Product Monograph

Including Patient Medication Information

Pr BREZTRI® AEROSPHERE®

budesonide / glycopyrronium / formoterol fumarate dihydrate pressurized inhalation suspension

For Inhalation use

160 mcg budesonide / 7.2 mcg glycopyrronium (as bromide) / 5 mcg formoterol fumarate dihydrate per delivered actuation

and

160 mcg budesonide / 14.4 mcg glycopyrronium (as bromide) / 5 mcg formoterol fumarate dihydrate per delivered actuation

Inhaled Corticosteroid (ICS) and Inhaled Bronchodilators (Long-Acting Muscarinic Antagonist (LAMA) and Long-Acting $Beta_2$-Adrenergic Agonist (LABA)) Combination

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Part 1: Healthcare Professional Information

1. Indications

BREZTRI® AEROSPHERE® (budesonide/glycopyrronium/formoterol fumarate dihydrate pressurized inhalation suspension) is a combination of an inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA), and a long-acting beta$_2$-adrenergic agonist (LABA).

COPD

BREZTRI AEROSPHERE 160/7.2/5 mcg is indicated for the long-term maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) and treat airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, who are not adequately treated by a combination of an ICS/LABA or a combination of a LAMA/LABA.

BREZTRI AEROSPHERE is **not** indicated for the treatment of acute episodes of bronchospasm (see 7 Warnings and Precautions, General).

Asthma

BREZTRI AEROSPHERE 160/14.4/5 mcg is indicated for the maintenance treatment of asthma in adult and adolescent patients 12 years of age and older who are not adequately controlled with a maintenance combination of a medium or high dose ICS and a LABA.

BREZTRI AEROSPHERE is **not** indicated for the treatment of acute episodes of bronchospasm (see 7 Warnings and Precautions, General).

1.1. Pediatrics

COPD

Pediatrics (< 18 years of age): The safety and efficacy of BREZTRI AEROSPHERE 160/7.2/5 mcg in pediatric patients under 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Asthma

Pediatrics (12 to < 18 years): Of the 1179 participants with asthma treated with BREZTRI AEROSPHERE 160/14.4/5 mcg in the two Phase 3 clinical trials, a total of 30 participants (2.5%) were aged 12 to less than 18 years. In general, the efficacy and safety in this age group were consistent with the overall study population. Therefore, Health Canada has authorized an indication for pediatric use in patients 12 years of age and older.

Pediatrics (< 12 years): The safety and efficacy of BREZTRI AEROSPHERE in pediatric patients under 12 years of age have not been established; therefore, Health Canada has not authorized an indication for patients under 12 years of age.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): No dosage adjustment is required in patients 65 years of age and older.

2. Contraindications

BREZTRI AEROSPHERE is contraindicated in patients who are hypersensitive to this drug or to any ingredient(s) in the formulation, including any non-medicinal ingredient(s), or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

COPD and Asthma

As with other inhaled drugs containing beta$_2$-adrenergic agents, BREZTRI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA or LAMA, as an overdose may result.

When beginning treatment with BREZTRI AEROSPHERE, patients who have been taking rapid onset, short duration, inhaled beta$_2$-agonists on a regular basis should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute respiratory symptoms while taking BREZTRI AEROSPHERE.

BREZTRI AEROSPHERE should not be used to treat acute symptoms of COPD or asthma. Patients should be prescribed a rapid onset, short duration inhaled bronchodilator to relieve the acute symptoms such as shortness of breath and advised to have this available for use at all times.

Patients should be made aware that for optimum benefit, BREZTRI AEROSPHERE must be used regularly, even when asymptomatic.

COPD

Counselling by healthcare professionals on smoking cessation should be the first step in treating patients with COPD who smoke, independent of the clinical presentation i.e., chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

4.2. Recommended Dose and Dosage Adjustment

COPD

Adults

The recommended and maximum dose is 2 inhalations in the morning and 2 inhalations in the evening of BREZTRI AEROSPHERE 160/7.2/5 mcg.

Asthma

Adults and adolescents 12 years and older

The recommended and maximum dose is 2 inhalations in the morning and 2 inhalations in the evening of BREZTRI AEROSPHERE 160/14.4/5 mcg.

Pediatrics (< 18 years of age): BREZTRI AEROSPHERE should not be used in patients under 18 years of age for treatment of COPD and in patients under 12 years of age for treatment of asthma. No dosage adjustment is necessary for pediatric patients 12 to less than 18 years of age for the treatment of asthma.

Geriatrics (≥ 65 years of age): No dosage adjustment is required in patients 65 years of age and older.

Renal Impairment: No dosage adjustment is necessary for patients with renal impairment. However, because glycopyrronium is primarily eliminated via renal metabolism, for patients with severe renal impairment (creatine clearance of ≤30 mL/min) or end-stage renal disease requiring dialysis, BREZTRI AEROSPHERE should only be used if the expected benefit outweighs the potential risk and patients should be closely monitored.

Hepatic Impairment: No dosage adjustment is necessary for patients with hepatic impairment. However because both budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment, and patients with hepatic disease should be closely monitored.

4.4. Administration

BREZTRI AEROSPHERE is for oral inhalation only.

BREZTRI AEROSPHERE should be administered as 2 inhalations, twice daily, in the morning and in the evening.

To ensure proper administration of BREZTRI AEROSPHERE patients should be instructed how to administer the product correctly and advised to read the instructions for use carefully (see Instructions For Use).

To assist patients with proper use of BREZTRI AEROSPHERE, an instructional video is available at:



www.breztri.ca/video

Patients who find it difficult to coordinate actuation with inhalation may use BREZTRI AEROSPHERE with a spacer to ensure proper administration of the product.

4.5. Missed Dose

If a dose is missed, it should be taken as soon as possible, and the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

5. Overdose

There is limited evidence on the management of overdose with BREZTRI AEROSPHERE. An overdose of BREZTRI AEROSPHERE may lead to exaggerated anticholinergic and/or β_2-adrenergic signs and symptoms; the most frequent of which include blurred vision, dry mouth, nausea, muscle spasm, tremor, headache, palpitations and systolic hypertension. Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects may appear.

BREZTRI AEROSPHERE should be discontinued in case of overdose. Supportive and symptomatic treatment should be initiated. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring including electrocardiogram monitoring is recommended in cases of overdosage.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Inhalation use	Pressurized inhalation suspension 160 mcg budesonide / 7.2 glycopyrronium (as bromide) / 5 mcg formoterol fumarate dihydrate per delivered actuation 160 mcg budesonide / 14.4 mcg glycopyrronium (as bromide) / 5 mcg formoterol fumarate dihydrate per delivered actuation	Hydrofluoroalkane (HFA-134a) Porous particles (1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); Calcium chloride).

BREZTRI AEROSPHERE is a pressurized inhalation suspension in a metered dose inhaler, comprising a coated aluminum canister, sealed with a metering valve, desiccated flow path (comprising a collar, seal and desiccant puck), a yellow plastic actuator and white mouthpiece with an attached grey plastic dust cap, and a shield-style dose indicator. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed into a carton.

BREZTRI AEROSPHERE 160/7.2/5 mcg: Each delivered dose per actuation (the dose that leaves the mouthpiece) contains budesonide 160 micrograms, glycopyrronium bromide 9 micrograms, equivalent to 7.2 micrograms of glycopyrronium, and formoterol fumarate dihydrate 5 micrograms, equivalent to 4.8 micrograms of formoterol fumarate. The metered dose per actuation contains budesonide 170 micrograms, glycopyrronium bromide 9.6 micrograms, equivalent to 7.7 micrograms of glycopyrronium, and formoterol fumarate dihydrate 5.3 micrograms, equivalent to 5.1 micrograms of formoterol fumarate.

BREZTRI AEROSPHERE 160/14.4/5 mcg: Each delivered dose per actuation (the dose that leaves the mouthpiece) contains budesonide 160 micrograms, glycopyrronium bromide 18 micrograms, equivalent to 14.4 micrograms of glycopyrronium, and formoterol fumarate dihydrate 5 micrograms, equivalent to 4.8 micrograms of formoterol fumarate. The metered dose per actuation contains budesonide 170 micrograms, glycopyrronium bromide 19.1 micrograms, equivalent to 15.3 micrograms of glycopyrronium, and formoterol fumarate dihydrate 5.3 micrograms, equivalent to 5.1 micrograms of formoterol fumarate.

BREZTRI AEROSPHERE also contains hydrofluoroalkane (HFA-134a) and porous particles (comprised of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride) that form a co-suspension with the drug crystals.

BREZTRI AEROSPHERE is available in a carton containing 1 inhaler with either 56 or 120 actuations.

7. Warnings and Precautions

General

Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of long-acting beta$_2$-agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death (see Salmeterol Multicenter Asthma Research Trial). Available data from controlled clinical trials also suggest that the use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta2-adrenergic Agonist Combination Products).

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonist Combination Products

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol with fluticasone propionate, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol with fluticasone propionate. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

The 3 adult and adolescent trials were designed to rule out a 2.0-fold increase in relative risk for ICS/LABA compared with ICS, and the pediatric trial was designed to rule out a 2.7-fold increase in this relative risk. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 2). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 2 – Meta-analysis of serious asthma-related events in subjects with asthma aged 12 years and older

	ICS/LABA (n=17,537)[a]	ICS (n=17,552)[a]	ICS/LABA vs. ICS Hazard Ratio (95% CI)[b]
Serious asthma-related event[c]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled corticosteroid; LABA = Long-acting beta2-adrenergic agonist.

[a] Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

[b] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

[c] Number of subjects with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects may have had one or more events, but only the first event was counted for analysis. A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

Salmeterol Multicenter Asthma Research Trial

A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in the Salmeterol Multicenter Asthma Research Trial. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Deterioration of disease

BREZTRI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD or asthma which may be a life-threatening condition. The use of BREZTRI AEROSPHERE in this setting has not been studied and is not considered appropriate.

COPD or asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If BREZTRI AEROSPHERE no longer controls symptoms of bronchoconstriction, the patient's inhaled, short-acting bronchodilator becomes less effective or the patient needs more inhalation of a short-acting bronchodilator than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the treatment regimen should be undertaken at once. Consideration should be given to the need for increased therapy such as a course of oral corticosteroids or antibiotic treatment if an infection is present.

Exacerbations may occur during treatment with BREZTRI AEROSPHERE. Patients should be advised to continue treatment and seek medical advice if symptoms remain uncontrolled or worsen after initiation of therapy with BREZTRI AEROSPHERE.

Patients should not stop therapy with BREZTRI AEROSPHERE without physician supervision since symptoms may recur after discontinuation.

Not for acute use

BREZTRI AEROSPHERE should not be used for the relief of acute symptoms of COPD or asthma (i.e., as rescue therapy for the treatment of acute episodes of bronchospasm).

Patients should be prescribed a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve acute symptoms such as shortness of breath and advised to have this available for use at all times.

When beginning treatment with BREZTRI AEROSPHERE, patients who have been taking a rapid onset, short duration, inhaled bronchodilator on a regular basis should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute symptoms while taking BREZTRI AEROSPHERE.

Excessive use and use with other LABA and LAMA products

BREZTRI AEROSPHERE should not be used more often or at higher doses than recommended.

BREZTRI AEROSPHERE should not be administered concomitantly with other medicines containing a long-acting beta$_2$-adrenergic agonist (e.g., salmeterol, formoterol fumarate, indacaterol, olodaterol), or a long-acting muscarinic antagonist (e.g., tiotropium, glycopyrronium, aclidinium, umeclidinium) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Anticholinergic activity

Due to its anticholinergic activity, BREZTRI AEROSPHERE should be used with caution in patients with symptomatic prostatic hyperplasia, urinary retention (see Renal) or narrow-angle glaucoma (see Ophthalmologic).

Cardiovascular

Cardiovascular effects, such as cardiac arrhythmias, e.g., atrial fibrillation and tachycardia, may be seen after the administration of sympathomimetic agents and muscarinic receptor antagonists, including BREZTRI AEROSPHERE. In case such effects occur, treatment may need to be discontinued.

Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Cardiovascular effects such as tachycardia, arrhythmia, palpitations, myocardial ischemia, angina pectoris, hypertension or hypotension have been associated with use of beta-adrenergic agonists. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Like all products containing sympathomimetic agents, BREZTRI AEROSPHERE should therefore be used with caution in patients with unstable or life-threatening cardiovascular disease, especially coronary insufficiency, cardiac arrhythmias (including tachyarrhythmias), or hypertension.

Heart rate

Like other beta$_2$-agonists, formoterol fumarate can produce clinically significant cardiovascular effects in some patients as measured by an increase in pulse rate, systolic or diastolic blood pressure or cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREZTRI AEROSPHERE may need to be discontinued.

QT Interval

As with other beta$_2$-agonists, caution is recommended if BREZTRI AEROSPHERE is administered to patients with a known history of QTc prolongation, risk factors for torsade de pointes (e.g., hypokalemia), or patients who are taking medications known to prolong the QTc interval (see Drugs Known to Prolong the QTc Interval and 10 Clinical Pharmacology).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. Based on the pharmacological profile (see 10 Clinical Pharmacology), BREZTRI AEROSPHERE is expected to have no or negligible influence on the ability to drive and use machines. The occurrence of headache or nausea may influence the ability to drive or to use machinery.

Ear/Nose/Throat

BREZTRI AEROSPHERE contains budesonide, an ICS. Therapeutic dosages of budesonide may cause the appearance of *Candida albicans* (thrush) in the mouth and throat. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Symptomatic candidiasis can be treated with topical anti-fungal therapy while continuing to use BREZTRI AEROSPHERE.

Endocrine and Metabolism

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods.

These effects are much less likely to occur with inhaled corticosteroid treatments than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma. Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Long-term studies with inhaled budesonide in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density (see Reduction in Bone Mineral Density and Ophthalmologic).

Hypercorticism and Adrenal Suppression

Budesonide, a component of BREZTRI AEROSPHERE, will often help control COPD or asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Inhaled budesonide is absorbed into the circulation and can be systemically active. Effects of budesonide on the HPA axis are not observed with the therapeutic doses of budesonide in BREZTRI AEROSPHERE. Exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction. The beneficial effects of BREZTRI AEROSPHERE in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Because of the possibility of systemic absorption of ICS, patients treated with BREZTRI AEROSPHERE should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects, such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, when appropriate, therapy should be initiated.

Systemic Steroid Replacement by Inhaled Steroid

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After

withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREZTRI AEROSPHERE may provide control of COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their healthcare professional for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREZTRI AEROSPHERE. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREZTRI AEROSPHERE. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to BREZTRI AEROSPHERE may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. If significant reductions in BMD are seen and BREZTRI AEROSPHERE is still considered medically important for that patient's COPD or asthma therapy, use of therapy to treat or prevent osteoporosis should be strongly considered. See Bone Density and Ocular Effects.

Growth monitoring in pediatric population

Healthcare professionals should closely follow the growth of adolescents taking long-term corticosteroids by any route and weigh the benefits of the corticosteroid therapy and asthma control against the possible risk of growth suppression if any adolescent’s growth appears slowed.

Hypokalemia and hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. There was no evidence of a treatment effect on potassium with BREZTRI AEROSPHERE. Metabolic effects of hyperglycemia and hypokalemia may be observed with high doses of β_2 adrenergic agonists. The decrease in serum potassium is usually transient, not requiring supplementation. BREZTRI AEROSPHERE should be used with caution in patients predisposed to low levels of serum potassium. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see 9 Drug Interactions), which may increase the susceptibility to cardiac arrhythmias.

Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with BREZTRI AEROSPHERE, plasma glucose should be monitored more closely in diabetic patients. BREZTRI AEROSPHERE has not been studied in patients whose diabetes mellitus is not controlled.

Co-existing conditions

BREZTRI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the rapid onset, short-duration, beta$_2$-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hematologic

Eosinophilic conditions

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome), a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroid. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between inhaled corticosteroid and these underlying conditions has not been established.

Hepatic/Biliary/Pancreatic

As budesonide and formoterol are primarily eliminated via hepatic metabolism an increased exposure can be expected in patients with severe hepatic impairment.

In patients with severe hepatic impairment, BREZTRI AEROSPHERE should be used only if the expected benefit outweighs the potential risk (see 10 Clinical Pharmacology). Patients with hepatic disease should be closely monitored.

Immune

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients using corticosteroids. In such patients who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may

be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

As with all medications containing a corticosteroid, BREZTRI AEROSPHERE should be administered with caution, and only if necessary, in patients with active or quiescent tuberculosis infections of the respiratory tract; chronic or untreated infections such as systemic fungal, bacterial, viral, or parasitic; or ocular herpes simplex.

Monitoring and Laboratory Tests

Potentially serious hypokalemia has been observed with other beta-agonist therapies, which may increase susceptibility to cardiac arrhythmias. It is therefore recommended that serum potassium levels be monitored in patients predisposed to low levels of serum potassium.

Due to the hyperglycemic effect observed with other beta-agonists, additional blood glucose monitoring is recommended in diabetic patients.

For patients at risk, monitoring of bone and ocular effects (cataract and glaucoma) should also be considered in patients receiving maintenance therapy with BREZTRI AEROSPHERE.

Patients with hepatic impairment should be monitored for corticosteroid effects due to potentially increased systemic exposure of budesonide.

Ophthalmologic

Glaucoma and increased intraocular pressure have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids or with use of inhaled anticholinergics. Cataracts have also been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids.

BREZTRI AEROSPHERE, like other antimuscarinic-containing products, should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare professional immediately if any of these signs or symptoms develops.

Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, and cataracts.

See Bone Density and Ocular Effects.

Renal

BREZTRI AEROSPHERE, like other antimuscarinic-containing products, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare professional immediately if any of these signs or symptoms develops.

Formal pharmacokinetic studies using BREZTRI AEROSPHERE have not been conducted in patients with renal impairment. As glycopyrronium is predominantly renally excreted, patients with severe renal impairment (creatinine clearance of <30 mL/min) should be treated with BREZTRI AEROSPHERE only if the expected benefit outweighs the potential risk. These patients should be closely monitored for potential adverse drug reactions.

Reproductive Health

- **Fertility**

  Studies in rats have shown slight reductions in fertility only at dose levels higher than the maximum human exposure to formoterol (see 16 Non-Clinical Toxicology). Budesonide and

glycopyrronium individually, did not cause any adverse effects on fertility in rats. It is unlikely that BREZTRI AEROSPHERE administered at the recommended doses will affect fertility in humans.

Respiratory

Paradoxical bronchospasm

As with other inhaled medicines, administration of BREZTRI AEROSPHERE may cause paradoxical bronchospasm. If this occurs, treatment with BREZTRI AEROSPHERE should be stopped and other treatments considered.

Pneumonia (COPD patients)

In line with the known class effect of inhaled corticosteroids, pneumonia events (including pneumonias resulting in hospitalization) were observed in patients with COPD receiving BREZTRI AEROSPHERE. In some instances, fatal events of pneumonia have been reported with use of inhaled corticosteroid budesonide-containing drugs, including BREZTRI AEROSPHERE (see 8 Adverse Reactions). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections can overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving inhaled corticosteroid-containing drugs include current smokers, patients with a history of prior pneumonia, patients with low body mass index and patients with severe COPD. These factors should be considered when BREZTRI AEROSPHERE is prescribed, and treatment should be re-evaluated if pneumonia occurs.

Sensitivity/Resistance

As with all medications, immediate hypersensitivity reactions may occur after administration of BREZTRI AEROSPHERE. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria or skin rash) occur, therapy with BREZTRI AEROSPHERE should be stopped at once and alternative treatments should be considered. The patient should NOT be re-challenged with BREZTRI AEROSPHERE if this is identified as the cause of the hypersensitivity reaction (see 2 Contraindications).

7.1. Special Populations

7.1.1. Pregnancy

There are no adequate data on the use of BREZTRI AEROSPHERE in pregnant women.

Data on the use of inhaled budesonide in more than 2500 exposed pregnancies indicate no increased teratogenic risk associated with budesonide. Single-dose studies in humans found that very small amounts of glycopyrronium passed the placental barrier. There are no adequate data from use of formoterol or glycopyrronium in pregnant women.

No animal reproductive toxicology studies have been conducted with BREZTRI AEROSPHERE. Budesonide has been shown to induce embryofoetal toxicity in rats and rabbits, a class effect of glucocorticoids. At very high doses/systemic exposure levels, formoterol caused implantation losses as well as decreases in birth weight and early postnatal survival, whereas glycopyrrolate had no significant effects on reproduction (see 16 Non-Clinical Toxicology).

BREZTRI AEROSPHERE should only be used during pregnancy if the expected benefits outweigh the potential risks.

7.1.2. Breastfeeding

A clinical pharmacology study has shown that inhaled budesonide is excreted in breast milk. However, budesonide was not detected in nursing infant blood samples. Based on pharmacokinetic parameters, the plasma concentration in the child is estimated to be less than 0.17% of the mother's plasma concentration. Consequently, no effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of BREZTRI AEROSPHERE. It is not known whether glycopyrronium or formoterol are excreted in human milk. Evidence of transfer of glycopyrronium and formoterol into maternal milk in rats has been reported.

Administration of BREZTRI AEROSPHERE to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

7.1.3. Pediatrics

COPD

Pediatrics (<18 years of age): The safety and efficacy of BREZTRI AEROSPHERE 160/7.2/5 mcg in pediatric patients under 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Asthma

Pediatrics (12 to < 18 years of age): No dosage adjustment is necessary for pediatric patients 12 to less than 18 years of age for treatment of asthma.

Pediatrics (< 12 years of age): The safety and efficacy of BREZTRI AEROSPHERE 160/14.4/5 mcg in pediatric patients under 12 years of age have not been established; therefore, Health Canada has not authorized an indication for patients under 12 years of age.

7.1.4. Geriatrics

No dosage adjustment is required in patients 65 years of age and older, however greater sensitivity in some older individuals cannot be ruled out.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The overall safety profile of BREZTRI AEROSPHERE was generally consistent with the known pharmacologic class effects of ICSs, LAMAs and/or LABAs.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

As BREZTRI AEROSPHERE contains budesonide, glycopyrronium and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the components may be expected with BREZTRI AEROSPHERE.

Clinical Trial Adverse Reactions in Subjects with COPD

The safety evaluation of the pivotal COPD program for BREZTRI AEROSPHERE 160/7.2/5 mcg per delivered actuation included 2144 subjects with COPD in one 52-week clinical trial (PT010005), and 639 subjects with COPD in one 24-week clinical trial (PT010006).

Adverse drug reactions that occurred at a frequency of ≥1% are listed by MedDRA system organ class.

Table 3 – Adverse drug reactions occurring in ≥1% of subjects with BREZTRI AEROSPHERE for the 52-week exacerbation trial (PT010005)

System organ class/preferred term	BREZTRI AEROSPHERE[1] n = 2144 N (%)	GFF MDI[1] n = 2125 N (%)	BFF MDI[1] n = 2136 N (%)
Gastrointestinal disorders			
Nausea	28 (1.3)	21 (1.0)	24 (1.1)
General disorders and administration site conditions			
Chest pain	21 (1.0)	14 (0.7)	22 (1.0)
Infections and infestations			
Pneumonia	98 (4.6)	61 (2.9)	107 (5.0)
Oral candidiasis	65 (3.0)	24 (1.1)	57 (2.7)
Metabolism and nutrition disorders			
Hyperglycemia	26 (1.2)	20 (0.9)	21 (1.0)
Musculoskeletal and connective tissue disorders			
Muscle spasms	60 (2.8)	19 (0.9)	53 (2.5)
Nervous system disorders			
Headache	57 (2.7)	60 (2.8)	68 (3.2)
Psychiatric disorders			
Anxiety	30 (1.4)	24 (1.1)	28 (1.3)
Insomnia	30 (1.4)	23 (1.1)	11 (0.5)
Renal and urinary disorders			
Urinary tract infection	58 (2.7)	60 (2.8)	41 (1.9)
Respiratory, thoracic and mediastinal			
Cough	58 (2.7)	50 (2.4)	51 (2.4)
Dysphonia	37 (1.7)	7 (0.3)	31 (1.5)

Table 3 – Adverse drug reactions occurring in ≥1% of subjects with BREZTRI AEROSPHERE for the 52-week exacerbation trial (PT010005)

System organ class/preferred term	BREZTRI AEROSPHERE[1] n = 2144 N (%)	GFF MDI[1] n = 2125 N (%)	BFF MDI[1] n = 2136 N (%)
Skin and subcutaneous tissue disorders			
Bruising	22 (1.0)	14 (0.7)	16 (0.7)

Abbreviations: GFF = glycopyrronium/formoterol fumarate dihydrate; BFF = budesonide and formoterol fumarate dihydrate; MDI = metered dose inhaler.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.

Table 4 – Adverse drug reactions occurring in ≥1% of subjects with BREZTRI AEROSPHERE for the 24-week lung function trial (PT010006)

System organ class/preferred term	BREZTRI AEROSPHERE[1] n = 639 N (%)	GFF MDI[1] n = 625 N (%)	BFF MDI[1] n = 314 N (%)
Gastrointestinal disorders			
Nausea	7 (1.1)	3 (0.5)	4 (1.3)
Infections and infestations			
Pneumonia	12 (1.9)	10 (1.6)	6 (1.9)
Oral candidiasis	10 (1.6)	5 (0.8)	5 (1.6)
Musculoskeletal and connective tissue disorders			
Muscle spasms	21 (3.3)	8 (1.3)	17 (5.4)
Renal and urinary disorders			
Urinary tract infection	12 (1.9)	10 (1.6)	4 (1.3)
Respiratory, thoracic and mediastinal disorders			
Dysphonia	20 (3.1)	5 (0.8)	15 (4.8)
Cough	11 (1.7)	9 (1.4)	3 (1.0)

Abbreviations: GFF = glycopyrronium/formoterol fumarate dihydrate; BFF = budesonide and formoterol fumarate dihydrate; MDI = metered dose inhaler.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.

Pneumonia in COPD Subjects

In PT010005, a 52-week trial of subjects with moderate to very severe COPD (N = 8,529) and a history of 1 or more moderate or severe COPD exacerbations in the year prior, the overall incidence of confirmed pneumonia was 4.2% for BREZTRI AEROSPHERE 160/7.2/5 mcg (n = 2144), 3.5% for budesonide, glycopyrronium and formoterol fumarate [BGF MDI 80/7.2/5 mcg] (n = 2124), 2.3% for GFF MDI 7.2/5 mcg (n = 2125) and 4.5% for BFF MDI 160/5.0 mcg (n = 2136). Fatal cases of pneumonia occurred in 2 subjects receiving BGF MDI 80/7.2/5 mcg, 3 subjects receiving GFF MDI 7.2/5 mcg, and no subjects receiving BREZTRI AEROSPHERE 160/7.2/5 mcg.

In PT010006, a 24-week trial of subjects with moderate to very severe COPD (N = 1,896), the incidence of confirmed pneumonia was low and similar across treatment groups and was 1.9% for BREZTRI AEROSPHERE 160/7.2/5 mcg (n = 639), 1.6% for glycopyrronium and formoterol fumarate [GFF MDI 7.2/5 mcg] (n = 625) and 1.9% for budesonide and formoterol fumarate [BFF MDI 160/5 mcg] (n = 320). There were no fatal cases of pneumonia with BREZTRI AEROSPHERE in the study.

Clinical Trial Adverse Reactions in Subjects with Asthma

The safety evaluation of the pivotal asthma program for BREZTRI AEROSPHERE 160/14.4/5 mcg per delivered actuation included 594 subjects with asthma in one 24 to 52-week lung function study (D5982C00007) and 585 subjects with asthma in another 24 to 52-week lung function study (D5982C00008).

Adverse drug reactions that occurred at a frequency of ≥1% in the pooled safety population (D5982C00007 and D5982C00008) are listed by MedDRA system organ class (Table 5).

Table 5 – Adverse drug reactions occurring in ≥1% of subjects in BREZTRI AEROSPHERE and with higher percentage compared to BFF MDI in the pooled studies D5982C00007 and D5982C00008

System organ class/preferred term	BREZTRI AEROSPHERE[1] n = 1179 N (%)	BFF MDI[1] n = 1208 N (%)
Nervous system disorders		
Headache	26 (2.2)	15 (1.2)
Renal and urinary disorders		
Urinary tract infection	12 (1.0)	12 (1.0)
Respiratory, thoracic and mediastinal disorders		
Dysphonia	22 (1.9)	11(0.9)

Abbreviations: BFF = budesonide and formoterol fumarate dihydrate; MDI = metered dose inhaler.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/14.4/5 mcg, or BFF MDI 160/5 mcg.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

The safety of BREZTRI AEROSPHERE for the treatment of asthma in patients 12 to less than 18 years of age is based on the pooled safety data from two, 24 to 52-week, randomized, double-blind, studies (D5982C00007 and D5982C00008). A total of 30 patients 12 to less than 18 years of age were treated with BREZTRI AEROSPHERE 160/14.4/5 mcg administered as 2 inhalations twice daily (see 14.1 Clinical Trials by Indication). There were no notable differences in the type

or frequency of adverse events reported in this age group compared with asthma patients 18 years of age and older.

8.3. Less Common Clinical Trial Adverse Reactions

Other less common adverse reactions that occurred with a frequency of <1.0% in patients receiving BREZTRI AEROSPHERE are listed below.

Cardiovascular disorders: angina pectoris, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles), palpitations, tachycardia

Endocrine disorders: signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunctions of the adrenal gland

Gastrointestinal disorders: dry mouth

Immune system disorders: hypersensitivity

Psychiatric disorders: depression, agitation, restlessness, nervousness, abnormal behaviour

Nervous system disorders: dizziness, tremor

Renal and urinary disorders: urinary retention

Respiratory, thoracic and mediastinal disorders: bronchospasm, throat irritation

8.5. Post-Market Adverse Reactions

No post-marketing Adverse Drug Reactions have been identified to date for BREZTRI AEROSPHERE.

9. Drug Interactions

9.2. Drug-Interactions Overview

No formal drug interaction studies have been performed with BREZTRI AEROSPHERE. Information on BREZTRI AEROSPHERE is based on the potential for interactions for each of its components.

COPD and asthma medicinal products

Co-administration of BREZTRI AEROSPHERE with other anticholinergic and/or long-acting β_2-adrenergic agonist containing medicinal products has not been studied and is not recommended.

9.3. Drug-Behaviour Interactions

The interaction of BREZTRI AEROSPHERE with individual behavioural risks has not been studied.

9.4. Drug-Drug Interactions

Metabolic interactions

The metabolism of budesonide is primarily mediated by CYP3A4. Co-treatment with strong CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects (see 7 Warnings and Precautions and 10 Clinical Pharmacology). If a patient requires long-term concomitant treatment with BREZTRI AEROSPHERE and a strong CYP3A4 inhibitor, the benefit should be weighed against the increased risk of systemic corticosteroid side effects, patients should be monitored for corticosteroid side effects.

Since glycopyrronium is eliminated mainly by the renal route, drug interactions could potentially occur with medicinal products affecting renal excretion mechanisms. *In-vitro* glycopyrronium is a substrate for the renal transporters OCT2 and MATE1/2K. The effect of cimetidine, a probe inhibitor of OCT2 and MATE1, on inhaled glycopyrronium disposition showed an increase in its total systemic exposure (AUC_{0-t}) by 22% and a decrease in renal clearance by 23% due to co-administration of cimetidine. No clinically relevant drug interaction is expected in patients with normal renal function and also in patients with mild to moderate renal impairment.

Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations (see 10 Clinical Pharmacology). Budesonide and glycopyrronium do not inhibit or induce CYP450 enzymes at therapeutically relevant concentrations (see 10 Clinical Pharmacology).

Sympathomimetic Agents

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of BREZTRI AEROSPHERE (see 7 Warnings and Precautions).

Treatments leading to hypokalemia

Concomitant treatment with methylxanthine derivatives, oral corticosteroids (e.g., prednisone), or non-potassium-sparing diuretics may potentiate the possible initial hypokalemic effect of $beta_2$-adrenergic agonists, therefore caution is advised in their concomitant use (see Hypokalemia and hyperglycemia).

β-adrenergic blockers

Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol. Therefore, patients should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives than to use beta-blockers. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Drugs Known to Prolong the QTc Interval

BREZTRI AEROSPHERE, as with other $beta_2$-agonists, should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval, as any effect of these on the QT interval may be potentiated. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias (see 7 Warnings and Precautions, and 10 Clinical Pharmacology).

Table 6 – Established or Potential Drug-Drug Interactions

Drug Type	Source of Evidence	Effect	Clinical comment
CYP3A4 inhibitors	CT	Expected to increase the risk of systemic side effects	Caution should be exercised during long-term treatment with a strong CYP3A4 inhibitor (e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products)

Drug Type	Source of Evidence	Effect	Clinical comment
Sympathomimetic Agents	T	Potential pharmacodynamic interaction (additive pharmacologic and adverse effects)	Caution is recommended during concomitant use with long acting sympathomimetic agents administered by any route
Methylxanthine derivatives, oral corticosteroids (e.g., prednisone), or non-potassium sparing diuretics	T	Potential pharmacodynamic interaction (increased risk of hypokalemia)	Caution is recommended during concomitant therapy
Beta-adrenergic blockers (including ophthalmic agents)	T	Beta-adrenergic blockers may weaken or antagonize the effect of beta$_2$-adrenergic agonists resulting in severe bronchospasm	If concomitant therapy is required, cardioselective beta-adrenergic blockers could be considered, although they should be administered with caution
Drugs known to prolong QTc interval Monoamine Oxidase Inhibitors Tricyclic Antidepressants	T	Potential pharmacodynamics interaction (prolongation of the QTc interval and increased risk of ventricular arrhythmias)	Caution is recommended during concomitant therapy
Anticholinergics	T	Potential for an additive interaction with concomitantly used anticholinergic medications	Avoid co-administration with other anticholinergic-containing drugs administered by any route

Legend: CT = Clinical Trial; T = Theoretical

9.5. Drug-Food Interactions

No formal drug-food interaction studies have been conducted. No clinically relevant effect of food would be expected and therefore a food interaction study was not conducted.

9.6. Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted.

9.7. Drug-Laboratory Test Interactions

No formal drug-laboratory test interaction studies have been conducted.

10. Clinical Pharmacology

10.1. Mechanism of Action

BREZTRI AEROSPHERE contains budesonide, a glucocorticosteroid, and two bronchodilators: glycopyrronium, a long-acting muscarinic antagonist (anticholinergic) and formoterol, a long-acting β_2-adrenergic agonist.

The combination of these substances with different mechanisms of action results in increased efficacy compared to use with any of the dual component therapies. The respective mechanism of action of each drug is discussed below.

Budesonide, when inhaled, has a rapid (within hours) and dose dependent anti-inflammatory action in the airways, resulting in reduced symptoms and exacerbations.

Glycopyrronium has a rapid onset of action and has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, bronchodilation is induced through inhibition of the M3 receptor at the smooth muscle.

Formoterol has a rapid onset of action. Bronchodilation is induced by causing direct relaxation of airway smooth muscle as a consequence of the increase in cyclic AMP through activation of adenylate cyclase.

As a consequence of the differential density of muscarinic receptors and β_2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists are more effective in relaxing central airways and β_2-adrenergic agonists are more effective in relaxing peripheral airways. Relaxation of both central and peripheral airways through the interactions of budesonide, glycopyrronium, and formoterol fumarate dihydrate in a combination treatment may contribute to its beneficial effects on lung function.

10.2. Pharmacodynamics

Time to Onset of Action

The median time to a 100 mL or larger improvement in FEV_1 with BREZTRI AEROSPHERE was within 5 minutes of the first dose on Day 1 in all treatment groups in the Phase 3 clinical trials. A change from baseline of 166 mL (PT010005),175 mL (PT010006) in COPD subjects, and 161 mL (D5982C00007), and 180 mL (D5982C00008) in asthma subjects was observed at 5 minutes post-dose for BREZTRI AEROSPHERE, indicating a rapid onset of bronchodilatory effect.

Class-Related Beta$_2$-Adrenoceptor Systemic Effects

Class-related systemic effects that are known to occur with systemic administration of beta-agonists include hypokalemia, hyperglycemia, and increases in blood pressure, heart rate and the QTc interval. Following inhaled administration these effects are limited by local topical administration in the lung, low clinical doses and first pass metabolism of the swallowed portion of the dose.

In PT010005, a 52-week trial of subjects with COPD, no clinically meaningful trends were observed in laboratory parameters (including potassium and glucose), vital signs (heart rate, systolic blood pressure, or diastolic blood pressure), or electrocardiogram (ECG) parameters (Calculated Fridericia-corrected QT, PR or QRS interval prolongation) over time across the treatment groups. The incidence of post-baseline newly occurring or worsening potentially clinically significant laboratory, vital sign parameters, and ECG parameters was generally low

and similar across treatment groups. Similarly, in D5982C00007 and D5982C00008, 24-52 week trials of subjects with asthma, no new safety findings related to clinical laboratory parameters (e.g. clinical chemistry, hematology, eGFR) were identified in the studies.

Cardiovascular effects

A thorough QT study was not performed with BREZTRI AEROSPHERE as budesonide is not known to affect the QT interval. The potential for QTc interval prolongation with glycopyrronium/formoterol fumarate was assessed in a randomized double-blind, single-dose, placebo- and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% confidence interval [CI]) differences from placebo in baseline-corrected Individual-specific corrected QT (QTcI) interval for a single-dose treatment of glycopyrronium/formoterol fumarate dihydrate 14.4/10 mcg (therapeutic dose) and 115.2/40 mcg (supra-therapeutic dose), administered as 2 inhalations, were 3.1 (90% CI [1.4, 4.7]) ms at 0.17 h and 7.6 (90% CI [6.0, 9.2]) ms at 0.33 h, respectively. No effect on the QTcI interval was observed in the glycopyrronium 132.8 mcg single component treatment arm.

A dose-dependent increase in heart rate was also observed. The largest mean (90% confidence interval) differences from placebo in baseline-corrected heart rate were 3.3 (90% CI [1.8, 4.9]) beats/min at 0.1h and 7.6 (90% CI [5.6, 9.5]) beats/min at 0.17 h with glycopyrronium/formoterol fumarate dihydrate 14.4/10 mcg (therapeutic dose) and 115.2/40 mcg (supra-therapeutic dose), respectively.

Budesonide is not known to effect cardiac rhythm.

COPD

The effect of glycopyrronium and/or formoterol fumarate on cardiac rhythm in subjects with COPD was assessed using 24-hour Holter monitoring at Week 16 in Study PT010005. All treatments were administered as 2 inhalations twice daily. The Holter monitoring population in Study PT010005 included 180 subjects on BREZTRI AEROSPHERE 160/7.2/5 mcg, 160 subjects on glycopyrronium and formoterol fumarate (GFF MDI 7.2/5 mcg), and 183 subjects on budesonide/formoterol fumarate (BFF MDI 160/5 mcg). The results of this sub-study in COPD patients showed no notable differences across treatment groups for any of the Holter endpoints, including heart rate (change from baseline: 24-hour mean, daytime mean, nighttime mean, 24-hour maximum, and 24-hour minimum), ventricular arrhythmias, and supraventricular arrhythmias. No clinically meaningful effects on cardiac rhythm were observed across treatment groups, including heart rate (change from baseline: 24-hour mean, daytime mean, nighttime mean, 24-hour maximum, and 24-hour minimum), ventricular arrhythmias, and supraventricular arrhythmias.

Asthma

The effects of BREZTRI AEROSPHERE 160/14.4/5 mcg on cardiac rhythm in subjects with asthma was assessed using 24-hour Holter monitoring at Week 4 or Week 24 in a 24 to 52-week trial (D5982C00007). The Holter monitoring population in D5982C00007 included 44 subjects on BREZTRI AEROSPHERE 160/14.4/5 mcg and 56 subjects on BFF MDI 160/5 mcg. All treatments were administered as 2 inhalations twice daily. No clinically meaningful effects on cardiac rhythm were observed.

HPA Axis Effects

Effects of BREZTRI AEROSPHERE on the HPA axis were assessed by measurement of 24-hour plasma cortisol at Baseline and Week 24 in subjects with COPD. The geometric mean ratio (Week 24/Baseline) was 0.86 for BREZTRI AEROSPHERE 160/7.2/5 mcg and 0.94 for GFF MDI 7.2/5 mcg, respectively, with all treatments administered as 2 inhalations twice daily.

Bone Density and Ocular Effects

Effects of BREZTRI AEROSPHERE on bone density and ocular outcomes were assessed in a subset of COPD patients in study PT010006 who were then treated in the 28-week extension study PT010008 for a total of up to 52 weeks. In study PT010006, BREZTRI AEROSPHERE 160/7.2/5 mcg was non-inferior to GFF MDI 7.2/5 mcg for the primary bone mineral density and ocular endpoints, with all treatments administered as 2 inhalations twice daily. In COPD patients in study PT010005 treated for up to 52 weeks, the incidence of cataracts was comparable across the budesonide-containing and non-budesonide-containing treatment groups.

10.3. Pharmacokinetics

COPD

Linear pharmacokinetics were demonstrated for budesonide (80 to 320 mcg), glycopyrronium bromide (18 to 144 mcg), and formoterol fumarate (2.4 to 38.4 mcg). Pharmacokinetic information for glycopyrrolate and formoterol fumarate is for the active moieties, glycopyrronium and formoterol, respectively. The pharmacokinetics of budesonide, glycopyrronium, and formoterol from BREZTRI AEROSPHERE 160/7.2/5 mcg are comparable to the pharmacokinetics of budesonide, glycopyrronium, and formoterol when administered as budesonide/formoterol (BFF MDI) or glycopyrronium bromide/formoterol (GFF MDI) in studies of healthy subjects (single dose) and subjects with COPD (repeated dose).

Table 7 – Summary of BREZTRI AEROSPHERE 160/7.2/5 mcg Pharmacokinetic Parameters in subjects with COPD

	C_{max}[1] (pg/mL)	T_{max}[2] (h)	$t_{½}$[1] (h)	AUC_{0-12}[1] (pg·h/mL)	CL[1] (L/h)
Single dose[3]					
Budesonide	709.3 (57.2)	0.33 (0.10, 1.03)	6.2 (24.7)	2407 (45.4)	106.8 (41.0)
Glycopyrronium	17.2 (80.7)	0.03 (0.03, 4.00)	8.5 (131.8)	42.5 (45.8)	235.5 (85.1)
Formoterol	6.4 (48.1)	0.33 (0.10, 9.97)	5.9 (40.7)	32.6 (30.3)	208.8 (33.7)
Repeat dose[4]					
Budesonide	663.2 (65.8)	0.67 (0.10, 2.00)	N/A	3005 (58.5)	N/A
Glycopyrronium	18.3 (65.4)	0.10 (0.03, 1.00)	N/A	73.9 (52.9)	N/A
Formoterol	7.4 (38.1)	0.67 (0.03, 12.00)	N/A	47.4 (30.0)	N/A

N/A = not applicable
[1] expressed as the geometric mean (coefficient of variation)
[2] expressed as median values (range)
[3] Assessed following a single dose administration (2 inhalations) on the first treatment day (Day 1)
[4] Assessed following 7 days of repeat dosing of 2 inhalations twice daily

Asthma

Study D5982C00007 included a 12-hour pharmacokinetic sub-study to characterize the steady

state pharmacokinetic parameters of budesonide, glycopyrronium, and formoterol fumarate when delivered from BREZTRI AEROSPHERE 160/14.4/5 mcg, administered as 2 inhalations twice daily at Week 12. The pharmacokinetics of budesonide and formoterol show generally higher systemic exposure for BREZTRI AEROSPHERE compared with budesonide/formoterol (BFF MDI). The pharmacokinetic parameters of glycopyrronium in subjects receiving BREZTRI AEROSPHERE 160/14.4/5 mcg showed a similar shaped profile as BREZTRI AEROSPHERE 160/7.2/5 mcg, with higher glycopyrronium concentrations for BREZTRI AEROSPHERE 160/14.4/5 mcg (Table 8).

Table 8 – Summary of BREZTRI AEROSPHERE 160/14.4/5 mcg Steady-State Pharmacokinetic Parameters in adults with Asthma

	C_{max}[1] (pg/mL)	T_{max}[2] (h)	AUC_{0-12}[1] (pg·h/mL)
Budesonide	777.0 (60.8)	0.67 (0.03, 8.00)	3201 (56.0)
Glycopyrronium	27.0 (76.3)	0.10 (0.00, 10.0)	116.6 (83.4)
Formoterol	12.3 (80.4)	1.52 (0.00, 11.9)	75.8 (66.3)

[1] expressed as the geometric mean (coefficient of variation)
[2] expressed as median values (range)

Absorption:

Use with a Spacer

The use of BREZTRI AEROSPHERE 160/14.4/5 mcg, given as 2 inhalations, with the Aerochamber Plus® Flow-Vu® spacer in healthy volunteers increased the total systemic exposure (as measured by AUC_{0-t}) to budesonide and glycopyrronium by 33% and 55%, respectively, while exposure to formoterol was unchanged. However, the highest increases in exposure with the spacer were observed in subjects showing low exposure without spacer (probably due to poor inhalation technique).

Budesonide

Following inhaled administration of BREZTRI AEROSPHERE in subjects with COPD or asthma, budesonide C_{max} occurred within 20 to 40 minutes. Steady state is achieved after approximately 1 day of repeated dosing of BREZTRI AEROSPHERE in subjects with COPD and the extent of exposure is approximately 1.3 times higher than after the first dose.

Glycopyrronium

Following inhaled administration of BREZTRI AEROSPHERE in subjects with COPD or asthma, glycopyrronium C_{max} occurred at 2 to 6 minutes. Steady state is achieved after approximately 3 days of repeated dosing of BREZTRI AEROSPHERE in subjects with COPD and the extent of exposure is approximately 1.8 times higher than after the first dose.

Formoterol

Following inhaled administration of BREZTRI AEROSPHERE in subjects with COPD or asthma, formoterol C_{max} occurred within 40 to 90 minutes. Steady state is achieved after approximately 2 days of repeated dosing with BREZTRI AEROSPHERE in subjects with COPD and the extent of exposure is approximately 1.4 times higher than after the first dose.

Distribution:

Budesonide

The estimated budesonide apparent volume of distribution at steady-state is 1200 L, via population pharmacokinetic analysis in subjects with COPD. Plasma protein binding is approximately 90% for budesonide.

Glycopyrronium

The estimated glycopyrronium apparent volume of distribution at steady-state is 5500 L, via population pharmacokinetic analysis in subjects with COPD. Over the concentration range of 2-500 nmol/L, plasma protein binding of glycopyrronium ranged from 43% to 54%.

Formoterol

The estimated formoterol apparent volume of distribution at steady-state is 2400 L, via population pharmacokinetic analysis in subjects with COPD. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.

Metabolism:

Budesonide

Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 beta-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide.

Glycopyrronium

Based on literature, and an *in-vitro* human hepatocyte study, metabolism plays a minor role in the overall elimination of glycopyrronium. CYP2D6 was found to be the predominant enzyme involved in the metabolism of glycopyrronium.

Formoterol

The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Elimination:

Budesonide

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. The effective terminal elimination half-life of budesonide derived via population pharmacokinetic analysis in subjects with COPD was 5 hours.

Glycopyrronium

After IV administration of a 0.2 mg dose of radiolabelled glycopyrronium, 85% of the dose was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile. The effective terminal elimination half-life of glycopyrronium derived via population pharmacokinetic analysis in subjects with COPD was 15 hours.

Formoterol

The excretion of formoterol was studied in six healthy subjects following simultaneous

administration of radiolabelled formoterol via the oral and IV routes. In that study, 62% of the drug-related radioactivity was excreted in the urine while 24% was eliminated in the feces. The effective terminal elimination half-life of formoterol derived via population pharmacokinetic analysis in subjects with COPD was 10 hours.

Special Populations and Conditions

- **Age, Sex, Ethnic Origin and Weight:**

  A population pharmacokinetic analysis of budesonide was performed based on data collected in a total of 220 subjects with COPD. The pharmacokinetics of budesonide was best described by a three-compartment disposition model with first order absorption. The typical clearance (CL/F) of budesonide was 122 L/h.

  A population pharmacokinetic analysis of glycopyrronium was performed based on data collected in a total of 481 subjects with COPD. The pharmacokinetics of glycopyrronium was best described by a two-compartment disposition model with first-order absorption and linear elimination. The typical clearance (CL/F) of glycopyrronium was 166 L/h.

  A population pharmacokinetic analysis of formoterol was performed based on data collected in a total of 663 subjects with COPD. The pharmacokinetics of formoterol was best described by a two-compartment disposition model with a first-order rate constant of absorption and linear elimination. The typical clearance (CL/F) of formoterol was 124 L/h.

  Dose adjustments are not necessary based on the effect of age, gender or weight on the pharmacokinetic parameters of budesonide, glycopyrronium and formoterol.

  There were no major differences in total systemic exposure (AUC) for all compounds among healthy Japanese, Chinese and Western subjects. Insufficient pharmacokinetic data is available for other ethnicities or races.

- **Pediatrics (12 to < 18 years of age):** There is limited pharmacokinetic data in pediatric patients with asthma 12 to less than 18 years of age treated with BREZTRI AEROSPHERE. However, no dosage adjustment is necessary for pediatric patients 12 to less than 18 years of age for the treatment of asthma. BREZTRI AEROSPHERE has not been evaluated in patients under 18 years of age in COPD.

  Pediatrics (< 12 years of age): BREZTRI AEROSPHERE has not been evaluated in patients under 18 years of age in COPD and under 12 years of age in asthma.

- **Geriatrics (≥ 65 years of age):** Based on available data, no adjustment of the dosage of BREZTRI AEROSPHERE in elderly patients is necessary.

  The confirmatory trials of BREZTRI AEROSPHERE for COPD and asthma included 1443 and 265 subjects aged 65 and older, respectively. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

- **Hepatic Insufficiency:** No pharmacokinetic studies have been performed with BREZTRI AEROSPHERE in patients with hepatic impairment.

  However, because both budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment. Glycopyrronium is primarily cleared from the systemic circulation by renal excretion and hepatic impairment would therefore not be expected to effect systemic exposure.

- **Renal Insufficiency:** Studies evaluating the effect of renal impairment on the pharmacokinetics of budesonide, glycopyrronium and formoterol were not conducted.

The effect of renal impairment on the exposure to budesonide, glycopyrronium and formoterol for up to 24 weeks was evaluated in a population pharmacokinetic analysis. Estimated glomerular filtration rate (eGFR) varied from 31-192 mL/min representing a range of moderate to no renal impairment. Simulation of the systemic exposure (AUC_{0-12}) in subjects with COPD with moderate renal impairment (eGFR of 45 mL/min) indicates an approximate 68% increase for glycopyrronium compared to subjects with COPD with normal renal function (eGFR of >90 mL/min). Renal function was found not to affect exposure to budesonide or formoterol.

11. Storage, Stability, and Disposal

Store between 15 to 30°C. Store in a dry place.

BREZTRI AEROSPHERE should be kept protected inside the sealed foil pouch until the administration period starts. After removal from the foil pouch BREZTRI AEROSPHERE should be used within:

- 6 weeks (56 actuation pack size)
- 3 months (120 actuation pack size).

Keep out of sight and reach of children.

12. Special Handling Instructions

The canister should not be broken, punctured or burnt, even when apparently empty. Do not use or store near heat or open flames. Do not expose to temperatures above 50°C and protect from freezing temperatures. If exposed to freezing temperatures, the inhaler should be equilibrated for 1 hour at room temperature prior to taking a dose.

The actuator should be rinsed weekly.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

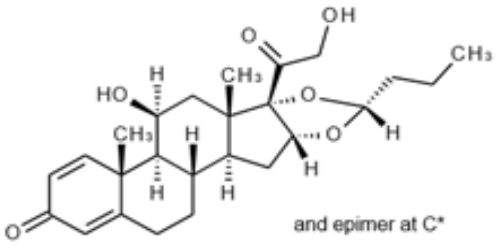
Non-proprietary name of the drug substance: budesonide

Chemical name:

(22RS)-16α,17α-Propylmethylenedioxypregna-1,4-diene-11β,21-diol-3,20-dione

Molecular formula and molecular mass: $C_{25}H_{34}O_6$; 430.5 g/mol

Structural formula:



Physicochemical properties: White to off-white powder. Budesonide contains the 22R and 22S epimers in an approximate 53:47 ratio. Melts at 224 – 232°C, with decomposition.

Practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

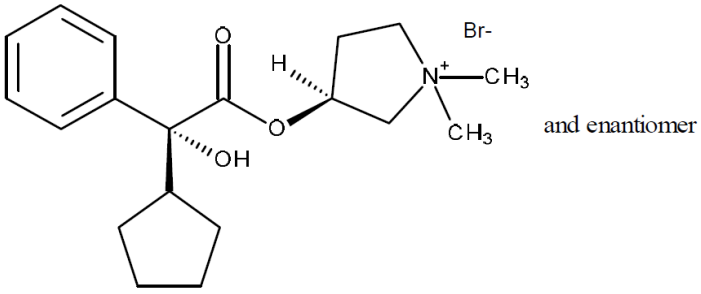
Non-proprietary name of the drug substance: glycopyrronium bromide

Chemical name:

3-[(2-cyclopent(3S*)-(±)-3-{[(2R*-(±))-2-cyclopentyl-2-hydroxy-2-phenylacetyl]oxy}-1,1-dimethylpyrrolidinium

Molecular formula and molecular mass: $C_{19}H_{28}BrNO_3$; 398.3 g/mol

Structural formula:



Physicochemical properties: White or almost white crystalline powder. Contains 2 chiral centers and is a racemate of the R,S and S,R diastereomers. Melts between 191 – 195°C.

Freely soluble in water, soluble in alcohol, insoluble in chloroform and insoluble in ether.

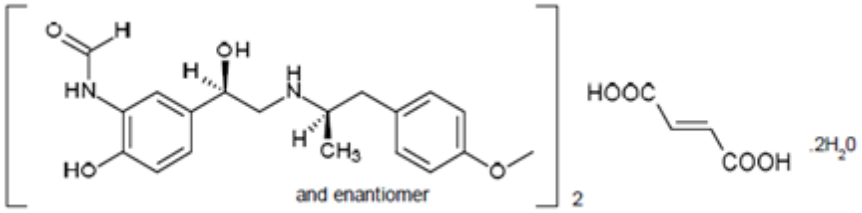
Non-proprietary name of the drug substance: formoterol fumarate dihydrate

Chemical name:

(R*,R*)-(±)-N-{2-hydroxy-5-[1-hydroxy-2-{[1-(4-hydroxyphenyl)-2-propanyl]amino}ethyl]phenyl}formamide (2E)-2-butenedioate (2:1), dihydrate

Molecular formula and molecular mass: $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot (H_2O)_2$; 840.9 g/mol

Structural formula:



Physicochemical properties: White to off-white or slightly yellow powder. Contains 2 chiral centers and is a racemate of a 1:1 mixture of the R,R and S,S diastereomers. Melts between 138 – 140°C.

Slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol and practically insoluble in acetonitrile.

14. Clinical Trials

14.1. Clinical Trials by Indication

COPD

Table 9 – Summary of Patient Demographics for Clinical Trials in COPD

Study #	Study design	Treatment and dosage[1]	Study Subjects[2]	Age (Range)	Sex
PT010005 (ETHOS)	A Randomized, Double-Blind, Multi-Center, Parallel-Group Study to Assess the Efficacy and Safety of BGF MDI Relative to GFF MDI and BFF MDI on COPD Exacerbations over a 52-Week Treatment Period in Subjects With Moderate to	BREZTRI AEROSPHERE MDI 160/7.2/5 mcg, 2 inhalations twice daily BGF MDI 80/7.2/5 mcg, 2 inhalations twice daily GFF MDI 7.2/5 mcg, 2 inhalations twice daily BFF MDI 160/5 mcg, 2 inhalations twice	Total: N = 8509 BREZTRI AEROSPHERE MDI: N = 2137 BGF MDI: N = 2121 GFF MDI: N = 2120 BFF MDI:	40-81 years of age	Male: 5081 (59.7%) Female: 3428 (40.3%)

Study #	Study design	Treatment and dosage[1]	Study Subjects[2]	Age (Range)	Sex
	Very Severe COPD	daily	N = 2131		
PT010006 (KRONOS)	A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of BGF MDI, GFF MDI, and BFF MDI Compared with budesonide/formoterol fumarate dihydrate dry powder for inhalation as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease	BREZTRI AEROSPHERE MDI 160/7.2/5 mcg, 2 inhalations twice daily GFF MDI 7.2/5 mcg, 2 inhalations twice daily BFF MDI 160/5 mcg, 2 inhalations twice daily Open label BFF DPI 200/6 mcg, 2 inhalations twice daily	Total: N = 1896 BREZTRI AEROSPHERE MDI: N = 639 GFF MDI: N = 625 BFF MDI: N = 314 Open label BFF DPI: N = 318	40-80 years of age	Male: 1350 (71.2%) Female 546 (28.8%)

Abbreviations: FEV1 = forced expiratory volume in 1 second; AUC0-4 = area under the curve from 0-4 hours; BGF = budesonide/glycopyrronium/formoterol fumarate; GFF = glycopyrronium/formoterol fumarate dihydrate; BFF = budesonide and formoterol fumarate dihydrate; MDI = metered dose inhaler; DPI = dry powder for inhalation.

[1] Administered via oral inhalation.

[2] Modified intent to treat (mITT) population: defined as all subjects randomized and treated with post-randomization data obtained prior to discontinuation from the study drug.

Study demographics and trial design

The efficacy and safety of BREZTRI AEROSPHERE 160/7.2/5 mcg was evaluated in two randomized, multicentre, double-blind, parallel-group trials (PT010005 and PT010006) in patients with moderate to very severe COPD who remained symptomatic (COPD Assessment Test (CAT) score of 10 or above) while receiving 2 or more inhaled maintenance treatments for COPD for at least 6 weeks prior to screening.

PT010005 was a 52-week trial (N=8,509) that compared BREZTRI AEROSPHERE 160/7.2/5 mcg or budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF MDI) 80/7.2/5 mcg with glycopyrronium/formoterol fumarate dihydrate (GFF MDI) 7.2/5 mcg, and budesonide/formoterol fumarate dihydrate (BFF MDI) 160/5.0 mcg, all administered as 2 inhalations twice daily. Patients

had moderate to very severe COPD (post-bronchodilator FEV_1 ≥25% to <65% predicted) with a history of 1 or more moderate or severe COPD exacerbation(s) in the year prior to screening. The mean age was 65 years, with 52% of patients aged 65 or over. During the screening period, the mean post-bronchodilator percent predicted FEV_1 was 43%. The mean CAT score was 19.6. A total of 81% of subjects were on ICS-containing treatments prior to screening. At study entry, the most common COPD medications were ICS + LAMA + LABA (39%), ICS + LABA (31%), and LAMA + LABA (14%).

The primary endpoint was the rate of moderate or severe COPD exacerbations. Exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum color) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: cough, wheeze, sore throat, colds (nasal discharge and/or nasal congestion), and fever without other cause for at least 2 consecutive days. Exacerbations were considered to be moderate severity if treatment with systemic corticosteroids and/or antibiotics for 3 or more days was required. Exacerbations were considered to be severe if they resulted in hospitalization or death. Secondary efficacy endpoints included: time to first moderate or severe COPD exacerbation, rate of severe COPD exacerbations, rate of moderate or severe COPD exacerbations in subjects with ≥2 moderate or severe COPD exacerbations in the prior year, change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 24 weeks, change from baseline in average daily rescue albuterol sulfate use over 24 weeks, Transition Dyspnea Index (TDI) focal score over 24 weeks, change from baseline in Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over 52 weeks, and time to death (all cause). Primary endpoints in the pulmonary function test (PFT) sub-study included change from baseline in trough FEV_1 over 24 weeks (BREZTRI AEROSPHERE vs. GFF MDI) and FEV_1 AUC_{0-4} over 24 weeks (BREZTRI AEROSPHERE vs. BFF MDI).

PT010006 was a 24-week trial (N=1,896) that compared BREZTRI AEROSPHERE 160/7.2/5 mcg, glycopyrronium/formoterol fumarate dihydrate (GFF MDI 7.2/5 mcg), budesonide/formoterol fumarate dihydrate (BFF MDI 160/5 mcg) and open-label active comparator budesonide/formoterol fumarate dihydrate dry powder for inhalation (DPI) 200/6 mcg, all administered as 2 inhalations twice daily.

The two primary endpoints in PT010006 were FEV_1 area under the curve from 0-4 hours (FEV_1 AUC_{0-4}) (BREZTRI AEROSPHERE 160/7.2/5 mcg vs. BFF MDI 160/5 mcg) and change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BREZTRI AEROSPHERE 160/7.2/5 vs. GFF MDI 7.2/5 mcg). Secondary efficacy endpoints included: change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BREZTRI AEROSPHERE 160/7.2/5 mcg vs. BFF MDI 160/5 mcg), peak change from baseline in FEV_1 within 4 hours post dosing over 24 weeks, rate of moderate or severe COPD exacerbations, TDI focal score over 24 weeks, time to CID, change from baseline in SGRQ total score over 24 weeks, change from baseline in average daily rescue Ventolin HFA use over 24 weeks, change from baseline in Evaluating Respiratory Symptoms in COPD total score (RS-Total Score) over 24 weeks, time to onset of action on Day 1.

Trial PT010006 was conducted in patients with moderate to very severe COPD (post-bronchodilator FEV_1 ≥25% to <80% predicted). A prior history of exacerbations in the last 12 months was not required in PT010006 and 74% of patients did not have a history of moderate/severe exacerbations in the prior year. The mean age was 65 years, with 55% of patients aged 65 or over. During the screening period, the mean post-bronchodilator percent predicted FEV_1 was 50%. The mean CAT score was 18.3 and a total of 72% of subjects were on ICS-containing treatments prior to screening. At study entry, the most common COPD medication combinations reported were ICS + LAMA + LABA (27%), ICS + LABA (38%), and LAMA + LABA (20%).

Effects on exacerbations - Study PT010005

Rate of moderate or severe exacerbations

Treatment with BREZTRI AEROSPHERE 160/7.2/5 mcg statistically significantly reduced the rate of moderate or severe COPD exacerbations over 52 weeks by 24% and 13% compared with GFF MDI and BFF MDI, respectively (see Table 10).

Rate of severe exacerbations (resulting in hospitalization or death)

Treatment with BREZTRI AEROSPHERE 160/7.2/5 mcg statistically significantly reduced the rate of severe COPD exacerbations over 52 weeks by 20% (hazard ratio [HR]: 0.80; 95%CI: 0.66, 0.97; p=0.0221) compared with BFF MDI.

Treatment with BREZTRI AEROSPHERE 160/7.2/5 mcg demonstrated a numerical reduction in the rate of severe COPD exacerbations over 52 weeks by 16% (HR: 0.84; 95%CI: 0.69, 1.03; p=0.0944) compared with GFF MDI.

Benefits on exacerbations were observed in patients with moderate, severe and very severe COPD.

Table 10 – Moderate/Severe COPD Exacerbations, Study PT010005

	BREZTRI AEROSPHERE[1] 160/7.2/5 mcg (N=2137)	**GFF MDI[1] 7.2/5 mcg (N=2120)**	**BFF MDI[1] 160/5 mcg (N=2131)**
Rate of moderate or severe exacerbations over 52 weeks			
Rate	1.08	1.42	1.24
Rate Ratio: BREZTRI AEROSPHERE 160/7.2/5 mcg vs. comparator		0.76	0.87
% reduction		24%	13%
95% CI		(0.69, 0.83)	(0.79, 0.95)
p-value		p<0.0001	p=0.0027

Abbreviations: CI = confidence interval

[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.

Effects on exacerbations - Study PT010006

Treatment with BREZTRI AEROSPHERE 160/7.2/5 mcg statistically significantly reduced the rate of moderate/severe COPD exacerbations over 24 weeks by 52% (HR: 0.48; 95%CI: 0.37, 0.64; p<0.0001) compared with GFF MDI. BREZTRI AEROSPHERE 160/7.2/5 mcg numerically reduced the rate of moderate/severe COPD exacerbations by 18% compared with BFF MDI.

Effects on lung function – Study PT010005 and Study PT010006

In PT010005 and PT010006, BREZTRI AEROSPHERE provided statistically significant improvements in lung function (FEV_1) compared with GFF MDI and BFF MDI (see Table 11 and Table 12 and Figure 1 and Figure 2). The improvements in lung function were sustained over 24 weeks in both studies and over 52-weeks in Study PT010005.

In both studies, there were consistent improvements in lung function in subgroups based on age,

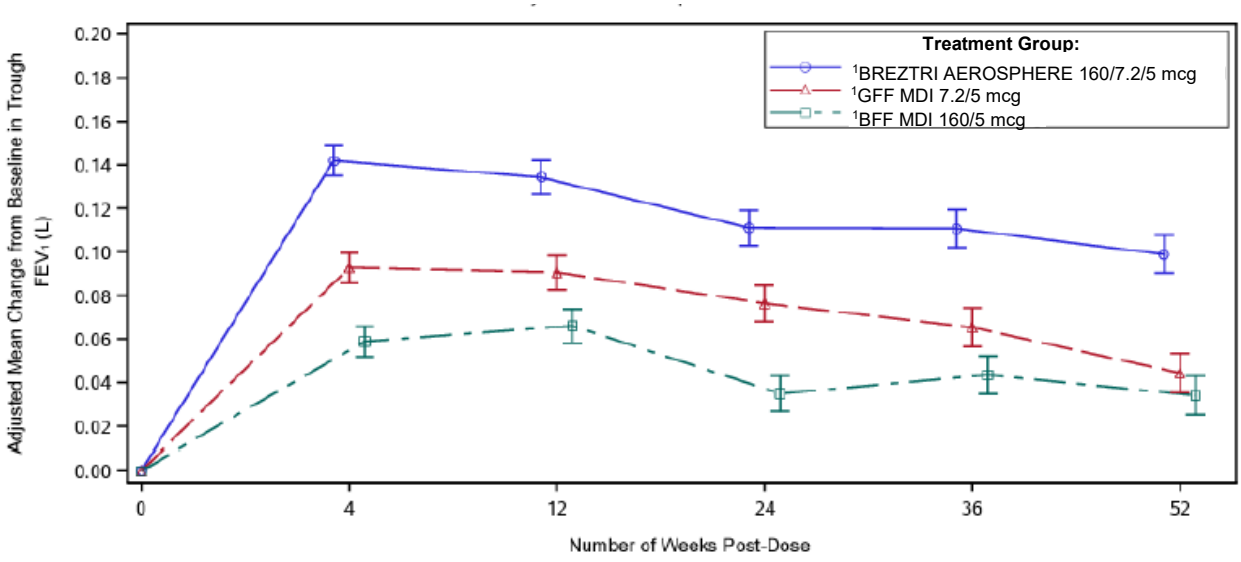
sex, degree of airflow limitation (moderate, severe and very severe), and previous inhaled corticosteroid use.

Table 11 – Lung function analyses, Study PT010005

	BREZTRI AEROSPHERE[1] 160/7.2/5 mcg (N=747)	GFF MDI[1] 7.2/5 mcg (N=779)	BFF MDI[1] 160/5 mcg (N=755)	Treatment difference 95% CI	
				BREZTRI AEROSPHERE vs. GFF MDI	BREZTRI AEROSPHERE vs. BFF MDI
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	129 (6.5)	86 (6.6)	53 (6.5)	43 mL (25, 60) p<0.0001*	76 mL (58, 94) p<0.0001
FEV_1 AUC_{0-4} over 24 weeks; LS mean change from baseline (SE)	294 (6.3)	245 (6.3)	194 (6.3)	49 mL (31, 66) p<0.0001	99 mL (82, 117) p<0.0001*

[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.
*Statistically significant

Figure 1 – Adjusted Mean Change from Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over Time – Pulmonary Function Test Sub-study (modified Intent-to-Treat population)



Abbreviations: FEV1 = forced expiratory volume in 1 second; GFF = glycopyrronium and formoterol fumarate dihydrate; BFF = budesonide and formoterol fumarate dihydrate; MDI = metered dose inhaler.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.

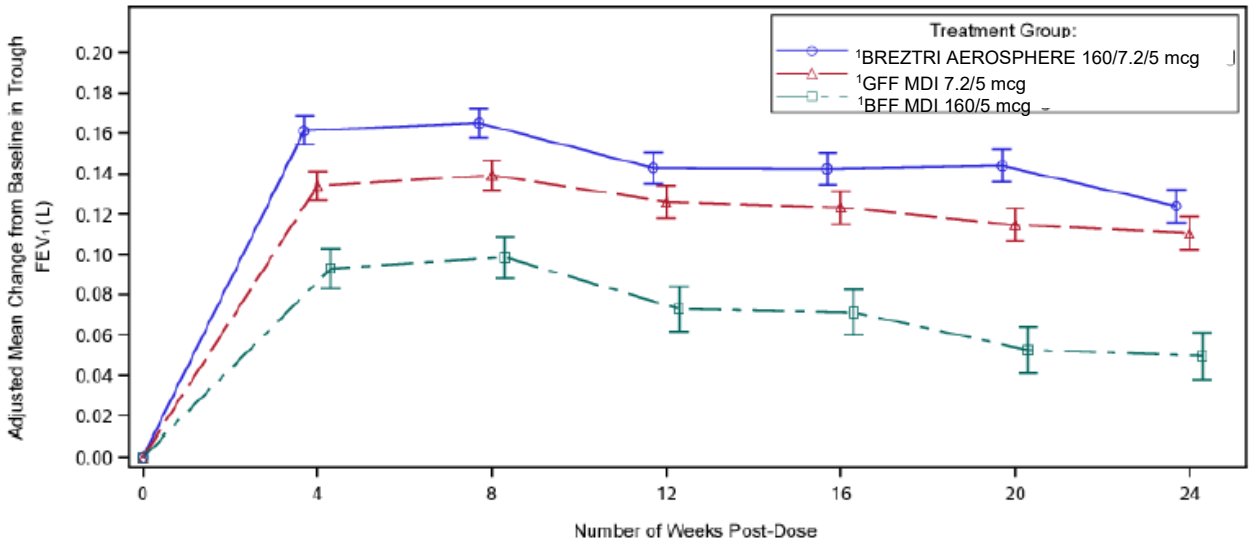
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Table 12 – Lung function analyses, Study PT010006

	BREZTRI AEROSPHERE[1] 160/7.2/5 mcg (N=639)	GFF MDI[1] 7.2/5 mcg (N=625)	BFF MDI[1] 160/5 mcg (N=314)	Treatment difference 95% CI	
				BREZTRI AEROSPHERE vs. GFF MDI	BREZTRI AEROSPHERE vs. BFF MDI
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	147 (6.5)	125 (6.6)	73 (9.2)	22 mL (4, 39) p=0.0139*	74 mL (52, 95) p<0.0001*
FEV1 AUC_{0-4} over 24 weeks; LS mean change from baseline (SE)	305 (8.4)	288 (8.5)	201 (11.7)	16 mL (-6, 38) p=0.1448	104 mL (77, 131) p<0.0001*

[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.
*Statistically significant

Figure 2 – Adjusted Mean Change from Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over Time (modified Intent-to-Treat Population)



Abbreviations: FEV1 = forced expiratory volume in 1 second; GFF = glycopyrronium and formoterol fumarate dihydrate; BFF = budesonide and formoterol fumarate dihydrate; MDI = metered dose inhaler.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg.

Effects on symptoms and quality of life

In study PT010005, treatment with BREZTRI AEROSPHERE 160/7.2/5 mcg showed statistically significant improvements over 24 weeks in breathlessness (assessed by TDI) and statistically significant improvements in disease-specific health status (as assessed by SGRQ) compared to GFF MDI and BFF MDI.

In study PT010006, treatment with BREZTRI AEROSPHERE 160/7.2/5 mcg showed numerical improvements in breathlessness (assessed by TDI) and numerical improvements in disease-specific health status (as assessed by SGRQ) compared to GFF MDI and BFF MDI.

In study PT010005, a SGRQ responder analysis (responder defined as a reduction in SGRQ versus baseline of greater than or equal to 4) showed that there was a greater percentage of responders over 24 weeks with BREZTRI AEROSPHERE 160/7.2/5 mcg (52%) compared to GFF MDI (42%) and BFF MDI (45%).

In study PT010006, a SGRQ responder analysis showed that there was a greater percentage of responders over 24 weeks with BREZTRI AEROSPHERE 160/7.2/5 mcg (47%) compared to GFF MDI (41%) and BFF MDI (40%).

Asthma

Table 13 – Summary of Patient Demographics for Clinical Trials in Asthma

Study #	Study design	Treatment and dosage[1]	Study subjects (n)[2]	Age (Range)	Sex
D5982C00007 (KALOS)	A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicentre 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of BGF MDI Relative to BFF MDI and BFF pMDI in Adult and Adolescent Participants with Inadequately Controlled Asthma	BREZTRI AEROSPHERE MDI 160/14.4/5 mcg, 2 inhalations twice daily BGF MDI 160/7.2/5 mcg, 2 inhalations twice daily BFF MDI 160/5 mcg, 2 inhalations twice daily BFF pMDI 160/4.5 mcg, 2 inhalations twice daily	Total: N = 2144 BREZTRI AEROSPHERE MDI: N = 594 BGF MDI: N = 342 BFF MDI: N = 606 BFF pMDI: N = 602	12-80 years of age	Male: 753 (35.1%) Female: 1391 (64.9%)
D5982C00008 (LOGOS)	A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicentre 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of BGF MDI Relative to BFF MDI and BFF pMDI in Adult and Adolescent Participants with Inadequately Controlled Asthma	BREZTRI AEROSPHERE MDI 160/14.4/5 mcg, 2 inhalations twice daily BGF MDI 160/7.2/5 mcg, 2 inhalations twice daily BFF MDI 160/5 mcg, 2 inhalations twice daily BFF pMDI 160/4.5 mcg, 2 inhalations twice daily	Total: N = 2160 BREZTRI AEROSPHERE MDI: N = 585 BGF MDI: N = 384 BFF MDI: N = 604 BFF pMDI: N = 594	12-80 years of age	Male: 846 (39.2%) Female: 1314 (60.8%)

Abbreviations: BGF = budesonide/glycopyrronium/formoterol fumarate; BFF = budesonide/formoterol fumarate dihydrate; MDI = metered dose inhaler; pMDI= pressurized metered dose inhaler.

[1] Administered via oral inhalation.

[2] Efficacy analyses set: defined as all subjects randomized to study treatment and received any amount of study treatment.

Study demographics and trial design

The efficacy and safety of BREZTRI AEROSPHERE for the maintenance treatment of asthma was evaluated in two randomized, double-blind, multicentre, parallel-group, active-controlled trials of 24 to 52-week duration with identical design (D5982C00007 and D5982C00008). The trials enrolled adult and adolescent patients 12 years of age and older with inadequately controlled asthma, as demonstrated by an Asthma Control Questionnaire (ACQ-7) total score ≥1.5 despite treatment with a medium or high dose of ICS/LABA, and a pre-bronchodilator FEV_1 <80% predicted normal value for participants ≥ 18 years of age or <90% predicted normal value for participants 12 to < 18 years of age. At screening visit, eligible participants discontinued treatment with their maintenance therapy of medium or high dose ICS/LABA and entered a 4-week run-in period of treatment with budesonide/formoterol fumarate dihydrate MDI (BFF MDI) 160/5 mcg, 2 inhalations twice daily.

Participants were randomized 1:1:1:1 to BREZTRI AEROSPHERE 160/14.4/5 mcg, budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF MDI) 160/7.2/5 mcg, BFF MDI 160/5 mcg or budesonide/formoterol fumarate dihydrate pMDI (BFF pMDI) 160/4.5 mcg all administered as 2 inhalations twice daily. The active comparators for BREZTRI AEROSPHERE were BFF MDI 160/5 mcg with the same AEROSPHERE inhaler device and BFF pMDI 160/4.5 mcg with a different inhaler device.

In trial D5982C00007, a total of 2144 participants were randomized and included in the efficacy analyses. The population demographics across all treatment arms were mean age of 52 years, 65% female, 64% White, mean body mass index (BMI) of 28 (range: 13.3 to 39.9), median asthma duration of 16 years (range: 1-74) and 67% of subjects reported having at least one severe exacerbation in the prior year. At baseline, the mean pre-bronchodilator percent predicted FEV_1 was 59% (standard deviation [SD]: 12%), and the mean ACQ-5 score was 2.5 (SD: 0.7).

At study entry in trial D5982C00007, 57% of participants were taking a medium dose ICS in combination with a LABA and 42% were taking a high dose ICS in combination with a LABA.

In trial D5982C00008, a total of 2160 participants were randomized and included in the efficacy analyses. The population demographics across all treatment arms were mean age of 52 years, 61% female, 44% White, mean body mass index (BMI) of 27 (range: 15.0 to 39.9), median asthma duration of 15 years (range: 1-76), and 49% of subjects reported having at least 1 severe exacerbation in the prior year. At baseline, the mean pre-bronchodilator percent predicted FEV_1 of 59% (SD: 13%), and the mean ACQ-5 score was 2.5 (SD: 0.7).

At study entry in trial D5982C00008, 73% of participants were taking a medium dose ICS in combination with a LABA and 26% were taking a high dose ICS in combination with a LABA.

In trial D5982C00007, a total of 70 participants were aged 12 to < 18 years, with 16 adolescents (2.7%) in the BREZTRI AEROSPHERE 160/14.4/5 mcg treatment group and 22 adolescents (3.6%) in the BFF MDI 160/5 mcg group. In trial D5982C00008, a total of 58 participants were aged 12 to < 18 years, with 14 adolescents (2.4%) in the BREZTRI AEROSPHERE 160/14.4/5 mcg treatment group and 17 adolescents (2.8%) in the BFF MDI 160/5 mcg treatment group. In the pooled group of 128 adolescents in the two trials, 72% were taking a medium dose of ICS in combination with a LABA and 27% were taking a high dose of ICS in combination with a LABA prior to study entry.

The primary endpoint in the individual trials, D5982C00007 and D5982C00008, was a change from baseline in FEV_1 area under the curve (FEV_1 AUC_{0-3}) at Week 24 for the BREZTRI AEROSPHERE 160/14.4/5 mcg treatment group compared to the BFF MDI 160/5 mcg group. The key secondary endpoint was a change from baseline in morning pre-dose trough FEV_1 at Week 24 for the BREZTRI AEROSPHERE 160/14.4/5 mcg treatment group compared to the BFF MDI 160/5 mcg group. The rate of severe asthma exacerbations was based on the pooled

analysis of D5982C00007 and D5982C00008, for the BREZTRI AEROSPHERE 160/14.4/5 mcg treatment group compared to the BFF MDI 160/5 mcg group.

Study Results

Lung Function

In trial D5982C00007 and D5982C00008, treatment with BREZTRI AEROSPHERE 160/14.4/5 mcg resulted in statistically significant increases in change from baseline in FEV_1 AUC_{0-3} and change from baseline in morning pre-dose trough FEV_1 compared to BFF MDI 160/5 mcg at Week 24 (Table 14).

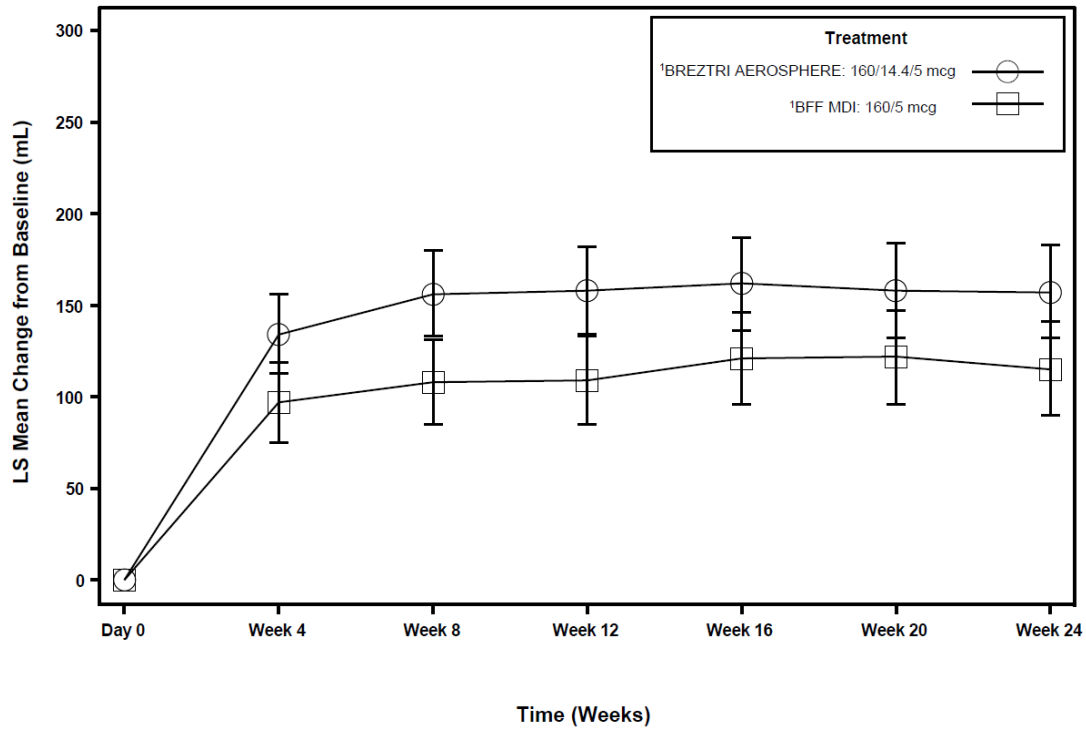
Table 14 – Lung Function Parameters at Week 24 in D5982C00007* and D5982C00008*

	D5982C00007		D5982C00008	
	BREZTRI AEROSPHERE† 160/14.4/5 mcg (N=594)	**BFF MDI 160/5 mcg† (N=606)**	**BREZTRI AEROSPHERE† 160/14.4/5 mcg (N=585)**	**BFF MDI 160/5 mcg† (N=602)**
Primary Endpoint: Change from baseline in FEV_1 AUC_{0-3} (mL) at Week 24				
n	575	580	555	569
Mean Change	316	249	354	219
Difference‡	-	68	-	134
95% CI	-	(29, 106)	-	(93, 175)
p-value	-	<0.001	-	<0.001
Key Secondary Endpoint: Change from baseline in morning pre-dose trough FEV_1 (mL) at Week 24				
n	578	582	556	572
Mean Change	157	115	177	69
Difference‡	-	42	-	107
95% CI	-	(6,78)	-	(68,147)
p-value	-	0.022	-	<0.001

*Analyses uses all observed data unless subsequent asthma medication is taken in conjunction with premature discontinuation of therapy (considered an unfavourable outcome).
†Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/14.4/5 mcg or BFF MDI 160/5 mcg.
‡Difference between BREZTRI AEROSPHERE 160/14.4/5 mcg and BFF MDI 160/5 mcg, 2 inhalations, twice daily.
AUC_{0-3} = area under the curve 0 to 3 hours; BFF = budesonide and formoterol fumarate; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler; N = number of subjects in treatment group; n = number of subjects with a non-missing value at Week 24; SE = standard error

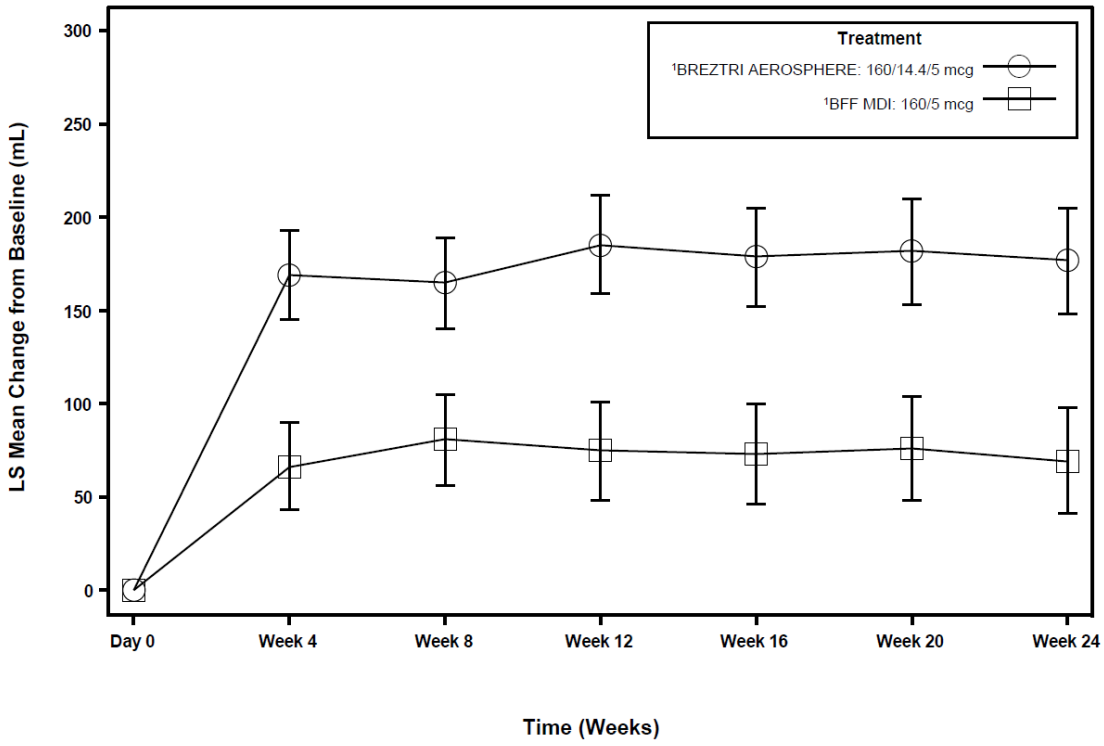
In D5982C00007 and D5982C00008, the effects on lung function (mean change from baseline in morning pre-dose trough FEV_1) with BREZTRI AEROSPHERE 160/14.4/5 mcg compared with BFF MDI 160/5 mcg were sustained over 24 weeks (Figure 3 and Figure 4).

Figure 3 Least Squares Mean Change from Baseline in Morning Pre-Dose Trough FEV_1 Over 24 Weeks of Treatment (D5982C00007)



Error bars represent the 95% Confidence Intervals for LS Mean Change from baseline at each timepoint.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/14.4/5 mcg or BFF MDI 160/5 mcg.

Figure 4 Least Squares Mean Change from Baseline in Morning Pre-Dose Trough FEV_1 Over 24 Weeks of Treatment (D5982C00008)



Error bars represent the 95% Confidence Intervals for LS Mean Change from baseline at each timepoint.
[1] Administered as 2 inhalations, twice daily, of BREZTRI AEROSPHERE 160/14.4/5 mcg or BFF MDI 160/5 mcg.

Severe Exacerbations

Asthma exacerbations were assessed over the entire 52-week blinded treatment period. Severe asthma exacerbations were defined as deterioration of asthma symptoms that required at least 3 days of systemic corticosteroids, emergency room or urgent care visit with systemic corticosteroid course, in-patient hospitalization, and/or resulted in death.

In the pooled analysis of D5982C00007 and D5982C00008, the mean annualized rate of severe asthma exacerbations was 0.54 for BREZTRI AEROSPHERE 160/14.4/5 mcg (398 of 1179 patients, 34%) and 0.60 for BFF MDI 160/5 mcg (444 of 1208 patients, 37%). The rate ratio of severe asthma exacerbations with BREZTRI AEROSPHERE 160/14.4/5 mcg compared to BFF MDI 160/5 mcg was 0.90 (95% CI 0.78, 1.03).

Asthma Control and Health-Related Quality of Life

The Asthma Control Questionnaire (ACQ) assesses asthma control with 5 questions based on recall of the previous week of symptom control (ACQ-5). The ACQ-7 also includes pre-bronchodilator FEV_1 percent predicted normal and rescue bronchodilator use. All items are assessed on a 7-point scale (0=no impairment, through 6=maximum impairment for symptoms and rescue use). Responders were defined as having a clinically relevant decrease (improvement) in ACQ score of ≥0.5 at Week 24.

The proportion of ACQ-7 responders was similar in all treatment groups in both studies. The ACQ-7 responder rate was 65% for BREZTRI AEROSPHERE 160/14.4/5 mcg and 64% for BFF MDI 160/5 mcg at Week 24 (OR 1.05; 95% CI 0.82, 1.34) in D5982C00007. The ACQ-7 responder rate was 68% for BREZTRI AEROSPHERE 160/14.4/5 mcg and 64% for BFF MDI 160/5 mcg at Week 24 (OR 1.27; 95% CI 0.98, 1.63) in D5982C00008. Responder rates with ACQ-5 (comprising the 5 questions on symptoms from ACQ-7) were similar to those with ACQ-7 at Week 24.

16. Non-Clinical Toxicology

General Toxicology

Non-clinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

The toxicity observed in animal studies with budesonide, glycopyrronium and formoterol was similar, whether they were given in combination or separately. The effects were associated with pharmacological actions or minor adaptive responses commonly observed in inhalation toxicology studies and dose dependent.

No genotoxicity, carcinogenicity or reproductive toxicology studies have been conducted with BREZTRI AEROSPHERE.

BREZTRI AEROSPHERE contains the excipients 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride as part of the spray-dried porous particle technology in the pressurized liquid propellant HFA-134a. The safety of HFA-134a has been fully evaluated in preclinical studies. DSPC and calcium chloride have a long history of safe use in man and are approved excipients worldwide. Furthermore, inhaled toxicology studies carried out with BREZTRI AEROSPHERE have shown no evidence of any toxicity attributable to the excipients.

Carcinogenicity/Mutagenicity

Budesonide: budesonide demonstrated no tumourigenic potential in mice. In rats, an increased incidence of hepatocellular tumours was observed, considered to be a class-effect in rats from long-term exposure to corticosteroids.

Glycopyrronium: no evidence of carcinogenicity was seen in 2-year studies in rats and mice.

Formoterol: a slight increase in the incidence of uterine leiomyomas has been observed in rats and mice treated with formoterol; an effect which is considered to be a class-effect in rodents after long-term exposure to high doses of β_2-adrenoreceptor agonists.

Reproductive and Developmental Toxicity

Budesonide: in animal reproduction studies, glucocorticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results are not relevant in humans at the recommended doses.

Glycopyrronium: Animal reproduction studies with glycopyrronium have shown reduced rat and rabbit foetal weights, and low body weight gain of rat offspring before weaning, only at very high doses compared to clinical use.

Formoterol: Animal reproduction studies with formoterol have shown a slightly reduced fertility in male rats at high systemic exposure and implantation losses, as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use.

17. Supporting Product Monographs

1. Glycopyrronium (as bromide) / Formoterol Fumarate Dihydrate Pressurized Inhalation Aerosol, 8.3 mcg / 5.8 mcg per metered actuation, Control number 256804, Product Monograph, AstraZeneca Canada Inc. (February 11, 2022).
2. OXEZE® TURBUHALER® Dry Powder for Oral Inhalation, formoterol fumarate dihydrate 6 mcg/dose and 12 mcg/dose, Control number 213703, Product Monograph, AstraZeneca Canada Inc. (April 23, 2018).
3. SYMBICORT® TURBUHALER® Dry Powder for Oral Inhalation, 100 mcg budesonide and 6 mcg formoterol fumarate dihydrate, 200 mcg budesonide and 6 mcg formoterol fumarate dihydrate, 400 mcg budesonide and 12 mcg formoterol fumarate dihydrate, Control number 244507, Product Monograph, AstraZeneca Canada Inc. (February 8, 2021).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr BREZTRI® AEROSPHERE®

budesonide / glycopyrronium / formoterol fumarate dihydrate pressurized inhalation suspension

This Patient Medication Information is written for the person who will be taking **BREZTRI® AEROSPHERE®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **BREZTRI AEROSPHERE**, talk to a healthcare professional.

What BREZTRI AEROSPHERE is used for:

Chronic Obstructive Pulmonary Disease (COPD):
BREZTRI AEROSPHERE 160 mcg / 7.2 mcg / 5 mcg is used in adults for the long-term treatment of a lung disease called chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

BREZTRI AEROSPHERE is used to make breathing easier and help prevent worsening of COPD symptoms ("flare ups"). You may experience "flare-ups" during which your symptoms become worse. If you have a history of experiencing "flare-ups" BREZTRI AEROSPHERE can help prevent them from developing in the first place.

Asthma:
BREZTRI AEROSPHERE 160 mcg / 14.4 mcg / 5 mcg is used for the maintenance treatment of asthma in adults and adolescents (12 years of age and older) whose asthma is not being adequately controlled with a maintenance combination of a medium or high dose inhaled corticosteroid and a long-acting $beta_2$-agonist.

How BREZTRI AEROSPHERE works:

BREZTRI AEROSPHERE contains 3 medicinal ingredients:

- budesonide is an inhaled corticosteroid (ICS).
- glycopyrronium is a long-acting muscarinic antagonist (LAMA).
- formoterol fumarate dihydrate is a long-acting $beta_2$ agonist (LABA).

Budesonide belongs to a group of medicines called corticosteroids. It reduces inflammation in the airways of your lungs, which can ease breathing problems, and help prevent "flare-ups" of your COPD or asthma attacks. Glycopyrronium and formoterol fumarate dihydrate belong to a group of medicines called bronchodilators. These two medicines work together to help open and relax the muscles of the airways. This allows more air to get in and out of the lungs. This makes it easier for people with COPD or asthma to breathe and helps prevent shortness of breath and wheezing. BREZTRI AEROSPHERE is not a cure for COPD or asthma, but it can help to control it. Therefore, it is important to continue to take it regularly, even if you feel fine.

The ingredients in BREZTRI AEROSPHERE are:

Medicinal ingredients: budesonide, glycopyrronium (as bromide), and formoterol fumarate dihydrate

Non-medicinal ingredients: hydrofluoroalkane (HFA-134a), porous particles (comprised of: 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride).

BREZTRI AEROSPHERE comes in the following dosage forms:

Pressurized inhalation suspension in a metered dose inhaler (for oral inhalation) that delivers:

- 160 mcg budesonide / 7.2 mcg glycopyrronium (as bromide) / 5 mcg formoterol fumarate dihydrate per actuation.
- 160 mcg budesonide / 14.4 mcg glycopyrronium (as bromide) / 5 mcg formoterol fumarate dihydrate per actuation.

Do not use BREZTRI AEROSPHERE:

- if you are allergic to budesonide, glycopyrronium, formoterol fumarate dihydrate or any of the other ingredients of BREZTRI AEROSPHERE;
- to treat sudden severe symptoms of COPD or asthma, such as shortness of breath or wheezing. Always have a rescue inhaler with you to treat sudden symptoms ("flare ups"). If you do not have a rescue inhaler, ask your healthcare professional to prescribe one for you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BREZTRI AEROSPHERE. Talk about any health conditions or problems you may have, including if you:

- are a smoker. It is important to quit smoking if you use BREZTRI AEROSPHERE, this will help decrease the symptoms of COPD and asthma and may increase your lifespan;
- are using a rescue inhaler on a regular basis;
- have heart problems, such as:
  - heart disease
  - rapid or irregular heart beat or any problems with how your heart beats
  - a condition called "QT prolongation"
- have high blood pressure;
- have eye problems such as increased pressure in the eye, glaucoma, cataracts, blurry vision or other changes in vision;
- have prostate or bladder problems, or any problems passing urine;
- used to take 20 mg or more of prednisone per day;
- have or are at risk for decreased bone mineral content;
- have ever had seizures;
- have problems with your thyroid gland;
- have diabetes;
- have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems;
- have been taking other corticosteroids by mouth or by inhalation;
- have any allergies to food or drugs;

- have or have a history of lung infections such as pneumonia (if you have COPD);
- have low levels of potassium in your blood;
- have kidney or liver problems;
- have or have ever had tuberculosis;
- have chronic or untreated infections:
  - bacterial infection
  - viral infection
  - fungal infection (yeast infection or thrush)
  - parasitic infection
  - herpes simplex infection of the eye
- are pregnant or trying to become pregnant. Your healthcare professional will consider the benefit to you and the risk to your unborn baby;
- are breastfeeding or planning to breastfeed.

Other warnings you should know about:

Do not stop taking BREZTRI AEROSPHERE without talking to your healthcare professional first. If you stop treatment on your own, your symptoms may worsen. Talk to your healthcare professional **right away** if:

- there is a change in your symptoms such as more coughing, wheezing, chest tightness or breathlessness;
- you find that you need to use your rescue inhaler more often than usual.

These could be warning signs that your condition may be getting worse.

Paradoxical bronchospasm: if you feel tightness of the chest, coughing, wheezing or breathlessness right after using BREZTRI AEROSPHERE, you may have a serious condition called “paradoxical bronchospasm” (an unexpected closing of your airways). Stop using BREZTRI AEROSPHERE and seek medical help right away.

Monitoring: During treatment with BREZTRI AEROSPHERE, your healthcare professional may monitor:

- your bones and eyes;
- the effects of corticosteroid therapy on your body;
- your blood sugar levels, especially if you have diabetes;
- your blood potassium levels, especially if you already have low levels of potassium.

Eye problems: BREZTRI AEROSPHERE can cause eye disorders such as:

- cataracts: clouding of the lens in the eye, blurry vision, eye pain;
- glaucoma: an increased pressure in your eyes, eye pain, halos around lights or coloured images, red eyes. Untreated, it may lead to permanent vision loss.

If you have any changes in your vision, tell your healthcare professional **right away**. You may need regular eye exams.

Chicken pox and measles: You should avoid exposure to chicken pox and measles, and tell your healthcare professional if you are exposed. This is important if you are taking any cortisone-type medicine and your immune system is not working well (if you have difficulty in fighting an infection).

Eosinophilic granulomatosis with polyangiitis (EGPA): Some people experience a flu-like illness called EGPA when taking an inhaled corticosteroid. Tell your healthcare professional if you have:

- a rash,
- pins and needles or numbness of your arms or legs,
- a severe sinus infection and
- worsening lung or breathing problems.

Driving and using machines: BREZTRI AEROSPHERE can cause headaches, or nausea which may affect your ability to drive and use machines. Use caution when driving and using machines until you know how BREZTRI AEROSPHERE affects you.

Slowed growth in adolescents. If you are an adolescent with asthma, your growth should be checked regularly by your healthcare professional while you are using BREZTRI AEROSPHERE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BREZTRI AEROSPHERE:

- medicines called beta-blockers (such as atenolol or propranolol), to treat high blood pressure or other heart problems, or to treat glaucoma (such as timolol);
- ketoconazole or itraconazole, to treat fungal infections;
- ritonavir, nelfinavir or cobicistat, to treat HIV infection;
- oral corticosteroids such as prednisone;
- medicines that lower the amount of potassium in your blood, such as some diuretics (“water pills”);
- other long-acting medicines similar to this medicine that are used to treat breathing problems, such as medicines containing tiotropium, ipratropium, aclidinium, umeclidinium or salmeterol, arformoterol, vilanterol, olodaterol or indacaterol;
- medicines which are used to treat heart rhythm problems, such as amiodarone;
- medicines used in the treatment of depression (antidepressants or monoamine oxidase inhibitors);
- medicines called “anticholinergics”.

Ask your healthcare professional if you are not sure. The use of BREZTRI AEROSPHERE with these medicines is not recommended.

How to take BREZTRI AEROSPHERE:

- Read the Instructions for Use for instructions on how to use BREZTRI AEROSPHERE. If you have any questions, talk to your healthcare professional.

- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- Take BREZTRI AEROSPHERE exactly as your healthcare professional tells you to.
- Take every day as prescribed, even if you have no symptoms of COPD or asthma.
- After you take your dose, always rinse your mouth with water and spit it out, do not swallow.

Usual dose:

If you have COPD

Adults (aged 18 years and over): The recommended dose is 2 oral inhalations (puffs) of BREZTRI AEROSPHERE 160 mcg / 7.2 mcg / 5 mcg taken twice daily, in the morning and evening

If you have asthma

Adults and adolescents (12 years of age and over): The recommended dose is 2 oral inhalations (puffs) of BREZTRI AEROSPHERE 160 mcg / 14.4 mcg / 5 mcg taken twice daily, in the morning and evening.

Always carry your separate rescue inhaler with you to treat sudden asthma symptoms when they happen. It is important that you contact your healthcare professional if you find the treatment ineffective at the recommended dose.

Using BREZTRI AEROSPHERE with a spacer:

If you find it difficult breathing in and pressing the inhaler at the same time, talk to your healthcare professional. You may be able to use a spacer with your inhaler.

Overdose:

Signs of an overdosage may include:

- blurred vision;
- dry mouth;
- nausea;
- muscle spasm;
- tremor;
- headache;
- increased heart rate; and
- increased blood pressure.

If you think you, or a person you are caring for, have taken too much BREZTRI AEROSPHERE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

Do not take a double dose to make up for a forgotten dose. If you miss a dose, take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose and go

back to your regular dosing schedule. Do not take more than 2 puffs twice a day.

Possible side effects from using BREZTRI AEROSPHERE:

These are not all the possible side effects you may have when taking BREZTRI AEROSPHERE. If you experience any side effects not listed here, tell your healthcare professional.

- feeling anxious;
- trouble sleeping;
- headache;
- feeling sick (nausea);
- cough and/or a hoarse voice;
- muscle spasms;
- shaking/tremors;
- dry mouth;
- mild irritation in the throat;
- bruising of the skin;
- feeling restless, nervous or agitated;
- feeling dizzy;
- changes in behaviour.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Hyperglycemia (high blood sugar): increased thirst, frequent urination, headache, blurred vision and fatigue		✓	
Palpitation (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly		✓	
Pneumonia (infection in the lungs) (in COPD patients): chest pain when you breathe or cough, confusion, cough which may produce phlegm, fatigue,		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
fever, sweating and shaking, chills, shortness of breath			
Thrush (yeast infection of the mouth or throat): thick white patches in the mouth, tongue or on the throat, sore throat		✓	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	
Uncommon			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling weak or light headed, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Angina (not enough oxygen to the heart muscle): discomfort in the shoulder, arm, back, throat, jaw or teeth; pain or pressure in the chest		✓	
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heart beat		✓	
Bronchospasm (when there is a sudden narrowing of the airway): difficulty breathing with wheezing or coughing			✓
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much,		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced sex drive and thoughts of death or suicide. If you have a history of depression, your depression may become worse			
Tachycardia (abnormally fast heart beat): dizziness, light headedness, shortness of breath, racing heart		✓	
Urinary retention (inability to pass urine or to empty the bladder): painful urination, pain or swelling in the lower abdomen		✓	
Very rare			
Decreased Adrenal Function: tiredness, weakness, nausea and vomiting, low blood pressure	✓		
Unknown			
Cataracts: clouding of the lens in the eye, blurry vision, dim vision and/or eye pain		✓	
Glaucoma: increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, changes in vision, hazy or blurred vision, sudden sight loss		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15 to 30°C. Store in a dry place.

Warning: The canister should not be broken, punctured or burnt, even when it seems empty. Do not use or store near heat or open flames. Do not expose to temperatures higher than 50°C and protect from freezing temperatures. If exposed to freezing temperatures, the inhaler should be equilibrated for 1 hour at room temperature prior to taking a dose.

Use by date: Do not use BREZTRI AEROSPHERE after the expiry date on the label/carton. The expiry date refers to the last day of the month.

After opening the pouch, the inhaler must be used within:

- 6 weeks for an inhaler that contains 56 actuations;
- 3 months for an inhaler that contains 120 actuations.

Dispose of your inhaler after the last dose, following local guidelines. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about BREZTRI AEROSPHERE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

This leaflet was prepared by AstraZeneca Canada Inc. Mississauga, Ontario L4Y 1M4

Date of Authorization: 2026-11-16

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AstraZeneca

Read prior to using inhaler

Instructions For Use

Pr BREZTRI® AEROSPHERE®

budesonide / glycopyrronium / formoterol fumarate dihydrate pressurized inhalation suspension

Please read these instructions carefully.

Your BREZTRI AEROSPHERE (called “inhaler” in this leaflet) may be different from inhalers you have used before.

Watch our video to make sure you use BREZTRI AEROSPHERE correctly.

www.breztri.ca/video

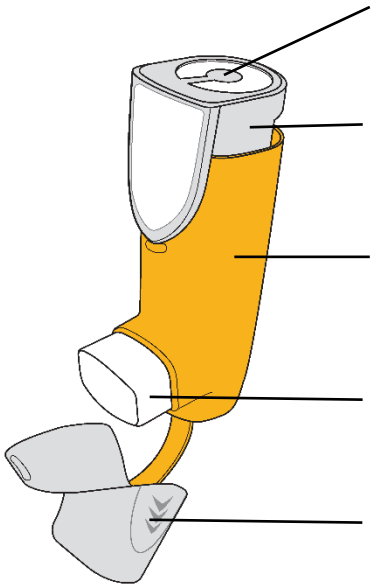
Important Information

- **For oral inhalation use only**
- **Prime your BREZTRI AEROSPHERE inhaler before using it for the first time**
- **Rinse your yellow actuator weekly**
- **Take 2 puffs of medicine in the morning and 2 puffs of medicine in the evening**

Storing your inhaler

- Store your inhaler at room temperature between 15°C to 30°C, in a dry place
- **Do not store in a humid environment, such as a bathroom**
- Keep your inhaler and all medicines out of the reach and sight of children

Parts of your inhaler



Puff indicator
Attached to the top of the pressurized canister.

Pressurized Canister (inside)
Holds the medicine.

Actuator
Contains the pressurized canister.

Mouthpiece
Sprays the medicine.

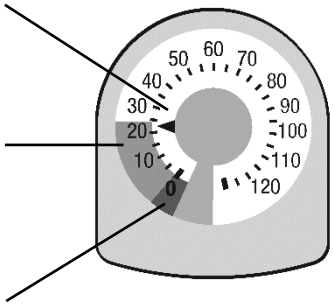
Mouthpiece cover
Protects the mouthpiece when the inhaler is not in use.

Reading the puff indicator

ⓘ **The puff indicator will count down by 1 each time you spray a puff of medicine.**

Pointer
Points to number of puffs remaining

Yellow zone
Order a new inhaler when the pointer is in the yellow zone



Red zone
Throw away your inhaler when the pointer is at 0 in the red zone

The display window for the 30-day inhaler shows 120 and the 14-day inhaler shows 60.

ⓘ **Do not try to take a puff when the pointer is at 0 because you will not receive a full dose.**

Ordering a new inhaler

- Order a new inhaler when the pointer on the puff indicator is in the yellow zone.

Throwing away your inhaler

Throw away your inhaler following local guidelines when:

- The puff indicator shows 0

or

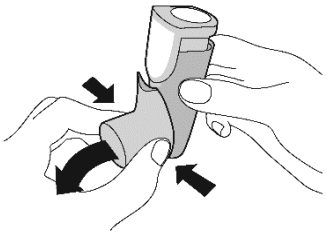
- **3 months** (for the 30-day inhaler) or **6 weeks** (for the 14-day inhaler) after your inhaler has been removed from the foil pouch

Do not reuse or use the actuator with medicine canisters from other inhalers.

Do not puncture or throw the canister into a fire or incinerator.

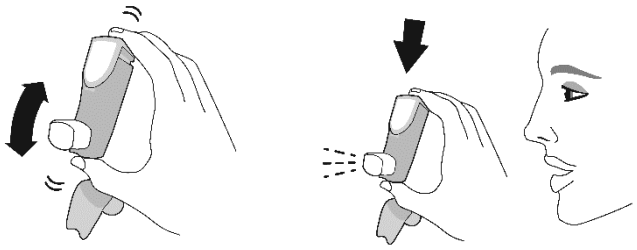
BEFORE FIRST USE – Prime your inhaler 4 times before first use

- Before you use your inhaler for the first time, prime it so that you will get the right amount of medicine when you use it.

Prime 1
Remove mouthpiece cover by squeezing both sides and pulling out. 

Prime 2
Shake the inhaler well and spray **1 Test-puff** into the air facing away from you. Repeat for a total of **4 Test-puffs**, shaking before each Test-puff.

x4 total
Shake and Test-puffs



ⓘ Extra puffs are provided for priming. **Do not skip priming.**

ⓘ **Re-prime your inhaler:**

- after rinsing the actuator
- if dropped
- if not used for more than 7 days

To re-prime, spray **2 Test-puffs**, shaking before each Test-puff.

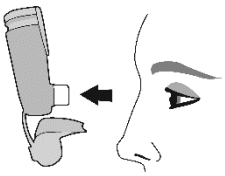
x2 total
Shake and Test-puffs

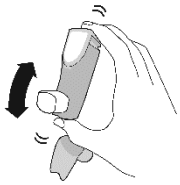
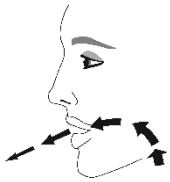
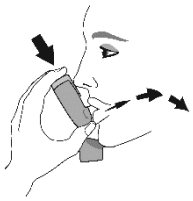
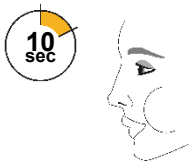
DAILY USE, morning & evening – Inhale your medicine

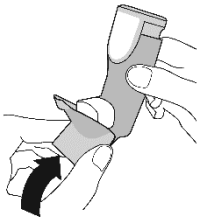
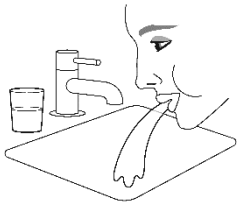
- **Daily Dose: 2 puffs in the morning and 2 puffs in the evening.**
- Rinse mouth with water after the 2 puffs to prevent fungal infection.

Step 1

Remove mouthpiece cover. **Check the mouthpiece for foreign objects and remove objects before use.**

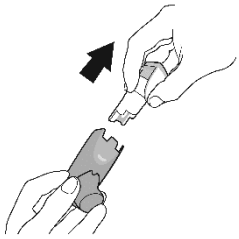
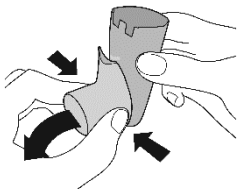


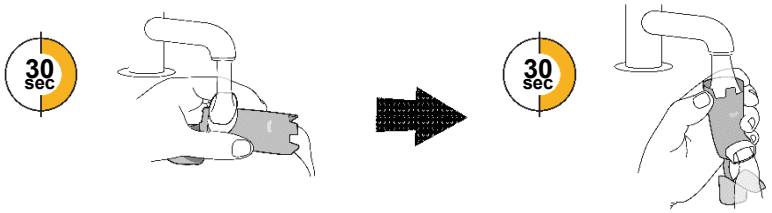
Step 2				
Shake the inhaler well before each puff. 	Breathe out fully. 	Place mouthpiece into mouth and close lips around the mouthpiece. 	Start to breathe in deeply and slowly while spraying **1 puff**. Continue breathing in until you cannot any more. 	Hold breath for as long as you can, up to **10 seconds.** 

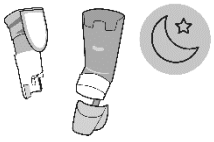
Step 3	Step 4	Step 5
	Put mouthpiece cover back on. 	Rinse mouth with water. Spit out water. **Do not swallow.** 

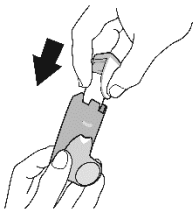
WEEKLY RINSE – Rinse your actuator once a week

- **Rinse yellow actuator weekly** so that medicine does not build up and block the spray through the mouthpiece.
- **Do not allow the canister to get wet.**
- **Re-prime after rinsing.**

Rinse 1	Rinse 2
Remove canister and set aside. **Do not allow the canister to get wet.** 	Remove mouthpiece cover. 

Rinse 3	Rinse 4
Run warm water through the mouthpiece for 30 seconds and then through the top of the actuator for 30 seconds. **Rinse for 60 seconds in total.** 	**Shake off as much water as you can.**  **Do not dry with a towel or tissue.**

Rinse 5	Rinse 6
Look into the actuator and mouthpiece for medicine build-up. If there is any build-up, repeat steps Rinse 3 through 5. 	Air-dry, preferably overnight. **Do not** put the canister back into the actuator if it is still wet. 

Rinse 7	Rinse 8
When dry, **replace the mouthpiece cover first** and then gently press the canister down into the actuator. 	Re-prime the inhaler by spraying **2 Test-puffs,** shaking before each Test-puff. **x2 total Shake and Test-puffs**

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