy endpoint was the assessment of change from predose in SKAMP Combined scores at 4 hours postdose measured during the laboratory school day (visit 8) in the intent-to-treat (ITT) population. The treatment difference between Dyanavel XR and placebo was determined using a two-sided test, with statistical significance set at alpha = .05.

Secondary Efficacy Outcomes:

Secondary key efficacy outcomes set by investigators were (1) change from predose in SKAMP-Combined scores at 1, 2, 6, 8, 10, 12, and 13 hours postdose during the laboratory school day (visit 8) in the ITT population; (2) change from predose in SKAMP-Attention and -Deportment scores at 1, 2, 4, 6, 8, 10, 12, and 13 hours postdose; (3) change from predose in PERMP scores (number of problems attempted and number of problems solved correctly) at 1, 2, 4, 6, 8, 10, 12,

and 13 hours postdose; (4) onset of clinical effect; (5) duration of clinical effect; and (6) changes in scores from other scales (i.e., CGI-S, CGI-I, ADHD-RS, and CPRS) at visits 3, 4, 5, 6, and 7.

Safety Outcomes:

Investigators monitored the participants for adverse events at each visit after beginning the dose-optimization phase or until 30 days after the final visit. In addition, all subjects were administered the C-SSRS at baseline and at each evaluation visit to uncover emergent suicidal thoughts or behaviors. Furthermore, all patients were monitored for physical problems, including the use of a 12-lead electrocardiogram and laboratory blood testing.

Pharmacokinetic Testing:

Blood was sampled from all subjects who completed the open-label dose-optimization phase (at the practice laboratory school day). Two blood samples were taken, predose and at 4.5 ± 0.5 hr postdose (roughly at the expected time of maximum concentration [T_{max}]).

TABLE 3.1: TRIAL TRI102-ADD-001 INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria	**Exclusion Criteria**
*A subject had to meet **all** of the following inclusion criteria to be eligible to enroll in this study:*	*The presence of **any** of the following exclusion criteria precluded a subject from study enrollment:*
1. Male or female 6 to 12 years of age at the time of screening, inclusive.	1. Diagnosed with a DSM-IV Axis I active disorder (other than ADHD): severe anxiety disorder, conduct disorder, psychotic disorders, pervasive developmental disorder, eating disorder, obsessive–compulsive disorder, major depressive disorder, bipolar disorder, substance use disorder, chronic tic disorder, autism spectrum disorder, or personal or family history of Tourette's syndrome as defined by DSM-IV criteria and supported by the K-SADS. Exceptions: specific phobias, learning disorders, motor skills disorders, communication disorders, oppositional defiant disorder, elimination disorders, and sleep disorders.
2. Diagnosed with ADHD by a psychiatrist, psychologist, developmental pediatrician, pediatrician, or an experienced licensed allied health professional approved by the sponsor using the following DSM-IV criteria:	2. Clinically significant cognitive impairment in the clinical judgment of the Investigator or a Wechsler Abbreviated Scale of Intelligence (WASI)–estimated IQ <80 at screening.
a. Positive confirmation of ADHD diagnosis by Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) questionnaire at screening.	3. History of chronic medical illnesses including seizure disorder (excluding a history of febrile seizures), severe hypertension, untreated thyroid disease, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy, known family history of sudden death, or glaucoma.

b. Investigator-administered Clinical Global Impression of Severity (CGI-S) score ≥3 at screening.	4. Clinically significant abnormal electrocardiogram (ECG) or cardiac findings on physical examination (including the presence of a pathologic murmur).
c. An ADHD-RS score at screening of ≥90th percentile for sex and age in at least 1 of the following categories: i. Hyperactive-impulsive subscale, ii. Inattentive subscale, or iii. Total score.	5. Use of monoamine oxidase inhibitors within 30 days of baseline visit.
3. In the clinical judgment of the investigator, the subject must have been in need of pharmacological treatment for ADHD. Any subjects at screening that were currently receiving ADHD medication must have shown signs of being inadequately managed on their current dose of stimulant treatment based on duration of action, safety, or tolerability. They must have met this criterion prior to washout. Use of noninvestigational stimulant medication for control of ADHD was allowed until 48 hours prior to the baseline visit.	6. Use of any psychotropic medication (except non-investigational stimulants for ADHD treatment until 48 hours prior to baseline visit).
	7. Use of atomoxetine within 30 days of baseline visit.
	8. Planned use of prohibited drugs or agents from the Screening visit through the end of the study (stimulant medications and sedative-hypnotics were allowed until 48 hours before baseline visit).
	9. Participation in a clinical study in which an investigational drug was administered within 30 days of the screening visit.
	10. Abnormal clinically significant laboratory test value at screening that, in the opinion of the Investigator, would have precluded study participation.
	11. A history of hypersensitivity to amphetamine.
	12. A history of lack of response to amphetamine.
	13. Parent or guardian's inability or unwillingness to follow directions of the Investigator or study research staff.
	14. Positive test for prohibited drugs at screening visit unless attributed to an allowed concomitant medication or to current stimulant therapy.
	15. History of human immunodeficiency virus (HIV) infection or active hepatitis B or active hepatitis C infection.
	16. Any uncontrolled medical condition that in the opinion of the Investigator would have precluded study participation.
Source: data on file, Tris Pharma.	

Study Results

Demographics. Of the 108 total subjects enrolled in this trial, 100 were included in the randomized, double-blind portion of the investigation. Forty-eight patients were assigned to receive placebo and 52 received Dyanavel XR.

Study Completion. Of this total, only one patient did not complete the study (from the active drug group). These 99 patients comprised the ITT population—they received at least one dose of either study medication or placebo. Of the nine patients in total who discontinued treatment, the vast majority (8 patients [89%]) did so during the open-label dose optimization phase (Table 3.2); one-half of these (4 patients) were terminated by sponsor decision—one study site did not enroll sufficient patients for the classroom laboratory testing, and these patients were included in the analysis of drug safety only. None of the discontinuations were the result of adverse events.

TABLE 3.2: REASONS FOR DISCONTINUATION

Reason for Premature Discontinuation	Not Randomized (N=8) n (%)	Placebo (N=48) n (%)	Dyanavel XR (N=52) n (%)	Total (N=108)
Consent Withdrawn	2 (25.0%)	0	0	2 (22.2%)
Lost to Follow-up	1 (12.5%)	0	0	1 (11.1%)
Study Terminated by Sponsor	4 (50.0%)	0	0	4 (44.4%)
Lack of Response to Treatment	1 (12.5%)	0	1 (100%)	2 (22.2%)

Source: data on file, Tris Pharma.

Forty-eight patients (66.7% boys, 33.3% girls; mean age ± SD, 9.6 ± 1.76 yr) were randomized to the placebo group and 52 patients (71.2% boys, 28.8% girls; mean age, 9.2 ± 1.95 yr) to the Dyanavel XR group. The age range of the subjects in each group was 6 to 12 years. Demographic characteristics in each group did not vary significantly with regard to race, ethnicity, height, weight, ADHD type, or ADHD-RS test scores.

Eighty-five percent of the enrolled patients had at least one significant comorbid finding. The category of respiratory, thoracic, and mediastinal disorders were most common (39.3% of the study population) and infections/infestations (27.1%), followed by immune system disorders (23.4%), and previous surgical or medical procedures (23.4%). None of these comorbidities varied significantly between the two study populations.

Medication Doses. Of the patients completing the open-label dose optimization phase, the final optimized doses were as follows: 32 received 10 mg/day; 35 received 15 mg/day; 40 received 20 mg/day (mean dose, 15.3 mg/day).

Medication-Taking Behavior. The vast majority used prior medications (83.3% in the control group, 71.2% in the study group), and the most common medications taken were centrally acting sympathomimetics (64.6% and 57.7%, respectively). Of previous amphetamines used, lisdexamfetamine dimesylate was most common (29.2% vs. 28.8%, respectively). Methylphenidate use was split between methylphenidate hydrochloride and dexmethylphenidate hydrochloride (14.6% each). Topical anesthetic use was reported by 22.9% and 21.2%, respectively. The topical anesthetic, EMLA cream, was used as needed to reduce discomfort during venipuncture (conducted to obtain screening laboratory values). No other medications were reported to be used by more than 10% of either group.

More patients taking Dyanavel XR received concomitant medication use during the double-blind treatment period compared with the placebo group (41.7% and 34.6%, respectively). The drug classes used most commonly during this study phase were propionic acid derivatives (NSAIDs) (12.5% vs. 9.6% of placebo subjects and study drug subjects, respectively); leukotriene-receptor antagonists (6.3% vs. 9.6%, respectively); and selective beta-2-adrenoreceptor agonists (8.3% vs.7.7%, respectively).

Adherence for both study groups was reported to be extremely high: for the dose-optimization phase of the study, more than 97% of the patients were >90% adherent. During the double-blinded treatment phase, approximately 94% of patients in each group were >90% adherent.

Primary Endpoint Results. The primary efficacy outcome was change in SKAMP-Combined score from predose (i.e., just prior to drug dosing) on the laboratory school day (visit 8) to 4 hours postdose (Table 3.3). A mean difference of -14.8 ± -1.61 ($P < .0001$) was observed between the two treatment groups (Figures 2A–D).

TABLE 3.3 PRIMARY EFFICACY RESULTS: DIFFERENTIAL IN 4 HOUR SKAMP-COMBINED SCORES AT VISIT 8: INTENT-TO-TREAT POPULATION[2]

Variable	Placebo Group (N = 48)	Dyanavel XR Group (N = 51)
Predose		
Mean ± SD Score	15.5 ± 7.35	17.3 ± 8.88
Median Score (Range)	14.0 (2 to 31)	14.0 (5 to 37)
4 Hours Postdose		
Mean ± SD Score	21.1 ± 10.14	8.2 ± 5.57
Median Score (Range)	19.5 (6 to 48)	7.0 (1 to 28)
Difference		
Mean ± SD Score	5.6 ± 7.85	–9.1 ± 7.51
Median Score (Range)	4.0 (–9 to 23)	–8.0 (–26 to 14)
LS Mean ± SE	6.0 ± 1.19	–8.8 ± 1.14*
95% CI	3.6 to 8.3	–11.1 to –6.6

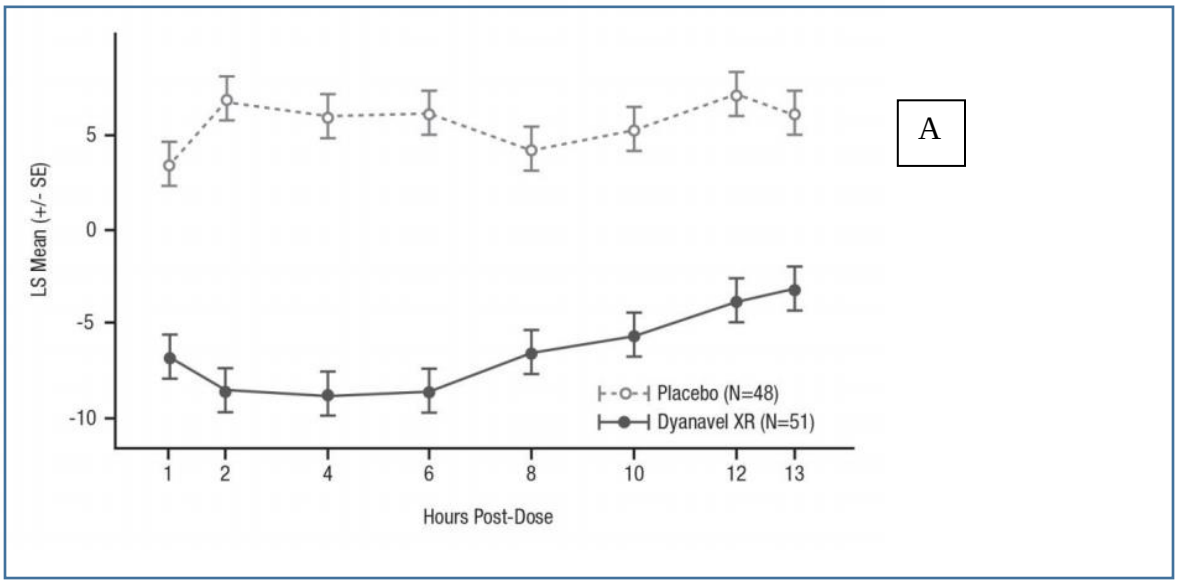
*$P < .0001$.

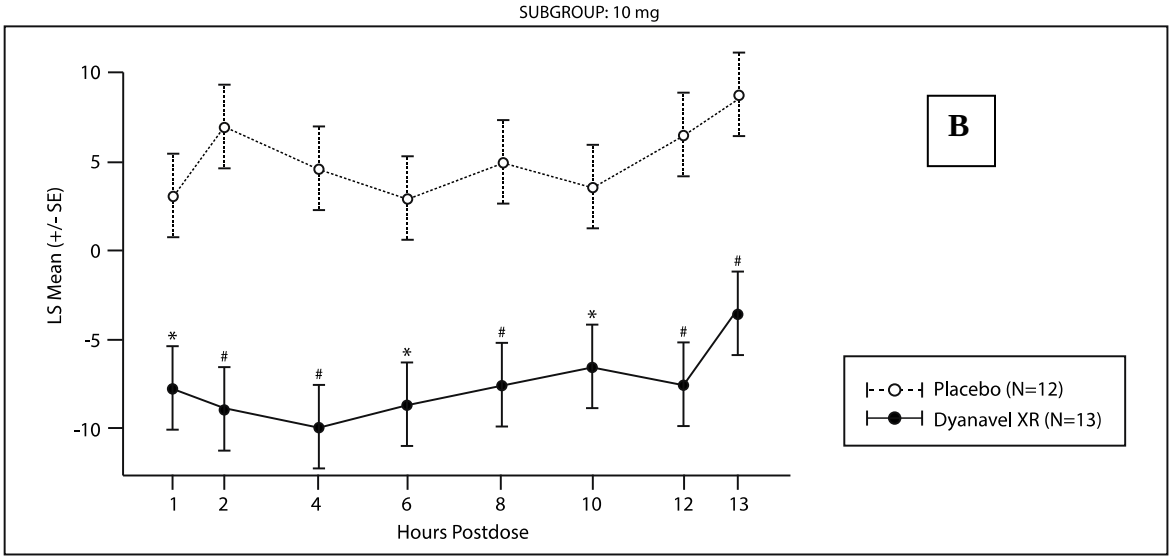
CI = Confidence interval; LS = least squares; SD = standard deviation; SE = standard error; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale.

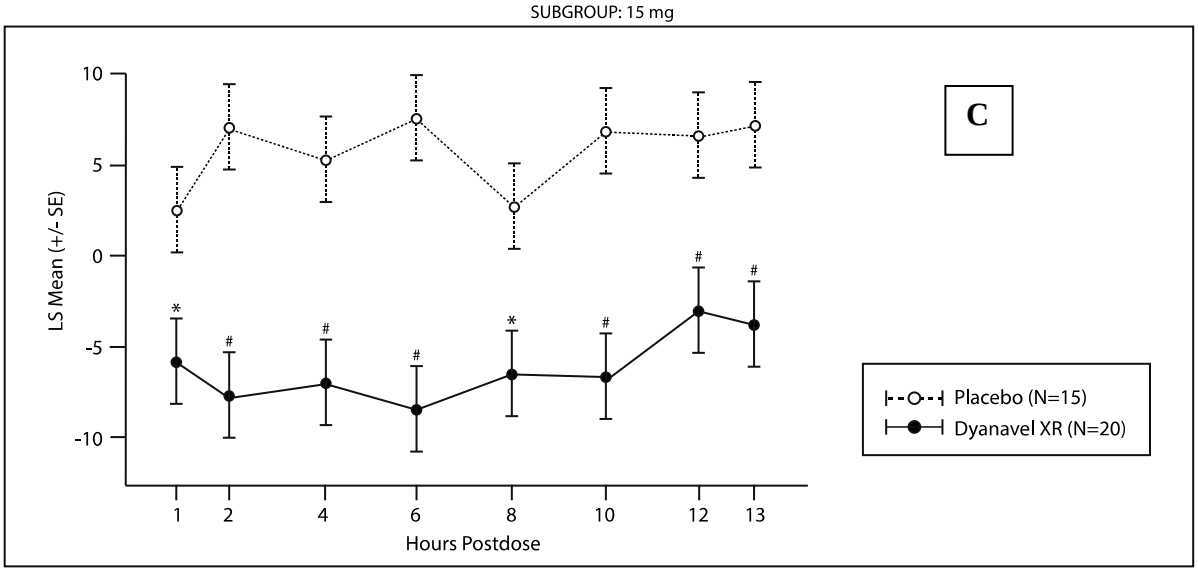
Source: data on file, Tris Pharma.

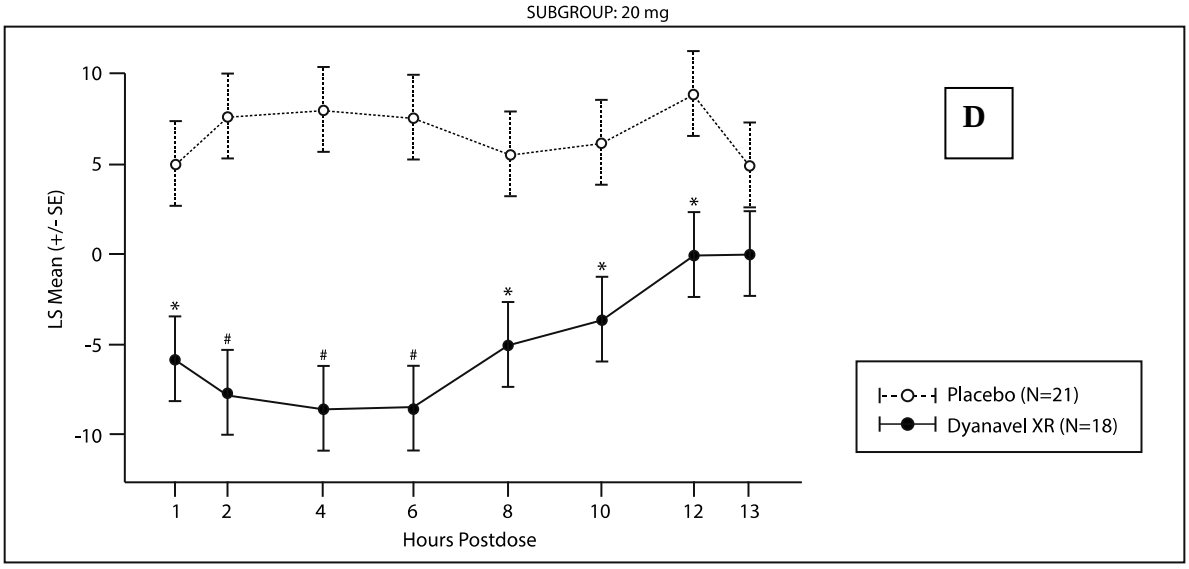
The SKAMP-Combined score subgroup analyses for the various doses were consistent with that for the ITT population analysis, with two exceptions: (1) In the 20-mg dose subgroup, the difference in SKAMP-Combined score at the 13-hour time point measurement was no longer statistically significant ($P = .11$); and (2) in the overall analysis of the "other" race subgroup, the SKAMP-Combined score difference was just beyond the threshold for statistical significance ($P = .0506$). The lack of significance at the 13-hour time point for the 20-mg dose group appears to be primarily due to combination of improving scores in the placebo group and easing of action of Dyanavel XR at that time point.

FIGURE 2. Change From Predose SKAMP-Combined Scores Over Time by Treatment Group and Final Optimized Dose: Intent-to-Treat Population. A: Overall results, B: 10 mg/day, C: 15 mg/day, D: 20 mg/day. LS = Least squares, SE = standard error. # *P* <.0001; **P* <.05. Source: data on file, Tris Pharma.



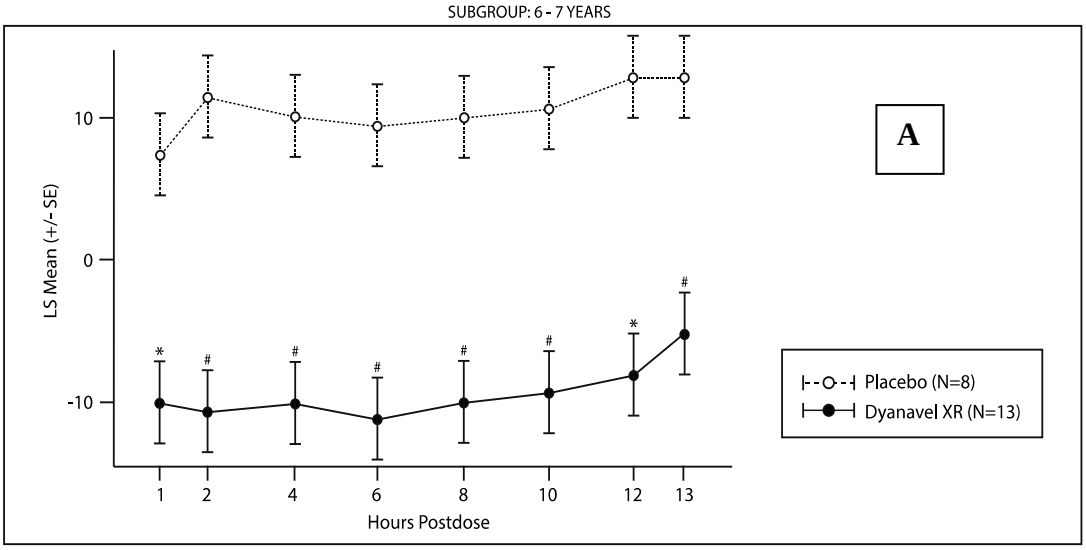


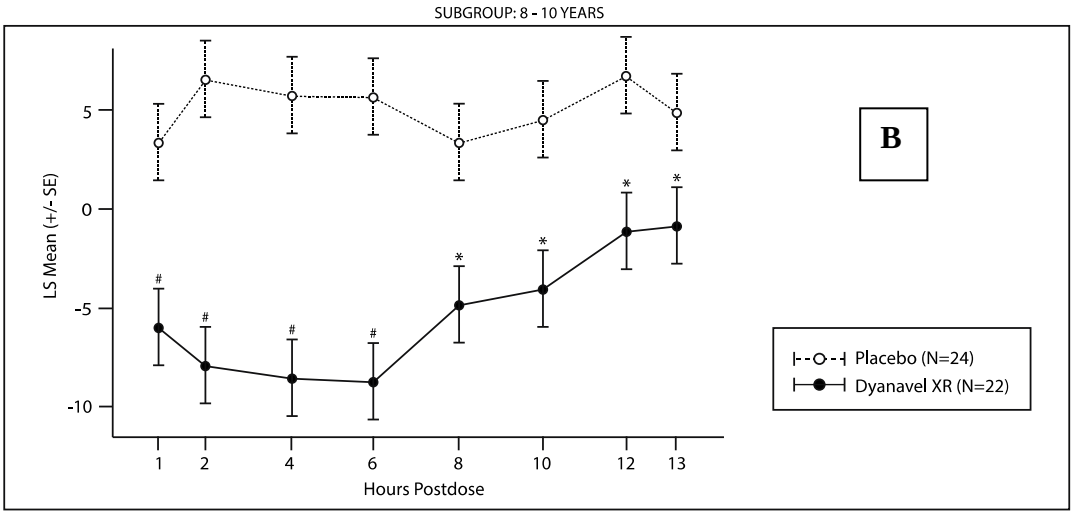


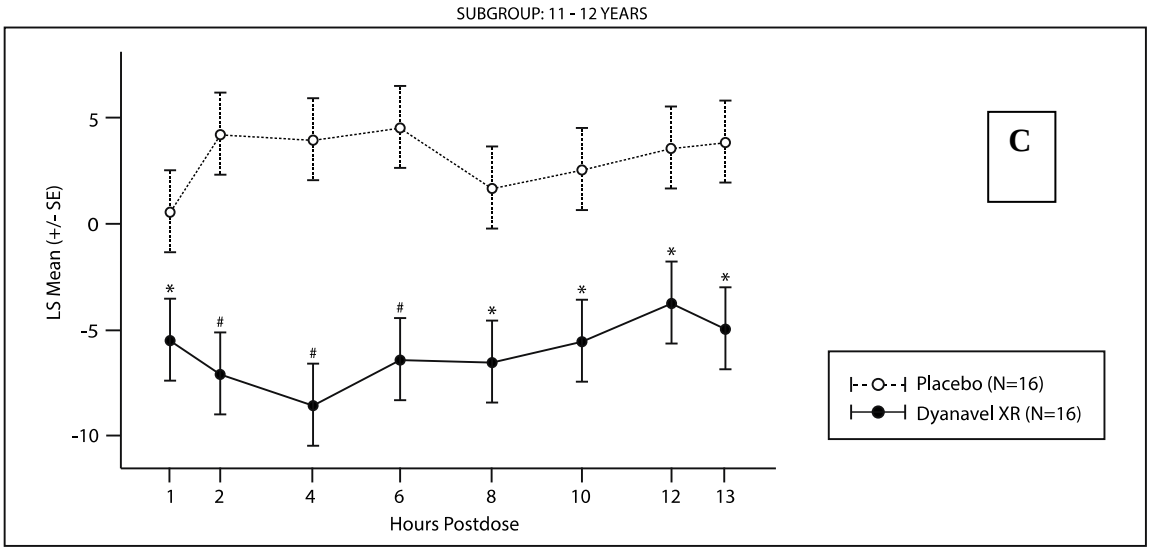


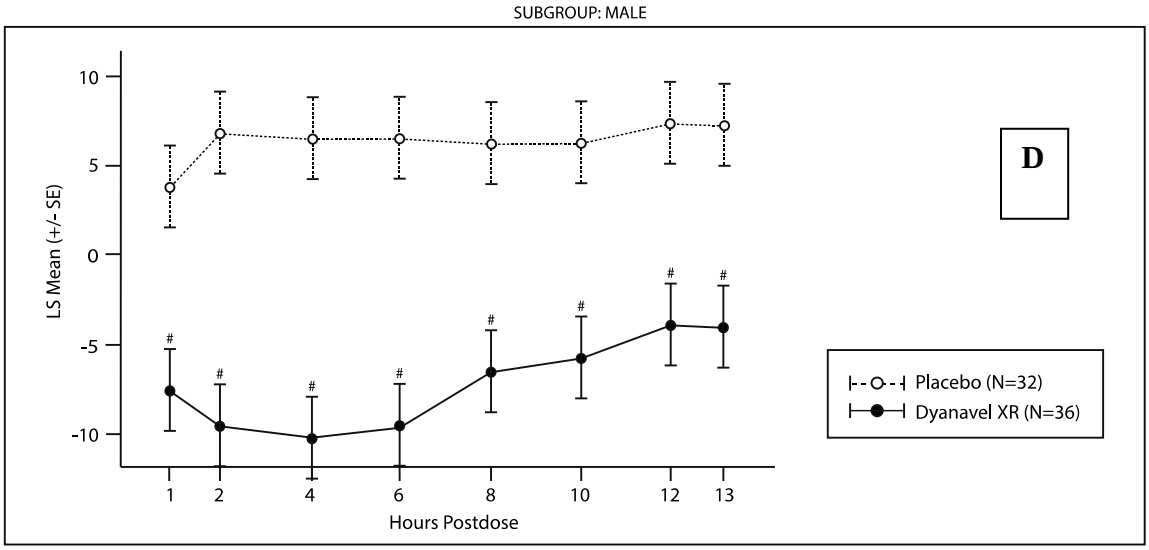
Other subgroup analyses demonstrate significant differences in SKAMP-Combined scores between patients taking Dyanavel XR and those taking placebo (Figures 3A–E). When stratifying patients by age and gender, significant differences are also seen over time.

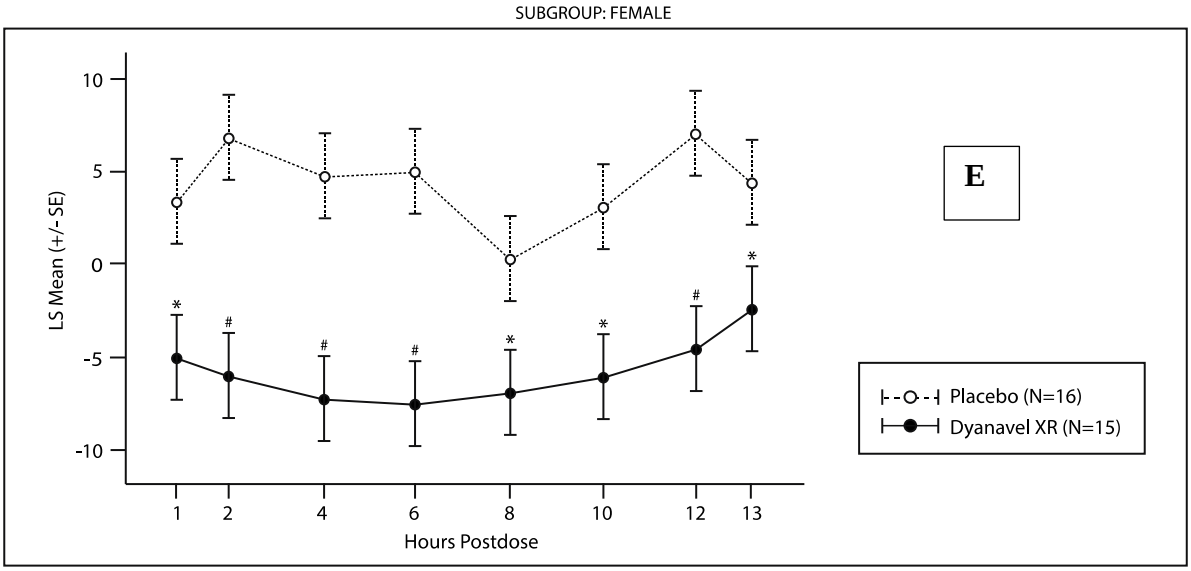
FIGURE 3. Change From Predose SKAMP-Combined Scores Over Time by Treatment Group at Individual Optimized Dose (10–20 mg/day) Determined in Open-Label Phase: Intent-to-Treat Population. (A)–(C): Age subgroups; (D)–(E): Gender subgroups. LS = Least squares, SE = standard error # *P* <.0001; **P* <.05. Source: data on file, Tris Pharma.





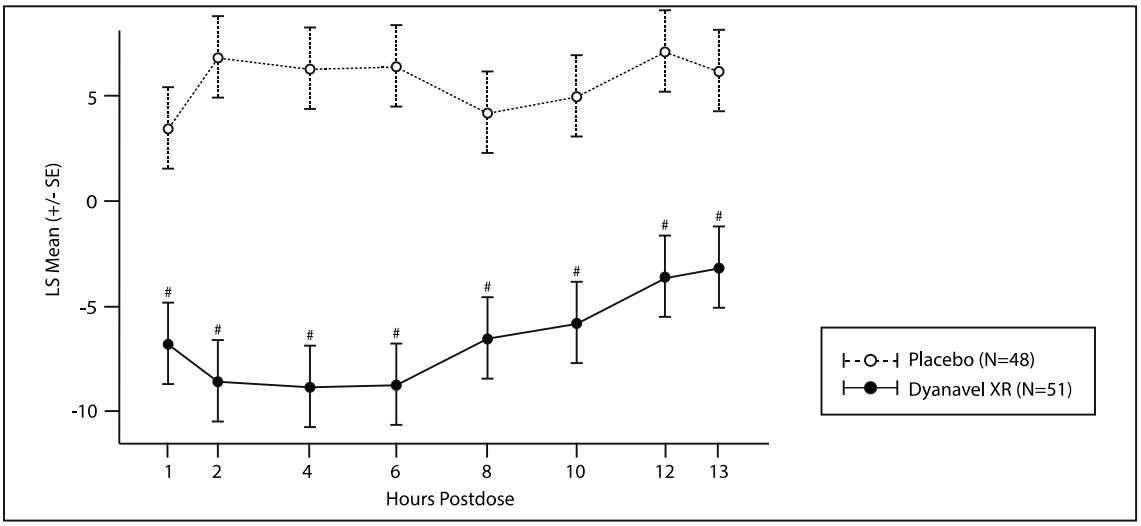

SUBGROUP: 11 - 12 YEARS
C
LS Mean (+/- SE)
5
0
-5
-10
1
2
4
6
8
10
12
13
Hours Postdose
Placebo (N=16)
Dyanavel XR (N=16)


SUBGROUP: MALE
D
LS Mean (+/- SE)
10
5
0
-5
-10
1
2
4
6
8
10
12
13
Hours Postdose
Placebo (N=32)
Dyanavel XR (N=36)



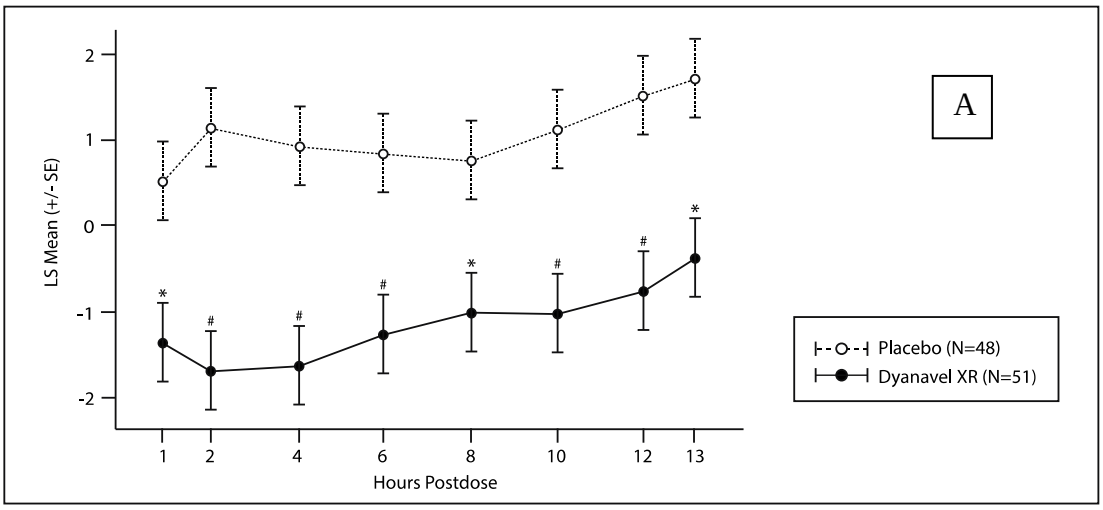
Secondary Endpoint Results. In terms of onset of treatment effect, a significant difference was seen in SKAMP-Combined scores from the earliest timepoint assessed (1 hr postdose). This difference, calculated as the least squares (LS) mean ± standard error was –10.2 ± 1.61 (P < .0001) (Figure 4). Significant differences in SKAMP-Combined scores persisted at each timepoint, through 13 hours postdose (–9.2 ± 1.61; P < .0001); the greatest relative difference in SKAMP-Combined scores was seen 2 hours postdose (–15.3 ± 1.61; P < .0001).

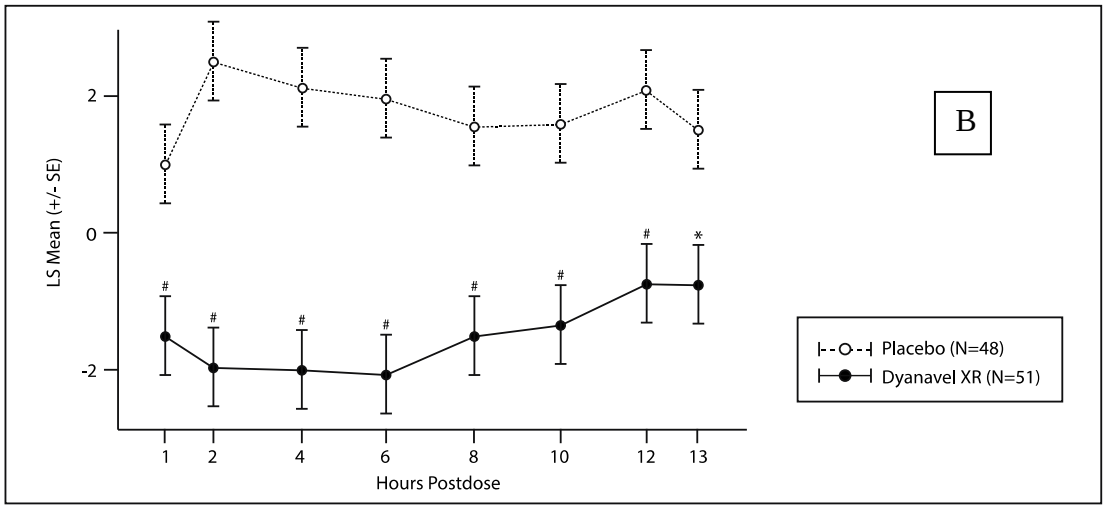
FIGURE 4: Change From Predose SKAMP-Combined Scores Over Time (Least Squares Mean ± Standard Error): Intent-to-Treat Population. $^{\#}P$ < .0001. Source: data on file, Tris Pharma).



Another secondary outcome analysis involved changes in the SKAMP Attention and Deportment subscale scores. A significant difference in scoring was observed in patients who used Dyanavel XR compared with placebo in both subscales at all timepoints postdose ($P < .001$). The LS mean ± standard error scoring difference was –2.2 ± 0.39 for the SKAMP Attention scale and –3.3 ± 0.51 for the SKAMP Deportment scale (Figure 5).

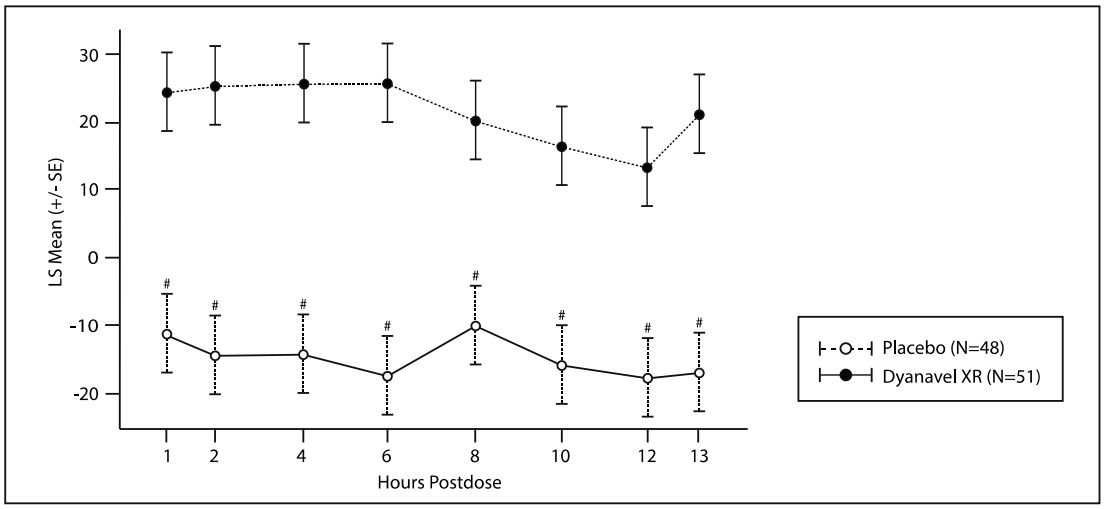
FIGURE 5: Change From Predose SKAMP-Attention (A) and -Deportment (B) Scores Over Time (Least Squares Mean ± Standard Error): Intent-to-Treat Population. $^{\#}P < .0001$; $^{*}P < .05$. Source: data on file, Tris Pharma.





Furthermore, changes in pre- to postdose PERMP scores for both the number of problems attempted and the number of problems answered correctly were significantly improved at all individual postdose timepoints compared with placebo ($P < .001$ for all values). The LS mean score differential across all time points was 35.7 ± 4.59 attempted and 33.0 ± 4.38 correct ($P < .0001$ for all values) (Figure 6).

FIGURE 6: Change From Predose PERMP Number of Problems Attempted Over Time (Least Squares Mean ± Standard Error): Intent-to-Treat Population. $^{\#}P < .0001$. Source: data on file, Tris Pharma.



The results of several other scales (CGI-S, CGI-I, ADHD-RS, and CPRS) were also evaluated as part of the secondary outcomes analysis. These scales were administered at baseline and during the open-label, dose-optimization period. The scales scores are summarized as change from baseline to the end of the dose-optimization phase (visit 7).

CGI-S. This study showed that the average CGI-S score decreased continuously from baseline (4.8 down to 2.0 by visit 7). Correspondingly, the percentage of subjects classified as at least moderately ill decreased from 97% at baseline to 1% at visit 7.

CGI-I. The CGI-I measures the subject's disease improvement relative to baseline (ratings as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse). The CGI-I scoring trends mirrored those of CGI-S scores, with the exception of a slight uptick in the score from visit 6 to visit 7 (mean, 1.2 and 1.3, respectively). At visit 3, 54.5% of patients were rated at least minimally improved; by visit 7, this figure increased to 100%.

ADHD-RS. A total of 90.9% of study patients were determined to be responders to Dyanavel XR (defined as having a change of ≥ 50% in the ADHD-RS total score).

TABLE 3.4: DRUG EXPOSURE TO DYANAVEL XR: ENROLLED SAFETY POPULATION

Treatment Phase	Placebo (N = 48)	Dyanavel XR ≤ 5 mg/day (N = 107)	Dyanavel XR > 5 to ≤ 10 mg/day (N = 107)	Dyanavel XR > 10 to ≤ 15 mg/day (N = 73)	Dyanavel XR >15 to ≤ 20 mg/day (N = 41)	Dyanavel XR All Doses (N = 107)
Open Label						
Length of Exposure (n)		107	107	73	41	107
Mean ± SD (days)		6.7 ± 0.88	12.3 ± 8.91	12.8 ± 6.66	13.9 ± 3.00	33.3 ± 5.03
Median (days)		7.0	7.0	9.0	14.0	34.0
Range (days)		3–9	5–30	5–23	7–22	12–37
Double Blind						
Length of Exposure (n)	48		14	20	18	52
Mean ± SD (days)	6.9 ± 0.24		7.0 ± 0.00	6.9 ± 0.31	6.9 ± 0.24	6.9 ± 0.24
Median (days)	7.0		7.0	7.0	7.0	7.0
Range (days)	6–7		7–7	6–7	6–7	6–7
Overall						
Length of Exposure (n)	48	107	107	73	41	107
Mean ± SD (days)	6.9 ± 0.24	6.7 ± 0.88	13.2 ± 10.58	14.7 ± 8.95	16.9 ± 5.40	36.6 ± 6.72
Median (days)	7.0	7.0	7.0	9.0	16.0	37.0
Range (days)	6–7	3–9	5–37	5–30	7–29	12–44

Source: data on file, Tris Pharma.

CPRS. The study revealed that CPRS scores decreased continuously for most categories in patients taking Dyanavel XR from baseline to the end of the open-label dose optimization study phase. The only exception was revealed in the peer-relations category, in which the lowest average score occurred at visit 6.

Drug Safety

Drug Exposure. As all of the study participants were given titrated doses of Dyanavel XR, they each had exposure to the lowest dosage levels, with decreasing numbers being exposed to higher doses, up to 20 mg/day (Table 3.4). The safety analysis was based on data collected not only from patients who participated in the double-blind phase of the study but any patient in the open-label dose optimization study who received at least one dose of the medication (i.e., the enrolled safety population).

Adverse Events. Treatment-emergent adverse events (TEAEs) were reported by 64 (59.8%) of the 107 subjects in the safety evaluable population during the open-label dose optimization period. Of the 177 TEAEs reported, 124 TEAEs (70.1%) in 51 subjects were considered to be related to treatment. None of the TEAEs were considered severe (78% were rated mild and 22% were rated moderate), and no one withdrew from the study as a result of a TEAE.

Twenty-four TEAEs were reported by 15 subjects during the double-blind treatment period (6 [12.5%] receiving placebo, 9 [17.3%] receiving study drug). Seven of these TEAEs were considered to be related to treatment (6 [50.0%] in the placebo group and 1 [8.3%] in the Dyanavel XR group) in 4 study participants (3 of whom were placebo group members). The TEAEs were deemed mild (66.7%) or moderate (33.3%); none were considered severe or led to study discontinuation.

In the open-label phase, the most common TEAEs were decreased appetite (26.2%), insomnia (13.1%), affect lability (9.3%), upper abdominal pain (7.5%), headache (5.6%), and mood swings (5.6%). All other TEAEs occurred in fewer than 5.0% of subjects. During the double-blind phase, no TEAE occurred in 5.0% or more of the study population (Tables 3.5 & 3.6).

TABLE 3.5: TREATMENT-EMERGENT ADVERSE EVENTS: OPEN-LABEL PHASE

System/Organ Class		Total (N = 107) n (%)
Overall		64 (59.8%)
Psychiatric disorders		33 (30.8%)
	Insomnia	14 (13.1%)
	Affect lability	10 (9.3%)
	Mood swings	6 (5.6%)

	Dysphoria	4 (3.7%)
	Irritability	4 (3.7%)
	Dermatillomania	1 (0.9%)
	Nail picking	1 (0.9%)
	Oppositional defiant disorder	1 (0.9%)
Metabolism/Nutrition Disorders		28 (26.2%)
	Decreased appetite	28 (26.2%)
Gastrointestinal disorders		21 (19.6%)
	Abdominal pain, upper	8 (7.5%)
	Nausea	5 (4.7%)
	Vomiting	4 (3.7%)
	Aphthous stomatitis	2 (1.9%)
	Gastritis	1 (0.9%)
	Glossodynia	1 (0.9%)
	Lip swelling	1 (0.9%)
Injury/Poisoning/Procedural complications		10 (9.3%)
	Arthropod bite	2 (1.9%)
	Muscle strain	2 (1.9%)
	Animal bite	1 (0.9%)
	Fall	1 (0.9%)
	Laceration	1 (0.9%)
	Limb injury	1 (0.9%)
	Lip injury	1 (0.9%)
	Scratch	1 (0.9%)
Nervous system disorders		10 (9.3%)
	Headache	6 (5.6%)
	Dizziness	2 (1.9%)
	Paraesthesia	1 (0.9%)
	Tremor	1 (0.9%)
Infections/Infestations		8 (7.5%)
	Gastroenteritis, viral	2 (1.9%)
	Upper respiratory tract infection	2 (1.9%)
	Gastroenteritis	1 (0.9%)
	Otitis externa	1 (0.9%)
	Otitis media, acute	1 (0.9%)

	Sinusitis	1 (0.9%)
General disorders/Administration site conditions		6 (5.6%)
	Fatigue	5 (4.7%)
	Thirst	1 (0.9%)
Respiratory/Thoracic/Mediastinal disorders		6 (5.6%)
	Cough	5 (4.7%)
	Epistaxis	1 (0.9%)
	Nasal congestion	1 (0.9%)
	Rhinorrhea	1 (0.9%)
Musculoskeletal/Connective tissue disorders		5 (4.7%)
	Arthralgia	1 (0.9%)
	Bone pain	1 (0.9%)
	Muscle spasms	1 (0.9%)
	Muscle twitching	1 (0.9%)
	Muscular weakness	1 (0.9%)
	Myalgia	1 (0.9%)
	Neck pain	1 (0.9%)
	Pain in extremity	1 (0.9%)
Eye disorders		3 (2.8%)
	Conjunctivitis	1 (0.9%)
	Conjunctivitis, allergic	1 (0.9%)
	Eye pruritus	1 (0.9%)
	Lacrimation increase	1 (0.9%)
Investigations		3 (2.8%)
	Weight decreased	3 (2.8%)
Cardiac disorders		1 (0.9%)
	Palpitations	1 (0.9%)
Reproductive system and breast disorders		1 (0.9%)
	Dysmenorrhoea	1 (0.9%)
Skin and subcutaneous tissue disorders		1 (0.9%)
	Rash	1 (0.9%)
Source: data on file, Tris Pharma.		

TABLE 3.6: TREATMENT-EMERGENT ADVERSE EVENTS*: DOUBLE-BLIND PHASE			
System/Organ Class		**Placebo (N = 48) n (%)**	**Dyanavel XR (N = 52) n (%)**
Overall		6 (12.5%)	9 (17.3%)
Respiratory/Thoracic/Mediastinal Disorders		0	3 (5.8%)
	Epistaxis	0	2 (3.8%)
	Rhinitis, allergic	0	2 (3.8%)
Gastrointestinal disorders		2 (4.2%)	2 (3.8%)
	Abdominal pain, upper	1 (2.1%)	2 (3.8%)
	Vomiting	1 (2.1%)	1 (1.9%)
Infections/Infestations		2 (4.2%)	1 (1.9%)
	Gastroenteritis, viral	1 (2.1%)	1 (1.9%)
	Upper respiratory tract infection	1 (2.1%)	0
Metabolism/Nutrition disorders		0	1 (1.9%)
	Decreased appetite	0	1 (1.9%)
Musculoskeletal/Connective tissue disorders		0	1 (1.9%)
	Musculoskeletal pain	0	1 (1.9%)
Nervous system		2 (4.2%)	1 (1.9%)
	Headache	1 (2.1%)	1 (1.9%)
	Sudden onset of sleep	1 (2.1%)	0
Psychiatric disorders		2 (4.2%)	1 (1.9%)
	Insomnia	1 (2.1%)	1 (1.9%)
	Initial insomnia	1 (2.1%)	0
General disorders/Administration site conditions		1 (2.1%)	0
	Malaise	1 (2.1%)	0
	Pyrexia	1 (2.1%)	0
Injury/Poisoning/Procedural complications		1 (2.1%)	0
	Arthropod bite	1 (2.1%)	0

*Some patients may have experienced more than one adverse effect; therefore, percentages may not add up to 100%.

Source: data on file, Tris Pharma.

No serious adverse events or deaths were recorded as TEAEs. No serious adverse events or deaths were determined to be associated with Dyanavel XR treatment.

Multiple clinical and laboratory evaluations conducted both during the open-label dose optimization phase and the double-blind phase failed to reveal any potential safety issues. None of the study participants had clinically significant changes in health status during the course of the study, from the screening to follow-up periods, as assessed by the investigators.

In summary, the safety data support that Dyanavel XR is safe and well tolerated at doses ranging to 20 mg/day.

Conclusions

This phase 3 trial provides evidence that Dyanavel XR appears to be safe and effective for the treatment of ADHD in children aged 6 to 12 years. The significant changes in SKAMP-Combined scores from 1 hour postdose to 13 hours postdose compared with placebo demonstrate a rapid onset of action and duration of clinical effect of up to 13 hours. The safety analysis revealed that Dyanavel XR was well tolerated across all optimized daily dose levels between 10 mg and 20 mg. The side-effect profile seems to be similar to that for other extended-release amphetamine-based ADHD products.

3.2 SUMMARIZED KEY CLINICAL STUDIES SUPPORTING OFF-LABEL INDICATIONS

The information presented in this dossier is focused on ADHD, and only contains information on trials conducted by Tris Pharma. Currently, no studies have been performed to support off-label indications (i.e., use in patients with ADHD < 6 yr of age or for different disorders). Please note, Tris Pharma does not recommend the use of Dyanavel XR outside of its FDA-approved product labeling.

3. 3 EVIDENCE TABLE SPREADSHEET OF TRIS PHARMA–CONDUCTED DYANAVEL XR ADHD CLINICAL TRIALS IN CHILDREN (6–12 YEARS OF AGE)

TABLE 3.7: EVIDENCE TABLE SPREADSHEET OF TRIS PHARMA–CONDUCTED DYANAVEL XR ADHD CLINICAL TRIALS IN CHILDREN (6–12 YEARS OF AGE)

Ref	Design	Treatment	N	Time	Endpoints	Results/Comments
TRI102-ADD-1 Dyanavel XR Prescribing Information	• Phase 3 (1) Open-label, dose-optimization • (2) Randomized, double-blind, placebo-controlled	• Dyanavel XR, initial dose: 2.5–5 mg/day titrated to 10–20 mg/day • Placebo This laboratory classroom study had a 5-week dose optimization phase prior to randomization to the 1-week double-blind placebo-controlled study. This study did not compare active treatments.	108 in the open-label phase 99 in the randomized, double-blind, placebo-controlled phase	5 weeks (open-label phase) 1 week (randomized, double-blind phase)	Primary: Change in SKAMP-Combined scores 4 hr postdose Secondary: • Change from predose in SKAMP-Combined scores at ≥ 13 hr postdose (onset and duration of clinical effect) • Change from predose in SKAMP-Attention and -Deportment scores ≥ 13 hr postdose • Change from predose in PERMP scores ≥ 13 hours postdose • Changes in scores of other scales (i.e., CGI-S, CGI-I, ADHD-RS, and CPRS) during the open-label phase • Safety Outcomes	Results: • Primary Endpoint: SKAMP-Combined scores were significantly improved at 4 hr postdose in the Dyanavel XR group (*P* < .0001) compared with the placebo group. • Secondary Endpoints: ○ SKAMP-Combined scores in patients taking Dyanavel XR were significantly different than those in the placebo group at all timepoints, from 1 hr up to 13 hr (*P* < .0001). ○ SKAMP-Attention and SKAMP-Deportment subscales were significantly different in the Dyanavel XR group compared with the placebo group at all timepoints post-dosing (*P* < .001). ○ PERMP scores for the number of problems attempted and the number of problems answered correctly were significantly improved for patients taking Dyanavel XR compared with placebo at all timepoints *(P* < .001) *for all values.* Open-label study scale results: CGI-S—average scores decreased continuously from baseline to the final visit in the open-label study. Percentage of those classified as moderately ill fell from 97% at baseline to only 1% at the final visit this study phase; CGI-I—The trend in CGI-I classification mirrored CGI-S classification: The percentage of subjects with a CGI-I classification of either minimally improved, much improved, or very much improved increased from 54.5% at openlabel Week 2 to 100% at open-label Week 6.; ADHD-RS—91% of patients were determined to have a change of ≥ 50% in this scale scoring by the end of the open-label phase; CPRS—The CPRS scores in all categories decreased continuously from baseline to end-of-the-study phase (in the peer-relations category, scores dropped through visit 6 but fell no further). Adverse Events: In the open-label phase, the most common TEAEs were decreased appetite (26.2%), insomnia (13.1%), affect lability (9.3%), upper abdominal pain (7.5%), headache (5.6%), and mood swings (5.6%). All other TEAEs occurred in fewer than 5.0% of subjects. The adverse events were rated as mild in 78% of cases and moderate in 22%. None were considered severe, and none of the patients withdrew from the study as a result of treatment-emergent side effects. During the double-blind phase of the study, no adverse event occurred in 5.0% or more of the study population.

4.3 ANTICIPATED UTILIZATION OF DYANAVEL XR

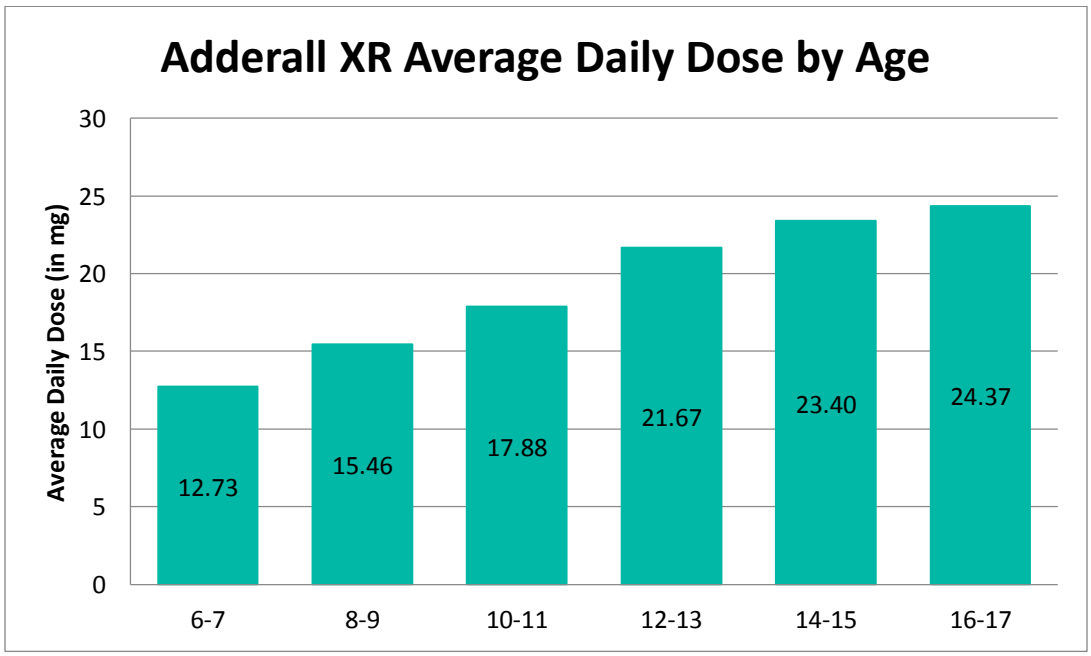
The optimal daily dose of an agent in the carefully controlled environment of a clinical trial may not reflect real-world daily consumption (DACON). In order to estimate the DACON of Dyanavel XR (as calculated below), Tris Pharma examined the utilization experience of two closely related products, Quillivant XR and Adderall XR, both in clinical trials and actual practice.

The starting daily dose of Dyanavel XR in the clinical trial was 2.5–5.0 mg/day, with titration up to an optimal dose or maximum dose of 20 mg/day, at the discretion of the prescriber. The average daily dose of Dyanavel XR in the clinical trial of 15.4 mg/day (covering both the dose-optimization period and the double blind study phase) (Study TRI 102-ADD-00104, data on file).

The overall DACON is based on dosing utilization data per age group of Adderall XR® (mixed salts of a single-entity amphetamine product). Age-based prescription distribution for Dyanavel XR is a weighted average. It is further informed by utilization data per age group of Quillivant XR®, another liquid ADHD medication that is primarily used for children under 12 years.

To determine the dosing utilization per age group for Adderall XR, an analysis of prescriptions dispensed between 2013 and 2015 was conducted. Figure 6 shows the average daily dose of Adderall XR per age group. (Symphony Phast [covering Oct 2013 – Sep 2015], extracted on November 11, 2015, data on file).

FIGURE 6: Adderall XR's average daily dose for ADHD patients aged 6–17 yr is 19.25 mg/day.



After determining the average dose of Adderall XR for each age group, that dose was converted to amphetamine base (using the conversion factor of 0.625). Each average dose expressed as amphetamine base was multiplied by the expected percentage usage based on Quillivant XR utilization data.

TABLE 4.3. DOSING FOR AGE GROUPS 6–17 FOR DYANAVEL XR BASED ON ADDERALL XR AND QUILLIVANT XR

Age	Adderall XR Average Dose by Age (mg/day)	Quillivant XR Usage by Age 6–17 yr	Amphetamine Weighted Average Dose by Age Group (mg/day expressed as salt)	Dyanavel XR Weighted Average (mg/day expressed as free base)
6-7	12.73	30.5%	3.887	2.429
8-9	15.46	33.5%	5.180	3.238
10-11	17.88	19.5%	3.496	2.185
12-13	21.67	9.6%	2.086	1.304
14-15	23.40	4.6%	1.074	0.671
16-17	24.37	2.2%	0.538	0.336
		100.0%		
	19.25 mg/day		16.260 mg/day	10.163 mg/day

The sum of the weighted average dose for each age group revealed a DACON for Dyanavel XR of 10.16 mg/day.

The rationale for using Quillivant XR (methylphenidate) extended-release for oral suspension, utilization data in the calculation of the Dyanavel XR DACON, is simply that Quillivant XR is an extended-release oral suspension that has more than 80% utilization in children aged 11 years and younger. In contrast, Adderall XR, an extended-release capsule that can be sprinkled on applesauce, has 17% utilization in children aged 11 years and younger. Presumably, the differential distribution in utilization between the two products is driven by the liquid formulation of Quillivant XR. A large prescription database [Symphony Fast] from October 2014 to September 2015 shows very different utilization profile by age group for Quillivant XR oral suspension compared with the solid dosage forms: 79% of Quillivant XR usage occurred in patients 11 years or younger. (Tris Pharma, data on file).

4.5 SIZE OF PATIENT POPULATION

When considering an average commercial health plan with 1 million members, the expected population with ADHD can be estimated based on the following assumptions: the national proportion of children (50.2 million children 6–17 yr of age; 29.0 million children 6–12 yr of age) to the general population of 321.3 million Americans in total.[44,45] The average 1 million member

health plan would therefore include 155,800 children and adolescents (6–17 yr of age) or 90,000 children ages 6 to 12 years.

The highest reported prevalence (parent-reported) for children (up to age 17 yr) ever diagnosed with ADHD is 11.0%[4] (5.5 million nationally or 17,140 in the health plan). The prevalence of those up to age 17 with current ADHD is 8.8%.[4] This translates into roughly 4.4 million children nationally or 13,600 in the children between 6 and 17 years of age (7,920 children between 6 and 12 yr of age) who have currently diagnosed ADHD.

Studies indicate that approximately two-thirds of this group (6.1%) are taking medications for their ADHD, yielding a plan population of 9,500 between the ages of 6 and 17 years and 5,500 between the ages of 5 and 12 years.

SECTION 5.0 OTHER SUPPORTING EVIDENCE

Not applicable—no other supporting evidence is available.

SECTION 6.0 REFERENCES

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APPENDIX: PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DYANAVEL XR (amphetamine) extended-release oral suspension, CII

Initial U.S. Approval: 1960

WARNING: ABUSE AND DEPENDENCE
See full prescribing information for complete boxed warning.

- **CNS stimulants, including DYANAVEL XR, other amphetaminecontaining products, and methylphenidate, have a high potential for abuse and dependence (5.1, 9.3)**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (9.2, 9.3)**

----------INDICATIONS AND USAGE----------
DYANAVEL XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (1)

----------DOSAGE AND ADMINISTRATION----------
Before administering the dose, shake bottle (2.2)

- May be taken with or without food (2.2)
- In children 6 years of age and older, recommended starting dose is 2.5 mg or 5 mg once daily in the morning (2.2)
- Dosage may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days until optimal response is obtained (2.2)
- Daily dose above 20 mg is not recommended (2.2)
- Do not substitute for other amphetamine products on a milligramper-milligram basis, because of different amphetamine base compositions and differing pharmacokinetic profiles (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Extended-release oral suspension containing 2.5 mg amphetamine base per mL (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to amphetamine products or other ingredients in DYANAVEL XR (4)
- Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- *Serious Cardiovascular Reactions:* Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use (5.4)
- *Long-Term Suppression of Growth:* Monitor height and weight in pediatric patients during treatment (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, tachycardia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tris Pharma, Inc. 1-732-940-0358 and www.trispharma.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Acidifying and Alkalinizing Agents:* Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents can decrease amphetamine blood levels, while alkalinizing agents can increase amphetamine blood levels. Adjust DYANAVEL XR dosage accordingly (7.1)

----------USE IN SPECIFIC POPULATIONS---------- •
Pregnancy: May cause fetal harm (8.1)

- *Lactation:* Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 11/2015

FULL PRESCRIBING INFORMATION CONTENTS*

WARNING: ABUSE AND DEPENDENCE
1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
2.1 Important Information Prior to Initiating Treatment
2.2 General Dosing Information
2.3 Switching from other Amphetamine Products
2.4 Dosage Modifications due to Drug Interactions
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
5.1 Potential for Abuse and Dependence
5.2 Serious Cardiovascular Reactions
5.3 Blood Pressure and Heart Rate Increases
5.4 Psychiatric Adverse Reactions
5.5 Long-Term Suppression of Growth
5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
6. ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7. DRUG INTERACTIONS
7.1 Drugs having clinically important interactions with Amphetamines
7.2 Drug Laboratory Test Interactions
8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
9. DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14. CLINICAL STUDIES
16. HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy [see *Warnings and Precautions (5.1, 9.3)*, and *Drug Abuse and Dependence (9.2, 9.3)*].

1. INDICATIONS AND USAGE

DYANAVEL XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [see *Clinical Studies (14)*].

2. DOSAGE AND ADMINISTRATION

2.1 Important Information Prior to Initiating Treatment

Prior to treating children, adolescents, and adults with CNS stimulants, including DYANAVEL XR, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) [see *Warnings and Precautions (5.2)*].

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for DYANAVEL XR use [see *Precautions (5.1),* and *Drug Abuse and Dependence (9)*].

2.2 General Dosing Information

DYANAVEL XR should be orally administered once daily in the morning with or without food. The dose should be individualized according to the needs and responses of the patient. Before administering the dose, shake the bottle of DYANAVEL XR.

In children 6 years of age and older, start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days up to a maximum dose of 20 mg per day.

Pharmacological treatment of ADHD may be needed for extended periods. Healthcare providers should periodically re-evaluate the long-term use of DYANAVEL XR, and adjust dosage as needed.

2.3 Switching from other Amphetamine Products

If switching from other amphetamine products, discontinue that treatment, and titrate with DYANAVEL XR using the above titration schedule.

Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine base compositions and differing pharmacokinetic profiles [see *Description (11), Clinical Pharmacology (12.3)*].

2.4 Dosage Modifications due to Drug Interactions

Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust DYANAVEL XR dosage accordingly [see *Drug Interactions (7.1)*].

3. DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension contains 2.5 mg amphetamine base per mL.

4. CONTRAINDICATIONS

DYANAVEL XR is contraindicated:

- In patients known to be hypersensitive to amphetamine, or other components of DYANAVEL XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products [see *Adverse Reactions (6)*].
- During treatment with MAOIs, and also within 14 days of following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis [see *Drug Interactions (7)*].

5. WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see *Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)*].

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during DYANAVEL XR treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Illness

CNS stimulants may induce a mixed or manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in patients without prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing DYANAVEL XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

5.5 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including DYANAVEL XR.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including DYANAVEL XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy,

including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Drug Dependence [see *Boxed Warning, Warnings and Precautions (5.1),* and *Drug Abuse and Dependence (9.2, 9.3)*]
- Hypersensitivity to amphetamine, or other components of DYANAVEL XR [see *Contraindications(4)*]
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors [see *Contraindications (4)* and *Drug Interactions (7.1)*]
- Serious Cardiovascular Reactions [see *Warnings and Precautions (5.2)*]
- Blood Pressure and Heart Rate Increases [see *Warnings and Precautions (5.3)*]
- Psychiatric Adverse Reactions [see *Warnings and Precautions (5.4)*]
- Long-Term Suppression of Growth [see *Warnings and Precautions (5.5)*]
- Peripheral Vasculopathy, including Raynaud's phenomenon [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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.

Clinical Trials Experience with Other Amphetamine Products in Pediatric Patients and Adults with ADHD

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, tics, aggression, anger, logorrhea.

Eye Disorders: Vision blurred, mydriasis.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

Skin: Alopecia.

Clinical Trials Experience with DYANAVEL XR *in Pediatric Patients with ADHD*

There is limited experience with DYANAVEL XR in controlled trials. Based on this limited experience, the adverse reaction profile of DYANAVEL XR appears similar to other amphetamine extended-release products. The most common (≥2% in the DYANAVEL XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 108 patients with ADHD (aged 6–12 years) were: epistaxis, allergic rhinitis and upper abdominal pain.

Table 1. Common adverse reactions occurring in ≥2% of Subjects on DYANAVEL XR and greater than Placebo during the double blind phase.

Preferred Term	DYANAVEL XR (N=52)	Placebo (N=48)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	3.8%	0%
Rhinitis allergic	3.8%	0%
Gastrointestinal disorders		
Abdominal pain upper	3.8%	2.1%

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of other amphetamine products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Endocrine: frequent or prolonged erections.

Musculoskeletal, Connective Tissue, and Bone Disorders: rhabdomyolysis.

Psychiatric Disorders: dermatillomania.

7. DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 2. Drugs having clinically important interactions with amphetamines.

MAO Inhibitors (MAOI)	
Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer DYANAVEL XR during or within 14 days following the administration of MAOI [see *Contraindications (4)*].
Examples	selegiline, isocarboxazid, phenelzine, tranylcypromine
Alkalinizing Agents	
Clinical Impact	Increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of DYANAVEL XR and gastrointestinal alkalinizing agents should be avoided.
Examples	Gastrointestinal alkalinizing agents (e.g., sodium bicarbonate). Urinary alkalinizing agents (e.g. acetazolamide, some thiazides).
Acidifying Agents	
Clinical Impact	Lower blood levels and efficacy of amphetamines.

Intervention	Increase dose based on clinical response.
Examples	Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid). Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts).
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.
Examples	desipramine, protriptyline
Proton Pump Inhibitors	
Clinical Impact	Time to maximum concentration (T_{max}) of amphetamine is increased compared to when administered alone.
Intervention	Monitor patients for changes in clinical effect and adjust therapy based on clinical response.
Example	omeprazole

7.2 Drug/Laboratory Test Interactions

Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited published data on the use of amphetamines in pregnant women. These data are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. No effects on morphological development were observed in embryo-fetal development studies with oral administration of amphetamine to rats and rabbits during organogenesis at doses 1.5 and 8 times, respectively, the maximum recommended human dose (MRHD). However, long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine (*d*- or *d, l*-) [see *Data*]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Amphetamines, such as DYANAVEL XR, may cause vasoconstriction, including vasoconstriction of placental blood vessels, and may increase the risk for intrauterine growth restriction. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Data

Animal Data

Amphetamine had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the MRHD of 20 mg/day (as base), on a mg/m^2 body surface area basis for an adolescent. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times the MRHD) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d, l*-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.2 Lactation

Risk Summary

Based on limited case reports in published literature, amphetamine (*d*- or *d, l*-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with DYANAVEL XR.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients with ADHD ages 6-17 years [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12)*, and *Clinical Studies (14)*]. Safety and efficacy in pediatric patients younger than 6 years with ADHD have not been established.

Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including DYANAVEL XR, and children who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions (5.5)*].

8.5 Geriatric Use

DYANAVEL XR has not been studied in the geriatric population.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DYANAVEL XR contains amphetamine, which is a Schedule II controlled substance in the U.S. Controlled Substance Act (CSA).

9.2 Abuse

DYANAVEL XR, is a CNS stimulant that contains amphetamine which has a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of amphetamine abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of amphetamines may use

other unapproved routes of administration which can result in overdose and death [see *Overdosage (10)*].

To reduce the abuse of DYANAVEL XR, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for DYANAVEL XR use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) may occur during the chronic therapy of CNS stimulants including DYANAVEL XR.

Dependence

Physical dependence (which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including DYANAVEL XR. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10. OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

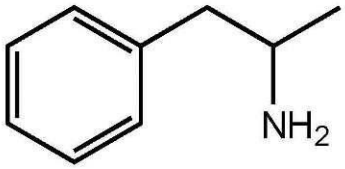
Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

11. DESCRIPTION

DYANAVEL XR (amphetamine) extended release oral suspension, a CNS stimulant, is an extendedrelease liquid formulation containing a 3.2 to1 ratio of d- to l-amphetamine.

Each 1 mL of DYANAVEL XR contains 2.5 mg of amphetamine which is the same as the amount of amphetamine (base equivalent) found in a 4 mg strength amphetamine mixed salts product.

Structural Formula:



$C_9H_{13}N$ MW 135.21

DYANAVEL XR utilizes an ion exchange resin where the drug is bound to the resin (sodium polystyrene sulfonate) through an ionic binding reaction. DYANAVEL XR contains immediate release and extendedrelease components. The extended-release component is coated with an aqueous, pH-independent polymer. After drug release the ion-exchange resin is excreted in the feces.

Inactive Ingredients: anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified food starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

Absorption

Following a single, 18.8 mg oral dose of DYANAVEL XR in 29 healthy adult subjects in a crossover study under fasting conditions, d-amphetamine and l-amphetamine, the median (range) time to peak plasma concentrations (T_{max}) were 4.0 (2 – 7) hours after dosing and peak concentration (C_{max}) were 102% and 106%, respectively of the C_{max} of immediate-release (IR) mixed amphetamine salts tablets. The relative bioavailability of DYANAVEL XR compared to an equal dose of mixed amphetamine salts IR tablets is 106% of d-amphetamine and 111% for l-amphetamine.

Metabolism and Excretion

DYANAVEL XR contains d-amphetamine and l-amphetamine in a ratio of 3.2 to 1. Following a single 18.8 mg oral dose of DYANAVEL XR in 29 healthy adult subjects under fasting conditions, the mean (± SD) plasma terminal elimination half-life of d-amphetamine was 12.36 (± 2.95 h) hours and the mean (± SD) plasma terminal half-life for l-amphetamine was 15.12 (± 4.40 h) hours. Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain A or B carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxyamphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alphahydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30% to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunctions have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that affect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic

polymorphisms is more likely to be clinically significant when renal elimination is decreased [see *Drug Interactions (7.1)*].

Food Effect

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of DYANAVEL XR at a dose of 18.8 mg, the presence of food delayed the time to peak concentration of both d- and l-amphetamine by approximately 1 hour (fed: median [range] 5 [3 – 8] hours vs. fasted: 4 [2 – 7] hours). Overall, a high-fat meal increased the average C_{max} of both isomers of DYANAVEL XR by about 2% and decreased the AUC by 5-7% (5.7% decrease for d-amphetamine and 7.4% for l-amphetamine). These changes are not considered clinically significant.

Specific Populations

Pediatric

Following a single 10 mg oral dose of DYANAVEL XR in 12 pediatric subjects with ADHD (aged 6-12 years) under fasting conditions, d-amphetamine and l-amphetamine peak plasma concentrations occurred at a median time of 3.9 and 4.5 hours after dosing, respectively. The mean plasma terminal elimination half-life of d-amphetamine was 10.43 (± 2.01 h) hours and the mean plasma terminal half-life for l-amphetamine was 12.14 (± 3.15 h) hours.

Alcohol Effect

There is no *in vivo* study conducted for the effect of alcohol on drug exposure. An *in vitro* dissolution study showed alcohol-induced dose dumping potential in the presence of 40% alcohol. Dose dumping was not observed in the presence of lower alcohol concentrations.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was found in studies in which d, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 20 mg/day (as base) on a mg/m^2 body surface area basis for a child.

Mutagenesis

Amphetamine, in the enantiomer ratio present in DYANAVEL XR (*d- to l-* ratio of 3.2 to 1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test *in vitro*. d, l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility

Amphetamine, in the enantiomer ratio present in DYANAVEL XR (*d- to l-* ratio of approximately 3.2 to 1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately 5 times the maximum recommended human dose of 20 mg/day (as base) on a mg/m^2 body surface area basis for an adolescent].

13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (*d-* or *d, l-*) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

14. CLINICAL STUDIES

The efficacy of DYANAVEL XR was evaluated in a laboratory classroom study conducted in 108 pediatric patients (aged 6 to 12 years) with ADHD. The study began with an open-label dose optimization period (5 weeks) with an initial DYANAVEL XR dose of 2.5 or 5 mg once daily in the morning. The dose could be titrated weekly in increments of 2.5 to 10 mg until an optimal dose or the maximum dose of 20 mg/day was reached. Subjects then entered a 1-week randomized, double-blind treatment with the individually optimized dose of DYANAVEL XR or placebo. At the end of the week, school teachers and raters evaluated the attention and behavior of the subjects in a laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. SKAMP is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. Each item is rated on a 7-point impairment scale.

The primary efficacy endpoint was change from pre-dose in the SKAMP-Combined score at 4 hours postdosing. The key secondary efficacy parameters were onset and duration of clinical effect. The change scores from pre-dose SKAMP-Combined scores at post-dose time points (1, 2, 4, 6, 8, 10, 12 and 13 hours) were used to evaluate the key secondary efficacy. Results from the double-blind, placebocontrolled week of the study are summarized in Table 3 and Figure 1.

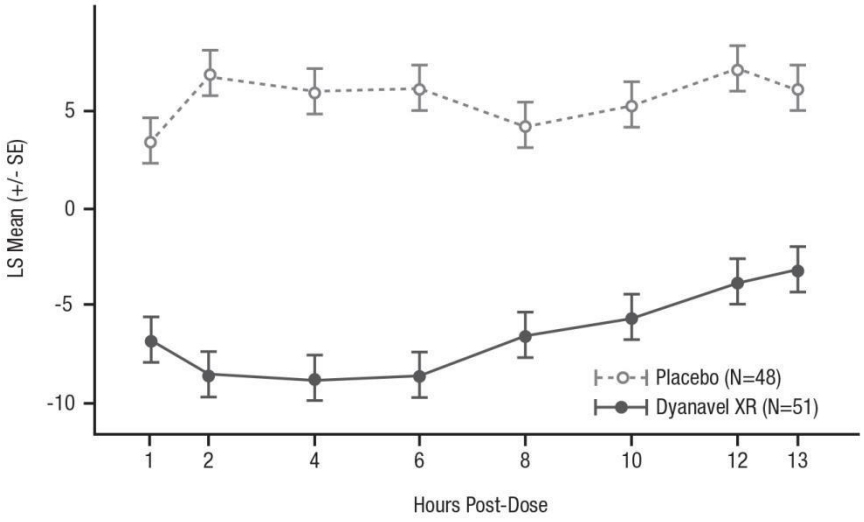
SKAMP-Combined change scores from pre-dose demonstrated a statistically significant improvement at all time points (1, 2, 4, 6, 8, 10, 12, 13 hours) post-dosing with DYANAVEL XR compared to placebo.

Table 3: Primary efficacy result.

Study Number Group	Treatment	Primary Efficacy Measure: SKAMP-Combined Score		
		Mean Pre-dose Score (SD) (SE)	LS Mean Change from Pre-Dose at 4 Hours Post-Dosing	Placebo-subtracted Difference [a] (95%)
Study 1	DYANAVEL XR	17.3 (8.88)	-8.8 (1.14)	-14.8 (-17.9, -11.6)
	Placebo	15.5 (7.35)	6.0 (1.19)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from pre-dose.

Figure 1. Change from pre-dose in SKAMP-Combined Score after treatment with DYANAVEL XR or Placebo.



16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DYANAVEL XR (amphetamine) extended-release oral suspension, the concentration is 2.5 mg/mL amphetamine base and is supplied as light beige to tan viscous suspension with bubblegum flavor in bottles of 464 mL (NDC 27808-102-01).

16.2 Storage and Handling

Dispense in a tight container with child-resistant closure.

Store at 20° to 25°C (68° to 77°F); excursions permitted from 15º to 30ºC (59º to 86ºF) [see USP Controlled Room Temperature].

The pharmacist should provide an oral dosing syringe or other suitable measuring device.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired DYANAVEL XR at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix DYANAVEL XR with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard DYANAVEL XR in the household trash.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/Potential for Abuse, Misuse, and Dependence

Advise patients that DYANAVEL XR is a federally controlled substance because it can be abused or lead to dependence. Advise patients to store DYANAVEL XR in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired DYANAVEL XR by a medicine take-back program if available [see *Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9)*].

Dosage and Administration Instructions

Provide the following instructions on administration to the patient:

- Use with an oral dosing device or other suitable measuring device.
- Shake the bottle of DYANAVEL XR before each dose.
- Measure the appropriate dose as prescribed by the physician.
- Using the filled oral dosing syringe or measuring device, dispense DYANAVEL XR directly into mouth.
- Replace bottle cap and store bottle as directed.
- Wash oral dosing syringe or measuring device after each use.

Serious Cardiovascular Risks

Advise patients of serious cardiovascular risk (including sudden death, myocardial infarction, stroke, and hypertension) with DYANAVEL XR. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [see *Warnings and Precautions (5.2)*].

Blood Pressure and Heart Rate Increases

Instruct patients that DYANAVEL XR can cause elevations of their blood pressure and pulse rate [see *Warnings and Precautions (5.3)*].

Psychiatric Risks

Advise patients that DYANAVEL XR, at recommended doses, may cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania [see *Warnings and Precautions (5.4)*].

Long-Term Suppression of Growth

Advise patients that DYANAVEL XR may cause slowing of growth and weight loss [see *Warnings and Precautions (5.5)*].

Circulation Problems in Fingers and Toes [Peripheral vasculopathy, including Raynaud's phenomenon]

Instruct patients beginning treatment with DYANAVEL XR about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red.

Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.

Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking DYANAVEL XR.

Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients [see *Warnings and Precautions (5.6)*].

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with DYANAVEL XR. Advise patients of the potential fetal effects from the use of DYANAVEL XR during pregnancy [see *Use in Specific Populations (8.1)*].

Lactation

Patients should be advised not to breastfeed if they are taking DYANAVEL XR [see *Use in Specific Populations (8.2)*].

Alcohol

Advise patients to avoid alcohol while taking DYANAVEL XR. Consumption of alcohol while taking DYANAVEL XR may result in a more rapid release of the dose of amphetamine [see *Clinical Pharmacology (12.3)*].

What are possible side effects of DYANAVEL XR?
DYANAVEL XR can cause serious side effects, including:

- See "**What is the most important information I should know about DYANAVEL XR?**" for information on reported heart and mental problems.
- slowing of growth (height and weight) in children

Common side effects of amphetamine products include:

- dry mouth
- decreased appetite
- weight loss
- stomach pain
- nausea
- trouble sleeping
- restlessness
- extreme mood changes
- dizziness
- increased heart rate

Talk to your doctor if you or your child have any side effects that bother you or do not go away. These are not all the possible side effects of DYANAVEL XR. Ask your doctor or pharmacist for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DYANAVEL XR?

- Store DYANAVEL XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Store DYANAVEL XR in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired DYANAVEL XR by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix DYANAVEL XR with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away DYANAVEL XR in the household trash.

Keep DYANAVEL XR and all medicines out of the reach of children.

General information about the safe and effective use of DYANAVEL XR

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use DYANAVEL XR for a condition for which it has not been prescribed. Do not give DYANAVEL XR to other people, even if they have the same condition. It may harm them and it is against the law.
This Medication Guide summarizes the most important information about DYANAVEL XR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DYANAVEL XR that was written for healthcare professionals.
For more information about DYANAVEL XR please contact Tris Pharma at 1-732-940-0358 or www.trispharma.com.

What are the ingredients in DYANAVEL XR?
Active Ingredient: amphetamine.
Inactive Ingredients: anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified food starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum.

Manufactured by:
Tris Pharma, Inc.
Monmouth Junction, NJ 08852
www.trispharma.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. LB8417 Rev. 02 11/15