RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Breztri Aerosphere™
Generic Name	glycopyrrolate and formoterol fumarate
Drug Manufacturer	AstraZeneca Pharmaceuticals LP

New Drug Approval

FDA Approval Date: 07/23/2020

Review Designation: Standard

Review Type: New Drug Application (212122)

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Chronic obstructive pulmonary disease, or COPD, refers to a group of diseases that cause airflow blockage and breathing-related problems. It includes emphysema and chronic bronchitis. COPD is a progressive disease, meaning it typically worsens over time Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by chronic airway inflammation, a decline in lung function over time, and progressive impairment in quality of life. The disease has relatively high prevalence rates worldwide (5–13%) and is mainly caused not only by the inhalation of noxious substances, predominantly cigarette smoking in the Western world, but also by indoor air pollution, particularly in the developing countries.

COPD continues to cause a heavy health and economic burden both in the United States and around the world. Some of the risk factors for COPD are well-known and include smoking, occupational exposures, air pollution, airway hyperresponsiveness, asthma, and certain genetic variations, although many questions, such as why < 20% of smokers develop significant airway obstruction, remain. Precise definitions of COPD vary and are frequently dependent on an accurate diagnosis of the problem by a physician. These differences in the definition of COPD can have large effects on the estimates of COPD in the population. Furthermore, evidence that COPD represents several different disease processes with potentially different interventions continues to emerge. In most of the world, COPD prevalence and mortality are still increasing and likely will continue to rise in response to increases in smoking, particularly by women and adolescents. Resources aimed at smoking cessation and prevention, COPD education and early detection, and better treatment will be of the most benefit in our continuing efforts against this important cause of morbidity and mortality.

Efficacy

The safety and efficacy of BEVESPI AEROSPHERE was evaluated in a clinical development program that included 8 dose-ranging trials and two placebo-controlled lung function trials of 24-weeks duration that included a 28-week extension study to evaluate safety over 1 year. The efficacy of BEVESPI AEROSPHERE is based on the dose ranging trials in 822 subjects with COPD and the 2 placebo-controlled confirmatory trials in 3,705 subjects with COPD.

Glycopyrrolate Dose selection for glycopyrrolate was supported by a 14-day, randomized, double-blind, placebo-controlled, incomplete-block crossover trial evaluating 6 doses of glycopyrrolate (GP MDI 18 to 0.6 mcg) administered twice daily and an open-label active control in 140 subjects with COPD.

The difference from placebo in change from baseline in trough FEV1 after 14 days for the 18, 9, 4.6, 2.4, 1.2, and 0.6 mcg doses were 97 mL (95% CI: 45, 149), 88 mL (95% CI: 37, 139), 75 mL (95% CI: 24, 125), 84 mL (95% CI: 33,

135), 76 mL (95% CI: 22, 129), and 37 mL (95% CI: -17, 91), respectively. Two additional dose ranging trials (single-dose and 7-day trials) in subjects with COPD demonstrated minimal additional benefit at doses above 18 mcg of glycopyrrolate. The results supported the selection of 18 mcg of glycopyrrolate twice daily in the confirmatory COPD trials.

Evaluations of the appropriate dosing interval for glycopyrrolate were conducted by comparing to open-label ipratropium bromide inhalation aerosol administered four times daily. The results supported the selection of a twice-daily dosing interval for further evaluation in the confirmatory COPD trials.

Formoterol Fumarate Dose selection for formoterol fumarate was supported by a single-dose, randomized, doubleblind, placebo-controlled, crossover trial evaluating 3 doses of formoterol fumarate (FF MDI 9.6, 4.8 and 2.4 mcg), an open-label active control, and placebo in 34 subjects with COPD. A dose ordering was observed with the formoterol fumarate 9.6 mcg dose demonstrating larger improvements in FEV1 over 12 hours compared with the lower doses of 4.8 and 2.4 mcg, These results provided support for the selection of 9.6 mcg of formoterol fumarate twice daily in the confirmatory COPD trials.

Confirmatory Trials The clinical development program for BEVESPI AEROSPHERE included two (Trial 1 and Trial 2) 24-week, randomized, double-blind, placebo-controlled, parallel-group trials in subjects with moderate to very severe COPD designed to evaluate the efficacy of BEVESPI AEROSPHERE on lung function. The 24-week trials included 3,699 subjects that had a clinical diagnosis of COPD, were between 40 and 80 years of age, had a history of smoking greater than or equal to 10 pack-years, had a post-albuterol FEV1 less than 80% of predicted normal values, and had a ratio of FEV1/FVC of less than 0.7. The majority of patients were male (56%) and Caucasian (91%) with a mean age of 63 years and an average smoking history of 51 pack-years (54% current smokers). During screening, mean post-bronchodilator percent predicted FEV1 was 51% (range: 19% to 82%) and mean percent reversibility was 20% (range: -32% to 135%).

Trial 1 and Trial 2 evaluated BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate) 18 mcg/9.6 mcg, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, and placebo administered twice daily (BID). Trial 1 also included an open-label active control. The comparison of BEVESPI AEROSPHERE with glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg was assessed to evaluate the contribution of the individual components to BEVESPI AEROSPHERE. In both trials, BEVESPI AEROSPHERE demonstrated a larger increase in mean change from baseline in trough FEV1 at Week 24 relative to placebo, glycopyrrolate 18 mcg, and formoterol fumarate 9.6 mcg.

With the limited data available, there were consistent improvements in trough FEV1 with respect to age, sex, degree of airflow limitation, GOLD stage, smoking status, or inhaled corticosteroid use. In Trials 1 and 2, serial spirometric evaluations were performed throughout the 12-hour dosing interval in a subset of subjects (n=718 and n=585, respectively) at Day 1 and Week 12. In Trial 2, the results for BEVESPI AEROSPHERE in FEV1 AUC0-12h were similar to those observed in Trial 1.

		Trough FEV1 (mL) at Week 24

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Treatment	N	Difference from		
		Placebo* LS Mean (95% CI)	Glycopyrrolate 18 mcg BID* LS Mean (95% CI)	Formoterol Fumarate 9.6 mcg BID* LS Mean (95% CI))
Trail 1				
BEVESPI AEROSPHERE	429	N=161 150 mL (114, 186)	N=344 59 mL (31, 88)	N=367 64 mL (36, 92)
Trail 2				
BEVESPI AEROSPHERE	433	N=170 103 mL (67, 140)	N=367 54 mL (25, 83)	N=350 56 mL (27, 85)

In both trials, peak FEV1 was defined as the maximum FEV1 recorded within 2 hours after the dose of trial medication. The mean peak FEV1 improvement from baseline with BEVESPI AEROSPHERE compared with placebo at Week 24 was 291 mL (95% CI: 252, 331) and 267 mL (95% CI: 226, 308) in Trial 1 and Trial 2, respectively. BEVESPI AEROSPHERE demonstrated an onset of bronchodilatory treatment effect at 5 minutes after the first dose based on a mean increase in FEV1 compared to placebo of 187 mL (95% CI: 168, 205) and 186 mL (95% CI: 164, 207) in Trial 1 and Trial 2, respectively. In both Trial 1 and 2, subjects treated with BEVESPI AEROSPHERE used less daily rescue albuterol compared to subjects treated with placebo.

ADVERSE EVENTS

Adverse reaction (1% to 10%)are :

- Gastrointestinal: Diarrhea (2%), oral candidiasis (3%
- Genitourinary: Urinary tract infection (3%)
- Infection: Influenza (3%)
- Nervous system: Voice disorder (3%)
- Neuromuscular & skeletal: Back pain (3%), muscle spasm (3%)
- Ophthalmic: Cataract (≤1%)
- Respiratory: Cough (3%), pneumonia (2% to 5%), sinusitis (3%), upper respiratory tract infection (6%)
- Frequency not defined: Respiratory: Paradoxical bronchospasm

WARNINGS & PRECAUTIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma controller medication. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

- Hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of this product.
- Do not initiate in acutely deteriorating COPD or to treat acute symptoms.
- Do not use in combination with an additional medicine containing a LABA because of risk of overdose.

- If paradoxical bronchospasm occurs, discontinue BEVESPI AEROSPHERE and institute alternative therapy.
- Use with caution in patients with cardiovascular disorders.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis.
- Be alert to hypokalemia and hyperglycemia.
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a physician immediately if symptoms occur.
- Worsening urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur.

CONTRAINDICATIONS

Hypersensitivity to budesonide, glycopyrrolate, formoterol, or any component of the formulation.

Clinical Pharmacology

MECHANISMS OF ACTION

Budesonide: A corticosteroid that controls the rate of protein synthesis, depresses the migration of polymorphonuclear leukocytes/fibroblasts, and reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.

Formoterol: Relaxes bronchial smooth muscle by selective action on beta-2 receptors with little effect on heart rate; formoterol has a long-acting effect.

Glycopyrrolate: Competitively and reversibly inhibits the action of acetylcholine at muscarinic receptor subtypes 1 to 3 (greater affinity for subtypes 1 and 3) in bronchial smooth muscle thereby causing bronchodilation.

Dose & Administration

ADULTS

Chronic obstructive pulmonary disease: Oral inhalation: Metered-dose inhaler: 2 inhalations (budesonide 160 mcg/glycopyrrolate 9 mcg/formoterol 4.8 mcg) twice daily (maximum dose: 2 inhalations twice daily [budesonide 640 mcg/glycopyrrolate 36 mcg/formoterol 19.2 mcg per day]).

PEDIATRICS

Breztri Aerosphere is not indicated for use in children.

GERIATRICS

No Dose adjustment is required

RENAL IMPAIRMENT

Formal pharmacokinetic studies using BREZTRI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m2) or end-stage renal disease requiring dialysis, BREZTRI AEROSPHERE should only be used if the expected benefit outweighs the

HEPATIC IMPAIRMENT

Formal pharmacokinetic studies using BREZTRI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with severe hepatic disease should be closely monitored.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Inhalation aerosol: Pressurized metered dose inhaler containing a combination of glycopyrrolate (9 mcg) and formoterol fumarate (4.8 mcg) as an inhalation aerosol. Two inhalations equal one dose.