

March 14, 2016

David Campana, R.Ph.
1400 Broadway
Room A206
Helena, MT 59620

Dear Mr. Campana:

Your AstraZeneca representative, Bradley Haas, has forwarded your request for information regarding TUDORZA® PRESSAIR® (aclidinium bromide inhalation powder). The following information is being provided, as a professional courtesy, in response to your request:

Montana Medicaid_TUDORZA PRESSAIR Clinical Executive Summary (Standard)

These materials may include information that is not found in the currently approved prescribing information for TUDORZA® PRESSAIR® (aclidinium bromide inhalation powder). The enclosed information is intended to provide pertinent data in response to your request and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for TUDORZA® PRESSAIR® (aclidinium bromide inhalation powder). Please consult the Warnings and Precautions section of the prescribing information for further details and other important safety information. Prescription drugs used in a manner other than their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. Prescribing information for TUDORZA® PRESSAIR® (aclidinium bromide inhalation powder) may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933.

Any attached publications and/or any tables or figures derived from the publications for use in the attached response are copyright protected works. AstraZeneca has obtained permission from the copyright owner to use this work in this response. You may not reproduce, prepare derivative works from, display or distribute this work unless you obtain the permission of the copyright owner, or as otherwise might be permitted by law.

Adverse Event Reporting

In order to monitor the safety of TUDORZA® PRESSAIR® (aclidinium bromide inhalation powder), we encourage clinicians to report suspected adverse events to AstraZeneca at 1-800-236-9933.

Tel 877 893 1510
Fax 302 885 1400
www.astrazeneca-us.com

Medical Resources FOC/CE1 706, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437

Thank you for your interest in TUDORZA® PRESSAIR® (aclidinium bromide inhalation powder). If we may be of further assistance to you, please contact AstraZeneca at 1-877-893-1510.

Sincerely,

Danielle Zielinski, PharmD
Senior Medical Information Manager

INQ 01017816

Overview of TUDORZA PRESSAIR

- AstraZeneca has recently acquired the development and commercial rights from Actavis for TUDORZA PRESSAIR in the US.¹
- TUDORZA PRESSAIR is a breath-actuated multi-dose dry powder inhaler with a dose indicator and a colored control window to confirm correct inhalation. TUDORZA PRESSAIR is available in 60 or 30 metered doses.²
- TUDORZA PRESSAIR contains aclidinium bromide, which is a long-acting muscarinic antagonist (LAMA), often referred to as an anticholinergic.²

Indications and Usage ²	Dosage ²
TUDORZA PRESSAIR is an anticholinergic indicated for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	400 mcg x 1 inhalation BID

Overview of COPD in the United States and Unmet Medical Need

- COPD, which is estimated to affect approximately 26 million Americans, is the third leading cause of death in the US.³⁻⁵
- In 2010, COPD claimed the lives of more than 134,000 Americans.⁶
- Bronchodilator therapy is central to the management of COPD symptoms.⁷

Mechanism of Action

- Aclidinium bromide, the active ingredient in TUDORZA PRESSAIR, has similar affinity to the subtypes of muscarinic receptors M₁ to M₅. In the airways, it exhibits pharmacological effects through the inhibition of acetylcholine on M₃ receptors at the smooth muscle leading to bronchodilation.²
- The bronchodilation following inhalation of TUDORZA PRESSAIR is predominantly a site-specific effect.²

Place in COPD Therapy

- The 2015 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines recommend a long-acting anticholinergic as a first-choice treatment option for patients with COPD in Patient Groups* B-D based on an assessment of symptoms, including breathlessness, spirometric classification, and risk of COPD exacerbations. A long-acting anticholinergic is also recognized as an alternative treatment option when used alone for Patient Group* A and when used in combination with other COPD treatments for Patient Groups* B-D.⁷

Clinical Data

The TUDORZA PRESSAIR clinical development program included a dose-ranging trial for nominal dose selection and 3 confirmatory trials.²

Dose-ranging Trial:

- The dose-ranging trial was a randomized, double-blind, placebo- and active-controlled, crossover trial with 7-day treatment periods separated by 5-day washout periods.²
- The trial enrolled 79 patients aged ≥ 40 years with COPD, a history of smoking ≥ 10 pack-years, a forced expiratory volume in 1 second (FEV₁) of $\geq 30\%$ and $< 80\%$ predicted normal value, and a FEV₁/forced vital capacity (FVC) < 0.7 .²
- The effect on trough and serial FEV₁ in patients treated with TUDORZA PRESSAIR 100 mcg and 200 mcg BID was lower compared to patients treated with TUDORZA PRESSAIR 400 mcg BID.²

Three Confirmatory Trials:

- The confirmatory trials consisted of two 3-month (ACCORD I⁸ and ACCORD II⁹) and one 6-month (ATTAIN¹⁰) randomized, double-blind, placebo-controlled trials.²
- These trials enrolled 1,276 patients (n=636 patients treated with TUDORZA PRESSAIR 400 mcg BID; n=640 patients treated with placebo) aged ≥ 40 years with COPD, a history of smoking ≥ 10 pack-years, a FEV₁ of $\geq 30\%$ and $< 80\%$ predicted normal value, and a FEV₁/FVC < 0.7 .²
- TUDORZA PRESSAIR 400 mcg BID demonstrated statistically significant improvement in predose FEV₁ (0.07 – 0.12 L increase from baseline) compared to placebo at 12 weeks.² Specific results are provide in the following table:²

*GOLD Guidelines: Patient Group A – Low risk of COPD exacerbations, less COPD symptoms, typically mild or moderate airflow limitation; Patient Group B – Low risk of COPD Exacerbations, more COPD symptoms, typically mild or moderate airflow limitation; Patient Group C – High risk of COPD Exacerbations, less COPD symptoms, typically severe or very severe airflow limitation; Patient Group D – High risk of COPD Exacerbations, more COPD symptoms, typically severe or very severe airflow limitation

TABLE: Primary Efficacy Endpoint: Change from Baseline in Predose FEV₁ (L) at Week 12

Treatment Arm	Baseline	LS Mean (SE) Change from Baseline	LS Mean (95% CI) Treatment Difference
Trial B (n=375)			
TUDORZA PRESSAIR 400 mcg	1.33	0.10 (0.01)	0.12 (0.08, 0.16)
Placebo	1.38	-0.02 (0.02)	
Trial C (n=359)			
TUDORZA PRESSAIR 400 mcg	1.25	0.06 (0.02)	0.07 (0.03, 0.12)
Placebo	1.46	-0.01 (0.02)	
Trial D* (n=542)			
TUDORZA PRESSAIR 400 mcg	1.51	0.06 (0.02)	0.11 (0.07, 0.14)
Placebo	1.50	-0.05 (0.02)	

LS=Least Square Mean; SE=Standard Error; *In the 6-month trial, placebo-adjusted change from baseline in trough FEV₁ at 24 weeks was 0.13 (0.09, 0.17).

- Serial spirometric evaluations were performed in a subset of patients. Improvement in lung function with TUDORZA PRESSAIR 400 mcg BID was maintained for 12 hours after a single dose and was consistent over 12 or 24 weeks.²
- Mean peak improvements in FEV₁ for TUDORZA PRESSAIR 400 mcg BID were assessed in patients after the first dose on day 1 and were similar at week 12.²
- In 2 of the 3 trials, patients treated with TUDORZA PRESSAIR 400 mcg BID used less daily rescue albuterol compared to those treated with placebo.²

Drug Interactions

- Formal drug interaction studies were not performed with TUDORZA PRESSAIR.²
- Acclidinium bromide, the active ingredient in TUDORZA PRESSAIR, is rapidly and extensively hydrolyzed into inactive metabolites. Due to low drug plasma levels at the clinically relevant doses, it is unlikely that acclidinium bromide causes CYP450-related drug interactions.²
- In clinical trials, there were no increases in adverse drug reactions during concomitant administration of TUDORZA PRESSAIR and other drugs commonly used in the treatment of COPD including sympathomimetics (short-acting beta₂-agonists), methylxanthines, and oral and inhaled corticosteroids.²
- Since there is a potential for an additive interaction with concomitantly used anticholinergic medications, avoid coadministration of TUDORZA PRESSAIR with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic effects.²

Safety

- In pooled data from 3 trials, the most common adverse reactions (incidence of ≥ 3% and greater than placebo) include headache (6.6% vs. 5.0%), nasopharyngitis (5.5% vs. 3.9%), and cough (3.0% vs. 2.2%), for TUDORZA PRESSAIR vs. placebo, respectively; dry mouth was observed with an incidence of < 1%.²
- TUDORZA PRESSAIR was studied in 3 long-term safety trials, 2 double-blind and one open-label, ranging from 40 to 52 weeks in patients with moderate-to-severe COPD. In these trials, 891 patients were treated with TUDORZA PRESSAIR 400 mcg BID. The adverse events reported in the long-term safety trials were similar to those occurring in the placebo-controlled trials of 3 to 6 months. No new safety findings were reported compared to the placebo-controlled trials.²
- Please refer to the TUDORZA PRESSAIR Prescribing Information for complete product information including Warnings and Precautions.²

References:

1. AstraZeneca Pharmaceuticals LP. AstraZeneca completes acquisition of rights to Actavis' branded respiratory portfolio in the US and Canada [press release]. <http://www.astrazeneca.com/Media/Press-releases/Article/20150303--astrazeneca-completes-acquisition>. Accessed July 21, 2015.
2. TUDORZA PRESSAIR Prescribing Information.
3. National Heart, Lung, and Blood Institute (NHLBI). Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. Available at: http://www.nhlbi.nih.gov/files/docs/research/2012_ChartBook_508.pdf. Accessed July 21, 2015.
4. Kochanek KD, Murphy SL, Xu J, et al. Mortality in the United States, 2013. National Center for Health Statistics Data Brief. 2014;178. Available at: <http://www.cdc.gov/nchs/data/databriefs/db178.pdf>. Accessed July 21, 2015.
5. National Vital Statistics Report. Deaths: final data for 2013. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf. Accessed July 21, 2015.
6. American Lung Association. Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet. May 2014. Available at: <http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html>. Accessed July 21, 2015.
7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2015 Update. Available at: <http://www.goldcopd.org/>. Accessed July 21, 2015.
8. Kerwin EM, D'Urzo AD, Gelb AF, et al. Efficacy and safety of a 12-week treatment with twice-daily acclidinium bromide in COPD patients (ACCORD COPD I). *COPD*. 2012;9:90-101.
9. Rennard SI, Scanlon PD, Ferguson GT, et al. ACCORD COPD II: a randomized clinical trial to evaluate the 12-week efficacy and safety of twice-daily acclidinium bromide in chronic obstructive pulmonary disease patients. *Clin Drug Investig*. 2013;33:893-904.
10. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily acclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J*. 2012;40:830-836.