

AUSTRALIAN PRODUCT INFORMATION

BREZTRI AEROSPHERE® 160/7.2/5 **(budesonide/glycopyrronium/formoterol (eformoterol) fumarate dihydrate)** **pressurised metered dose inhaler**

1 NAME OF THE MEDICINE

Budesonide

Glycopyrronium (as glycopyrronium bromide; also known as glycopyrrolate)

Formoterol (eformoterol) fumarate dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Table 1 below provides the quantities of the active moieties and their salts as the delivered dose (ex-mouthpiece/quantity delivered to the patient). In Australia, BREZTRI AEROSPHERE 160/7.2/5 is labelled as the delivered dose per actuation (puff) of budesonide, glycopyrronium and formoterol (eformoterol) fumarate dihydrate (herein referred to as “formoterol”). This may differ to other regions in the world.

Table 1 BREZTRI AEROSPHERE active ingredient quantities

Active ingredient	Quantity per actuation	Quantity per dose (2 actuations)
Budesonide	160 µg*	320 µg
Glycopyrronium bromide (glycopyrrolate)	9 µg	18 µg
Equivalent to glycopyrronium	7.2 µg*	14.4 µg
Formoterol (eformoterol) fumarate dihydrate	5 µg*	10 µg
Equivalent to formoterol (eformoterol) fumarate	4.8 µg	9.6 µg

*Quantity presented on the product packaging.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Pressurised inhalation

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Maintenance treatment to prevent exacerbations and relieve symptoms in adults with moderate, severe, or very severe chronic obstructive pulmonary disease (COPD) who require treatment with a combination of an inhaled corticosteroid (ICS), a long-acting β_2 -agonist (LABA), and a long-acting muscarinic antagonist (LAMA).

BREZTRI AEROSPHERE 160/7.2/5 is not indicated for the initiation of therapy in COPD.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults (18 years and over)

The recommended dose is two actuations twice daily (two actuations in the morning and two actuations in the evening).

Patients should be advised not to take more than two actuations twice daily.

Special patient populations

Renal impairment

No dosage adjustment is necessary for patients with renal impairment (see Section 4.4 Special warnings and precautions for use [*Use in renal impairment*] and Section 5.2 Pharmacokinetic properties [*Special patient populations/Renal impairment*]).

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see Section 4.4 Special warnings and precautions for use [*Use in hepatic impairment*] and Section 5.2 Pharmacokinetic properties [*Special patient populations/Hepatic impairment*]).

Use in the elderly

No dosage adjustment is necessary for elderly patients (see Section 5.2 Pharmacokinetic properties [*Special patient populations/Use in the elderly*]).

Paediatric use

There is no relevant use of BREZTRI AEROSPHERE in children and adolescents (under 18 years of age) in the indication of COPD.

Method of administration

For inhalation use.

For detailed instructions, see the *Instructions for use* leaflet provided in each pack of BREZTRI AEROSPHERE. Patients should be instructed on how to administer the product correctly and advised to read the *Instructions for use* carefully.

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substances or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Treatment of COPD should be in accordance with current national treatment guidelines. Patients should have a personal action plan designed in association with their treating physician.

Asthma

BREZTRI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of disease

If patients find the treatment ineffective, despite taking the highest recommended dose of BREZTRI AEROSPHERE, medical attention must be sought. Sudden and progressive deterioration in control

of COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy such as a course of oral corticosteroids (OCS) or antibiotic treatment if an infection is present.

Transfer from oral therapy

Particular care is needed in patients transferring from OCS, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high dose corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids (ICS) may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Paradoxical bronchospasm

As with other inhaled medicines, administration of BREZTRI AEROSPHERE may cause paradoxical bronchospasm that may be life-threatening. If this occurs, treatment with BREZTRI AEROSPHERE should be discontinued immediately and alternative treatments instituted.

Not for acute use

BREZTRI AEROSPHERE is not indicated for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy).

Use with other LABA and/or LAMA products

BREZTRI AEROSPHERE should not be administered concomitantly with other medicines containing a long-acting β_2 -agonist (LABA) or long-acting muscarinic antagonist (LAMA) (see Section 4.5 Interactions with other medicines and other forms of interactions [*COPD Medicines*]).

Cardiovascular effects

Cardiovascular effects including cardiac arrhythmias, may occur after the administration of muscarinic receptor antagonists and sympathomimetics, including glycopyrronium and formoterol.

Caution should also be exercised in patients with thyrotoxicosis and in patients with a clinically significant cardiovascular disease such as ischemic heart disease, acute myocardial infarction, cardiomyopathy, cardiac arrhythmias, and severe heart failure.

Caution should also be exercised when treating patients with known or suspected prolongation of the QTc interval, either congenital or induced by medicinal products.

Systemic effects

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

These effects are much less likely to occur with ICS treatments than with OCS. 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 Section 5.1 Pharmacodynamic properties).

Ophthalmic effects

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids or with use of inhaled anticholinergics. Rare diseases such as central serous chorioretinopathy (CSCR) have been reported after use of systemic and topical corticosteroids.

Worsening of narrow-angle glaucoma may occur. BREZTRI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma.

Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI AEROSPHERE long term.

Hypokalaemia

β_2 -adrenergic agonists may produce significant hypokalaemia, which may increase the susceptibility to cardiac arrhythmias. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see Section 4.5 Interactions with other medicines and other forms of interactions). Clinically relevant effects of hypokalaemia have not been observed in clinical studies of BREZTRI AEROSPHERE at the recommended therapeutic dose.

Hyperglycaemia

Inhalation of high doses of β_2 -adrenergic agonists may produce increases in plasma glucose. Clinically relevant effects of hyperglycaemia have not been observed in clinical studies of BREZTRI AEROSPHERE at the recommended therapeutic dose.

Anticholinergic activity

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

Pneumonia

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively across all studies.

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 include current smoking, older age, low body mass index (BMI) and severe COPD.

Oropharyngeal candidiasis

Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing inhaled corticosteroids. Rinsing the mouth with water swallowing following administration of BREZTRI AEROSPHERE reduces the risk of oropharyngeal candidiasis. If such an infection develops, treatment with appropriate local or systemic antifungal therapy should be initiated.

Use in hepatic impairment

Formal pharmacokinetic studies using BREZTRI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since budesonide and formoterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol in plasma. Therefore, patients with severe hepatic disease should be closely monitored and BREZTRI AEROSPHERE should only be used if the expected benefit outweighs the potential risk (see Section 5.2 Pharmacokinetic properties [*Special patient populations/Hepatic impairment*]).

Use in renal impairment

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 (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²) should be treated with BREZTRI AEROSPHERE only if the expected benefit outweighs the potential risk. (see Section 5.2 Pharmacokinetic properties [*Special patient populations/Renal impairment*]).

Use in the elderly

No dosage adjustment is necessary for elderly patients (see Section 5.2 Pharmacokinetic properties [*Special patient populations/Use in the elderly*]).

Paediatric use

There is no relevant use of BREZTRI AEROSPHERE in children and adolescents (under 18 years of age) in the indication of COPD.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been performed with BREZTRI AEROSPHERE.

COPD medicines

Co-administration of BREZTRI AEROSPHERE with other LAMA and/or LABA containing medicinal products has not been studied and is not recommended.

No formal *in-vivo* drug interaction studies have been performed with BREZTRI AEROSPHERE. Clinical studies with BREZTRI AEROSPHERE indicate no clinical evidence of interactions when used concomitantly with other COPD medicines including short-acting β_2 -agonists (SABA), methylxanthines, OCS and ICS.

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 Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties). This is of limited clinical importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment with a strong CYP3A4 inhibitor.

Since glycopyrronium is eliminated mainly by the renal route, drug interaction could potentially occur with medicines 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 a limited increase in its total systemic exposure (Area under the curve (AUC)_{0-t}) by 22% and a slight decrease in renal clearance by 23% due to co-administration of cimetidine.

Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations. Budesonide and glycopyrronium do not inhibit or induce CYP450 enzymes at therapeutically relevant concentrations.

Drug-induced hypokalaemia

Possible initial hypokalaemia may be potentiated by concomitant medications, including non-potassium sparing diuretics (see Section 4.4 Special warnings and precautions for use [*Hypokalaemia*]).

β-adrenergic blockers

Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol.

Medicines known to prolong QTc interval

BREZTRI AEROSPHERE as with other β₂-agonist containing medicines, should be administered with caution to patients being treated with medicines known to prolong the QTc interval, including monoamine oxidase inhibitors and tricyclic antidepressants as any effect of these on the QT interval may be potentiated. Medicines known to prolong the QT-interval may increase the risk of ventricular arrhythmia.

Other antimuscarinics and sympathomimetics

Co-administration of this medicinal product with other anticholinergic and/or long-acting β₂-adrenergic agonist containing medicinal products has not been studied and is not recommended as it may potentiate known inhaled muscarinic antagonist or β₂-adrenergic agonist adverse reactions.

Concomitant use of other beta-adrenergic medicinal products can have potentially additive effects; therefore, caution is required when other beta-adrenergic medicinal products are prescribed concomitantly with formoterol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been performed with budesonide, glycopyrronium and formoterol in combination.

Budesonide did not affect male or female fertility in rats at subcutaneous doses up to 20 µg/kg/day.

Glycopyrronium bromide did not affect male or female fertility in rats at subcutaneous doses up to 10 mg/kg/day).

Formoterol fumarate reduced fertility in male rats with oral administration at 15 mg/kg/day, but not at 3 mg/kg/day. No effect on female fertility was observed in rats with oral administration at 60 mg/kg/day.

The doses of glycopyrronium bromide and formoterol fumarate that were without effect on fertility in rats produced very large multiples of the systemic exposure (plasma AUC) obtained in patients.

Use in pregnancy – Category B3

There are no adequate data on the use of BREZTRI AEROSPHERE in pregnant women. No animal embryofetal development studies have been performed with budesonide, glycopyrronium and formoterol in combination.

Data on the use of inhaled budesonide in more than 2,500 exposed pregnancies indicate no increased teratogenic risk associated with budesonide. There are no adequate data from use of formoterol or glycopyrronium in pregnant women.

Single-dose studies in humans found that very small amounts of glycopyrronium passed the placental barrier. Placental transfer of budesonide and formoterol, and/or their metabolites, has been demonstrated in animals.

Budesonide has been shown to cause malformations and embryofetal loss in rats and rabbits, a class effect of glucocorticoids. In rabbits, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at subcutaneous doses as low as 25 µg/kg/day, less than the maximum recommended human daily inhaled dose (MRHDID) on a µg/m² basis. In an embryofetal development study in rats, budesonide produced similar adverse fetal effects at doses ≥100 µg/kg/day subcutaneously, only modestly above the MRHDID. In another embryofetal development study in pregnant rats, no malformations or embryofetal lethality were seen at doses up to 250 µg/kg/day by inhalation.

Glycopyrronium bromide was not teratogenic in rats or rabbits following subcutaneous administration at doses up to 10 mg/kg/day in the respective species. Reduced rat and rabbit fetal weights were seen at 10 mg/kg/day (approximately 2,500 and 5,000 times the MRHDID on a µg/m² basis). Maternal treatment at this dose during gestation and lactation was also associated with reduced birth weight and pre-weaning body weight gain in rat offspring. No adverse effects on embryofetal development were observed in the rat or rabbit at 1 mg/kg/day subcutaneously.

No teratogenic effects were observed in rats receiving formoterol fumarate at doses up to 60 mg/kg/day orally or 1.2 mg/kg/day by inhalation. Fetal cardiovascular malformations were observed in one study in which pregnant rabbits were dosed orally at 125 or 500 mg/kg/day during the period of organogenesis, but similar results were not obtained in another study at the same dose range. In a third study, an increased incidence of subcapsular hepatic cysts was observed in fetuses from rabbits dosed orally at 60 mg/kg/day. These doses yielded very large multiples of the clinical plasma AUC for formoterol. Decreased birth weight and increased peri/postnatal mortality were observed when formoterol fumarate was given to rats at oral doses of 0.2 mg/kg/day or greater during late gestation (estimated relative exposure, 3). As a β₂-adrenoceptor agonist, formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

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

Use in lactation

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. Significant lactational excretion of glycopyrronium (and its metabolites) has been observed in rats, with

concentrations in milk up to 10-times higher than in maternal blood. Small amounts of formoterol have also been detected in maternal milk in rats.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

Based on the pharmacological profile, at clinical doses, BREZTRI AEROSPHERE is expected to have no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Clinical trials experience

The safety evaluation of the pivotal Phase 3 programme for BREZTRI AEROSPHERE 160/7.2/5 included 639 patients with COPD in one 24-week lung function study (KRONOS) followed by two long-term safety extension studies of 28 weeks (Study PT010007 - subset of Japanese patients (139 patients) and Study PT010008 - subset assessing bone mineral density and ocular safety (194 patients)), and 2,144 patients in a 52-week exacerbation study (ETHOS). A lower strength of BREZTRI AEROSPHERE (BGF MDI 80/7.2/5 µg) was also assessed within the ETHOS study however the outcomes have not been provided.

Treatment emergent adverse events (TEAE) reported in the 52-week pooled safety population (ETHOS and KRONOS follow-up studies PT010007 and Study PT010008) in ≥2% of patients receiving BREZTRI AEROSPHERE 160/7.2/5 are presented in Table 2. The safety results of the individual studies (ETHOS, KRONOS, PT010007 and PT010008) and the pooled 24-Week Safety Populations (ETHOS/KRONOS) were generally consistent with the 52-week pooled safety population.

Table 2 Treatment-emergent adverse events (all-causality) reported in ≥2% of patients receiving BREZTRI AEROSPHERE 160/7.2/5 (ETHOS and KRONOS follow-up studies PT010007/PT0100008 52-week pooled safety populations – double blind treatment groups only)

MedDRA preferred term	Patients (%)		
	BREZTRI AEROSPHERE 160/7.2/5 (N=2477)	GFF MDI 7.2/5 (N=2437)	BFF MDI 160/5 (N=2294)
Nasopharyngitis	11.4	10.3	11.5
COPD	9.0	9.8	10.7
Upper respiratory tract infection	6.1	5.3	5.3
Pneumonia ^{a, b}	4.7	3.0	4.9
Bronchitis	3.8	3.9	3.4
Back pain	3.1	2.7	2.9
Hypertension	2.8	2.8	3.5

MedDRA preferred term	Patients (%)		
	BREZTRI AEROSPHERE 160/7.2/5 (N=2477)	GFF MDI 7.2/5 (N=2437)	BFF MDI 160/5 (N=2294)
Dyspnoea	2.4	2.7	3.7
Headache ^a	2.5	2.7	3.1
Urinary tract infection ^a	2.8	2.8	2.0
Influenza	2.9	2.0	2.8
Sinusitis	2.7	2.2	2.5
Muscle spasms ^a	3.3	1.2	3.0
Cough ^a	2.6	2.3	2.2
Oral candidiasis ^a	3.0	1.1	2.7
Diarrhoea	2.1	2.0	1.8

^a Adverse drug reaction (ADR) associated with BREZTRI AEROSPHERE treatment

^b See *Pneumonia* section below for further detail

MedDRA – Medical Dictionary for Regulatory Activities; BFF – budesonide/formoterol fumarate; GFF – glycopyrronium/formoterol fumarate; MDI – pressurised metered dose inhaler; COPD – chronic obstructive pulmonary disease

Other adverse drug reactions (ADR) associated with BREZTRI AEROSPHERE treatment, including those reported by less than 2% of patients in the 52-week pooled safety data, are presented in Table 3.

Table 3 Additional adverse drug reactions (ADRs) associated with BREZTRI AEROSPHERE treatment

Frequency	System Order Class (SOC)	MedDRA preferred term
^a Common (≥1% - <10%)	<i>Metabolism & nutrition disorders</i>	Hyperglycaemia
	<i>Psychiatric disorders</i>	Anxiety, insomnia
	<i>Cardiac disorders</i>	Palpitations
	<i>Respiratory, thoracic & mediastinal disorders</i>	Dysphonia
	<i>Gastrointestinal disorders</i>	Nausea
Uncommon (≥0.1% - <1%)	<i>Immune system disorders</i>	Hypersensitivity
	<i>Psychiatric disorders</i>	Depression, agitation, restlessness, nervousness
	<i>Nervous system disorders</i>	Tremor, dizziness
	<i>Cardiac disorders</i>	Angina pectoris, tachycardia, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles)
	<i>Respiratory, thoracic & mediastinal disorders</i>	Throat irritation, bronchospasm
	<i>Gastrointestinal disorders</i>	Dry mouth
	<i>Skin & subcutaneous tissue disorders</i>	Bruising
	<i>Renal & urinary disorders</i>	Urinary retention
<i>General disorders & administration site conditions</i>	Chest pain	

Frequency	System Order Class (SOC)	MedDRA preferred term
Very rare (<0.01%)	<i>Endocrine disorders</i>	Signs or symptoms of systemic glucocorticosteroid effects (e.g. hypofunctions of the adrenal gland)
	<i>Psychiatric disorders</i>	Abnormal behaviour

^a See Table 2 for common ADR reported in 2% or more of patients receiving BREZTRI AEROSPHERE
MedDRA – Medical Dictionary for Regulatory Activities

Pneumonia

In KRONOS the incidence of confirmed pneumonia was 1.9% with BREZTRI AEROSPHERE 160/7.2/5, 1.9% with BFF MDI 160/5 and 1.6% with GFF MDI 7.2/5.

In ETHOS the incidence of confirmed pneumonia was 4.2% with BREZTRI AEROSPHERE 160/7.2/5, 4.5% with BFF MDI 160/5 and 2.3% with GFF MDI 7.2/5.

Bone mineral density and ocular endpoints

In a subset of patients treated for up to 52 weeks (KRONOS follow-up study PT010008), BREZTRI AEROSPHERE 160/7.2/5 was non-inferior to GFF MDI for the primary bone mineral density and ocular endpoints with treatment differences [95% CI]: -0.5% [-1.4%, 0.5%] and [95% CI]: 0.1% [0.0, 0.2%], respectively.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

BREZTRI AEROSPHERE contains budesonide, a glucocorticosteroid, and two bronchodilators: glycopyrronium, a LAMA (anticholinergic) and formoterol, a LABA.

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 substance 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 fewer COPD exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids.

Glycopyrronium has a rapid onset of action and works by blocking the bronchoconstrictor activity of acetylcholine on airway smooth muscle cells. Bronchodilation is chiefly induced through inhibition of the M₃ receptor at the smooth muscle. Glycopyrronium shows 4- to 5-fold higher affinity for human M₃ and M₁ receptors than for the M₂ receptor subtype.

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 with combination treatment may contribute to its beneficial effects on lung function.

Clinical trials

The efficacy and safety of BREZTRI AEROSPHERE was evaluated in patients with moderate to very severe COPD in two randomised, double-blind, parallel-group trials.

ETHOS was a 52-week trial (N=8,588 randomised) that compared 2 inhalations twice daily of BREZTRI AEROSPHERE 160/7.2/5 with 2 inhalations twice daily of GFF MDI 7.2/5 (glycopyrronium/formoterol fumarate dihydrate 7.2/5 μg) and BFF MDI 160/5 (budesonide/formoterol fumarate dihydrate 160/5 μg). A lower strength of BREZTRI AEROSPHERE (BGF MDI 80/7.2/5 μg) was also assessed however the outcomes have not been provided.

The ETHOS primary endpoint was the rate of moderate or severe COPD exacerbations.

ETHOS was conducted in patients with moderate to very severe COPD (post-bronchodilator forced expiratory volume in 1 second (FEV₁) $\geq 25\%$ to $< 65\%$ predicted) with a history of 1 or more moderate or severe COPD exacerbations in the year prior to screening. Patients were symptomatic with a COPD Assessment Test (CAT) score of 10 or above while receiving 2 or more inhaled maintenance therapies for at least 6 weeks prior to screening. During the screening period, the mean post-bronchodilator percent predicted FEV₁ was 43%. The mean CAT score was 19.6. A total of 81% of subjects were on ICS-containing treatments prior to screening. The modified intention to treat (mITT) population consisted of all randomised patient who received treatment and had post-randomisation data prior to discontinuation, with 2137, 2120 and 2131 patients in the BREZTRI AEROSPHERE 160/7.2/5, GFF MDI 7.2/5 and BFF MDI 160/5 arms respectively.

KRONOS was a 24-week trial (N=1,896 randomised) that compared 2 inhalations twice daily of BREZTRI AEROSPHERE 160/7.2/5, with 2 inhalations twice daily of GFF MDI 7.2/5, BFF MDI 160/5 and open-label active comparator BFF Turbuhaler 200/6 (budesonide/formoterol fumarate dihydrate delivered dose 160/4.5 μg). There were two 28-week safety extension studies, for up to 52 weeks of treatment, in a subset of KRONOS patients (Study PT010007 Japanese extension and Study PT010008 ocular extension) (see Section 4.8 Adverse effects (Undesirable effects)), however some efficacy outcomes were also reported.

The two primary endpoints in KRONOS were FEV₁ AUC from 0-4 hours (FEV₁ AUC₀₋₄) and change from baseline in morning pre-dose trough FEV₁ over 24 weeks.

KRONOS was conducted in patients with moderate to very severe COPD (post-bronchodilator FEV₁ ≥25% to <80% predicted), who had a CAT score of 10 or above while receiving 2 or more inhaled maintenance therapies for at least 6 weeks prior to screening. During the screening period, the mean post-bronchodilator percent predicted FEV₁ was 50%. A prior history of exacerbations in the last 12 months was not required in KRONOS and approximately 74% of patients did not have an exacerbation in the preceding 12 months. The mean CAT score was 18.3 and a total of 72% of subjects were on ICS-containing treatments prior to screening. The mITT population consisted of all randomised patient who received treatment and had post-randomisation data prior to discontinuation with 639, 625, 314 and 318 patients in the BREZTRI AEROSPHERE 160/7.2/5, GFF MDI 7.2/5, BFF MDI 160/5 and BFF Turbuhaler 200/6 arms respectively.

Effects on exacerbations - ETHOS

Rate of moderate or severe exacerbations

BREZTRI AEROSPHERE 160/7.2/5 significantly reduced the rate of moderate or severe COPD exacerbations over 52 weeks compared with GFF MDI 7.2/5 and BFF MDI 160/5 (see Table 4).

Rate of severe exacerbations

BREZTRI AEROSPHERE 160/7.2/5 significantly reduced the rate of severe COPD exacerbations over 52 weeks compared with BFF MDI 160/5 (see Table 4). There was a numerical reduction in the rate of severe COPD exacerbations over 52 weeks for BREZTRI AEROSPHERE 160/7.2/5 compared with GFF MDI 7.2/5(see Table 4), but it did not reach statistical significance.

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

Table 4 Rates of COPD exacerbations over 52 weeks (ETHOS; mITT population)

	BREZTRI[^] 160/7.2/5	GFF MDI[^] 7.2/5	BFF MDI 160/5
Moderate^a/severe^b exacerbations (primary endpoint)			
Rate	1.08	1.42	1.24
Rate ratio: BREZTRI [^] vs. comparator (95% CI); p-value	N/A	0.76 (0.69, 0.83); p<0.0001	0.87 (0.79, 0.95); p=0.0027
% reduction		24%	13%
Severe^b exacerbations			
Rate	0.13	0.15	0.16
Rate ratio: BREZTRI [^] vs. comparator (95% CI); p-value	N/A	0.84 (0.69, 1.03); p=0.0943	0.80 (0.66, 0.97); p=0.0221
% reduction		16%	20%

mITT – modified intention to treat; CI – confidence intervals; [^]AEROSPHERE

^a Moderate exacerbation - systemic corticosteroids and/or antibiotics for at least 3 days

^b Severe exacerbation - inpatient COPD-related hospitalisation or COPD-related death

Effects on exacerbations - KRONOS

BREZTRI AEROSPHERE 160/7.2/5 significantly reduced the rate of moderate/severe COPD exacerbations over 24 weeks compared with GFF MDI 7.2/5. The rate of moderate/severe COPD exacerbations was numerically lower in subjects treated with BREZTRI AEROSPHERE 160/7.2/5 compared to BFF MDI 160/5 and BFF Turbuhaler 200/6 (see Table 5).

In a subset of patients treated for up to 52 weeks (extension Study PT0100008), the effects of BREZTRI AEROSPHERE 160/7.2/5 on reducing moderate/severe exacerbations were generally consistent with the results up to 24 weeks.

The rate of severe exacerbations (i.e. resulting in hospitalisation or death) was significantly lower during treatment with BREZTRI AEROSPHERE 160/7.2/5 relative to GFF MDI 7.2/5. Improvement compared to BFF MDI 160/5 and BFF Turbuhaler 200/6 did not reach statistical significance (see Table 5). The rate of severe COPD exacerbations was numerically lower in subjects treated with BREZTRI AEROSPHERE 160/7.2/5 compared to BFF MDI 160/5 and BFF Turbuhaler 200/6 (see Table 5), but it did not reach statistical significance.

Table 5 Annualised rates of COPD exacerbations over 24 weeks (KRONOS; mITT population)

	BREZTRI[^] 160/7.2/5	GFF MDI[^] 7.2/5	BFF MDI 160/5	BFF^{^^} 200/6
Moderate^a/severe^b exacerbations (adjusted)				
Rate	0.46	0.95	0.56	0.55
Rate Ratio: BREZTRI [^] vs. comparator (95% CI); p-value	N/A	0.48 (0.37, 0.64); p<0.0001	0.82 (0.58, 1.17); p=0.2792	0.83 (0.59, 1.18); p=0.3120
% reduction		52	18	17
Severe^b exacerbations (adjusted)				
Rate	0.05	0.13	0.05	0.07
Rate Ratio: BREZTRI [^] vs. comparator (95% CI); p-value	N/A	0.36 (0.18, 0.70); p=0.0026*	0.85 (0.34, 2.13); p=0.7363	0.69 (0.29, 1.61); p=0.3861
% reduction		64	15	31

CI – confidence intervals; [^]AEROSPHERE; ^{^^} Turbuhaler (open label); *unadjusted p-value

^a Moderate exacerbation - systemic corticosteroids and/or antibiotics for at least 3 days

^b Severe exacerbation - inpatient COPD-related hospitalisation or COPD-related death

Effects on lung function

In both studies, BREZTRI AEROSPHERE 160/7.2/5 provided significant improvements in lung function (morning pre-dose trough FEV₁) compared with GFF MDI 7.2/5 and BFF MDI 160/5 (see Table 6). The improvements in lung function were sustained over 52-weeks.

The median time to a 100 mL or larger improvement was within 5 minutes of the first dose on Day 1 for all treatment groups, with a change from baseline of 166 mL (ETHOS) and 175 mL (KRONOS) for BREZTRI AEROSPHERE 160/7.2/5 observed at 5 minutes post-dose.

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 ICS use.

Table 6 ETHOS and KRONOS effects on lung function outcomes (mITT population)

Breztri[^] 160/7.2/5 vs treatment	ETHOS		KRONOS		
	GFF MDI[^] 7.2/5	BFF MDI 160/5	GFF MDI[^] 7.2/5	BFF MDI 160/5	BFF^{^^} 200/6
Change from baseline over 24 weeks (LSM difference (95% CI); p value)					
Morning pre-dose trough FEV ₁ (mL) ^a	43 (25, 60) p<0.0001	76 (58, 94) p<0.0001*	22 (4, 39) p=0.0139	74 (52, 95) p<0.0001	59 (38, 80) p<0.0001
FEV ₁ AUC ₀₋₄ (mL) ^a	49 (31, 66) p<0.0001*	99 (82, 117) p<0.0001	16 (-6, 38) p=0.1448	104 (77, 131) p<0.0001	91 (64, 117) p<0.0001
Peak FEV ₁ within 4 hours post-dose (mL) ^b	51 (33, 69) p<0.0001*	104 (86, 123) p<0.0001*	17 (-6, 40) p=0.1425	105 (78, 133) p<0.0001	90 (62, 118) p<0.0001

[^]AEROSPHERE; ^{^^} Turbuhaler (open label); *unadjusted p-value

mITT – modified intention to treat; LSM – least square mean; CI – confidence intervals; FEV₁ - forced expiratory volume in 1 second; AUC -area under the curve

^a KRONOS coprimary endpoint; ETHOS secondary endpoint

^b Secondary endpoint both studies

Effects on symptoms and quality of life outcomes

In ETHOS, BREZTRI AEROSPHERE 160/7.2/5 showed significant improvements over 24 weeks in breathlessness (assessed by the Transition Dyspnoea Index [TDI]), significant reductions in the use of rescue medication and significant improvements in disease-specific health status (as assessed by the St. George’s Respiratory Questionnaire [SGRQ]) compared to GFF MDI 7.2/5 and BFF MDI 160/5 (see Table 7). These effects were maintained in patients treated for up to 52 weeks.

In KRONOS, BREZTRI AEROSPHERE 160/7.2/5 improvement compared to GFF MDI 7.2/5 and BFF MDI 160/5 did not reach statistical significance (see Table 7).

Table 7 ETHOS and KRONOS effects on symptoms, quality of life and other outcomes (mITT population)

Breztri ^a 160/7.2/5 vs treatment	ETHOS		KRONOS		
	GFF MDI ^a 7.2/5	BFF MDI 160/5	GFF MDI ^a 7.2/5	BFF MDI 160/5	BFF ^{^^} 200/6
Change from baseline over 24 weeks (LSM difference (95% CI); p value)					
TDI focal score (units) ^a	0.40 (0.24, 0.55) p<0.0001	0.31 (0.15, 0.46) p<0.0001	0.18 (-0.071, 0.43) p=0.1621	0.24 (-0.068, 0.54) p=0.1283	0.46 (0.16, 0.77) p=0.0031
Mean daily rescue medication usage (puffs/day) ^b	-0.51 (-0.68, -0.34) p<0.0001	-0.37 (-0.54, -0.20) p<0.0001	-0.25 (-0.60, 0.09) p=0.1446	-0.24 (-0.65, 0.18) p=0.2661	0.23 (-0.17, 0.63) p=0.2667
SGRQ total score (units)	-1.62 (-2.27, -0.97) p<0.0001	-1.38 (-2.02, -0.73) p<0.0001	-1.22 (-2.30, -0.15) p=0.0259*	-0.45 (-1.78, 0.87) p=0.5036	-1.26 (-2.58, 0.06) p=0.0617
RS-total score (units)	N/A	N/A	-0.38 (-0.74, -0.01) p=0.0430*	-0.16 (-0.61, 0.28) p=0.4790	-0.16 (-0.60, 0.29) p=0.4923
Change from baseline over 52 weeks (LSM difference (95% CI); p value)					
Mean daily EXACT total score	-1.14 (-1.64, -0.65) p<0.0001	-1.04 (-1.53, -0.55) p<0.0001	N/A	N/A	N/A
Other					
Risk of a CID event (HR (95%CI); p-value)	N/A	N/A	0.877 (0.76, 1.01) p=0.0593	0.831 (0.70, 0.98) p=0.0276*	0.811 (0.69, 0.96) p=0.0119*

^aAEROSPHERE; ^{^^}Turbuhaler (open label); *not statistically significant due to procedure to control Type I error

mITT – modified intention to treat; LSM – least square mean; CI – confidence intervals; TDI – Transition Dyspnoea Index; SGRQ - St. George’s Respiratory Questionnaire; EXACT – Exacerbations of Chronic Pulmonary Disease Tool; RS – Evaluating Respiratory Symptoms in COPD tool; CID – clinically important deterioration; HR – Hazard ratio

^a Baseline dyspnoea index (BDI) was similar across the treatment groups (range: 6.330 to 6.496)

^b Evaluated in a subset of subjects from ITT population with mean baseline Rescue Ventolin use of ≥ 1.0 puff/day

In ETHOS, 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 significantly greater percentage of responders (p<0.0001) over 24 weeks with BREZTRI AEROSPHERE 160/7.2/5 (52.2%) versus GFF MDI 7.2/5 (42.2%) and BFF MDI 160/5 (45.0%).

In KRONOS, a SGRQ responder analysis showed that there was a significantly greater percentage of responders over 24 weeks with BREZTRI AEROSPHERE 160/7.2/5 (47.3%) versus GFF MDI 7.2/5 (41%; unadjusted p=0.0348), BFF MDI 160/5 (39.5%; unadjusted p=0.0339) and BFF Turbuhaler 200/6 (39.5%; unadjusted p=0.0321).

Time to clinically important deterioration (CID) - KRONOS

Time to CID is a composite endpoint defined by the first instance of deterioration in either lung function (≥ 100 mL decrease in trough FEV₁), symptoms (≥ 4 -point increase in SGRQ total score), TDI focal score (of 1 point or less) or a treatment-emergent moderate or severe COPD exacerbation occurring up to Week 24. The median time to a CID event was longer during treatment with BREZTRI AEROSPHERE 160/7.2/5 (13.5 weeks) relative to GFF MDI 7.2/5 (12.2 weeks), BFF MDI 160/5 (12.2 weeks) and BFF Turbuhaler 200/6 (12.2 weeks).

The risk of a CID event was significantly lower during treatment with BREZTRI AEROSPHERE 160/7.2/5 relative to BFF MDI 160/5; a numerically lower risk of a CID event was observed during treatment with BREZTRI AEROSPHERE 160/7.2/5 relative to GFF MDI 7.2/5 (see Table 7).

Patient reported outcomes (PRO) questionnaires

Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a 14-item PRO questionnaire from the daily diary used to measure the effect of treatment on exacerbations, and on the severity of respiratory symptoms. In ETHOS, BREZTRI AEROSPHERE 160/7.2/5 demonstrated a significant improvement over 52 weeks for EXACT total score compared with GFF MDI 7.2/5 (see Table 7).

Evaluating Respiratory Symptoms in COPD (E-RS) is an 11-item PRO questionnaire from the daily diary used to measure the effect of treatment on the severity of respiratory symptoms. In KRONOS, BREZTRI AEROSPHERE 160/7.2/5 demonstrated a significant improvement over 24 weeks for RS-total score compared with GFF MDI 7.2/5, but not when compared with BFF MDI 160/5 and BFF Turbuhaler 200/6 (see Table 7).

5.2 PHARMACOKINETIC PROPERTIES

Lung deposition

A lung deposition study with BREZTRI AEROSPHERE 160/7.2/5 conducted in healthy volunteers demonstrated that on average, 38% of the nominal dose is deposited into the lung following administration with a 10 second breath-hold. The corresponding value following a 3 second breath-hold was 35%. Deposition was consistent with the width of the aerodynamic particle size distribution with both central and peripheral deposition observed.

Absorption

Budesonide

Following inhaled administration of BREZTRI AEROSPHERE in subjects with COPD, budesonide C_{max} occurred within 20 to 40 minutes. Steady state is achieved after approximately 1 day of repeated dosing of BREZTRI AEROSPHERE 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, glycopyrronium C_{max} occurred at 6 minutes. Steady state is achieved after approximately 3 days of repeated dosing of BREZTRI AEROSPHERE 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, formoterol C_{max} occurred within 40 to 60 minutes. Steady state is achieved after approximately 2 days of repeated dosing with BREZTRI AEROSPHERE 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 1,200 L, via population pharmacokinetic analysis. Plasma protein binding is approximately 90% for budesonide.

Glycopyrronium

The estimated glycopyrronium apparent volume of distribution at steady-state is 5,500 L, via population pharmacokinetic analysis. 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 2,400 L, via population pharmacokinetic analysis. 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 16 α -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. No metabolism was observed *in vitro* in human lung microsomes. The major metabolic pathway for glycopyrronium is likely direct hydrolysis catalysed by members of the cholinesterase family. CYP2D6 was found to be the predominant CYP isoform 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. Multiple isozymes catalyse the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9 and 2A6) of formoterol.

Excretion

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 was 5 hours.

Glycopyrronium

After IV administration of a 200 μ g 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 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 faeces. The effective terminal elimination half-life of formoterol derived via population pharmacokinetic analysis was 10 hours.

Special populations

Age, gender, race/ethnicity 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.

Use in the elderly

Based on available data, no adjustment of the dosage of BREZTRI AEROSPHERE in elderly patients is necessary.

The confirmatory trials of BREZTRI AEROSPHERE 160/7.2/5 for COPD included 1,144 patients aged 65 to less than 75 years of age, and 303 patients aged 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic impairment

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 liver 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 impairment

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Individually, budesonide, glycopyrronium bromide and formoterol fumarate showed no genotoxic effects in assays for bacterial mutagenicity, chromosomal aberrations *in vitro* (human lymphocytes) and *in vivo* clastogenicity (rat or mouse bone marrow micronucleus test), except for a slight increase in reverse mutation frequency in *Salmonella typhimurium* at high concentrations of formoterol fumarate.

Carcinogenicity

The carcinogenic potential of budesonide, glycopyrronium and formoterol in combination has not been investigated in animal studies.

In a 91-week carcinogenicity study in mice, budesonide produced no treatment-related increases in the incidence of tumours at oral doses up to 200 $\mu\text{g}/\text{kg}/\text{day}$ (approximately 1.4 times the MRHDID on a $\mu\text{g}/\text{m}^2$ basis). A 2-year carcinogenicity study in rats, along with two additional 2-year studies in male rats comparing effects in an alternative rat strain and effects of reference corticosteroids (prednisone and triamcinolone acetonide), were conducted. It was concluded that budesonide caused a statistically significant increase in the incidence of hepatocellular tumours at an oral dose of ≥ 25 $\mu\text{g}/\text{kg}/\text{day}$ (approximately one-third of the MRHDID on a $\mu\text{g}/\text{m}^2$ basis). Prednisone and triamcinolone acetonide showed similar findings, indicating that this is a class effect of corticosteroids.

Carcinogenicity studies of six months duration by the oral route in transgenic mice (ras H2), of 24 months duration by inhalational administration in normal mice, and of 19 and 24-months duration in rats using inhalational administration revealed no evidence of carcinogenicity with glycopyrronium bromide. The highest dose levels employed in the transgenic mouse study and the 24-month rat study (75 and 100 $\text{mg}/\text{kg}/\text{day}$ in male and female mice and 0.45 $\text{mg}/\text{kg}/\text{day}$ in rats) were associated with systemic exposures (plasma AUC) approximately 120-fold higher in mice and 180-fold higher in rats than in humans at the maximum recommended dose of glycopyrronium bromide with BREZTRI AEROSPHERE. The highest doses used in the 24-month study in mice (1440 $\mu\text{g}/\text{kg}/\text{day}$) and the 19-month study in rats (652 $\mu\text{g}/\text{kg}/\text{day}$), are approximately 165-180 times greater than the maximum recommended clinical dose of glycopyrronium bromide on a $\mu\text{g}/\text{m}^2$ basis.

With formoterol fumarate, there was a dose-dependent increase in the incidence of uterine leiomyomas in mice dosed orally at 0.1, 0.5 and 2.5 $\text{mg}/\text{kg}/\text{day}$ for two years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 $\text{mg}/\text{kg}/\text{day}$ for two years. The effects observed are expected findings with high dose exposure to β_2 -adrenoceptor agonists. Additional carcinogenic activity was observed with formoterol in rats and mice in other studies involving systemic exposure levels thousands of times higher than in patients treated with BREZTRI AEROSPHERE. In view of the dose levels and the genotoxic profile of the drug, it is concluded that the cancer risk in patients treated with formoterol fumarate is no greater than for other β_2 -adrenoceptor agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BREZTRI AEROSPHERE 160/7.2/5 also contains the inactive ingredients - porous particles (comprised of distearoylphosphatidylcholine (DSPC) and calcium chloride dihydrate) and the propellant norflurane (also known as hydrofluroalkane (HFA)-134a).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

The inhaler should be discarded within 3 months (120 actuations) or 3 weeks (28 actuations sample pack) after removal from the foil pouch.

6.5 NATURE AND CONTENTS OF CONTAINER

Two pack sizes are registered*:

- 120 actuations
- 28 actuations (sample pack)

* not all pack sizes may be available in Australia.

Two types of pressurised metered dose inhalers (pMDI) are registered#:

Bespak / Trudell device

BREZTRI AEROSPHERE 160/7.2/5 pMDI consists of an internally coated aluminium canister, sealed with a metering valve, fitted with an attached dose indicator device and fitted into a white plastic actuator (body) with a grey plastic cap (dust cover). Each inhaler is individually wrapped in a foil-laminate pouch with a desiccant sachet, and packed in a carton.

DFP-EvoCap XS / EvoCap XS device

BREZTRI AEROSPHERE 160/7.2/5 pMDI consists of an internally coated aluminium canister, sealed with a metering valve, a yellow plastic actuator and white mouthpiece (body) with an attached grey plastic cap (dust cover), and a shield style dose indicator. Each inhaler is individually wrapped in a foil-laminate pouch with a desiccant sachet, and packed in a carton.

The 120 actuations pack size also contains a desiccated flow path (comprising a collar, seal and desiccant puck).

not all pMDIs may be available in Australia.

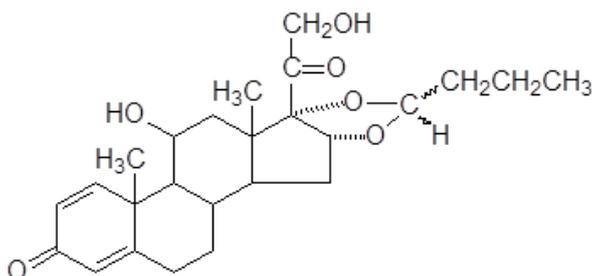
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Always be sure to dispose of your used inhaler responsibly since some of the medicine may remain inside it. Please ask your pharmacist what to do with any medicine that is left over. The canister in your inhaler contains pressurised liquid. 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 above 50°C and do not freeze. If exposed to freezing temperatures, the inhaler should be equilibrated for 1 hour at room temperature prior to taking a dose.

6.7 PHYSICOCHEMICAL PROPERTIES

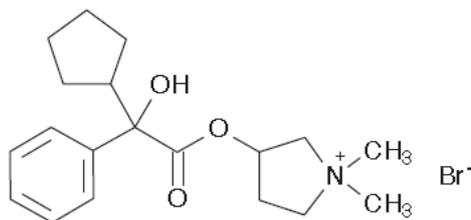
Chemical structure

Budesonide



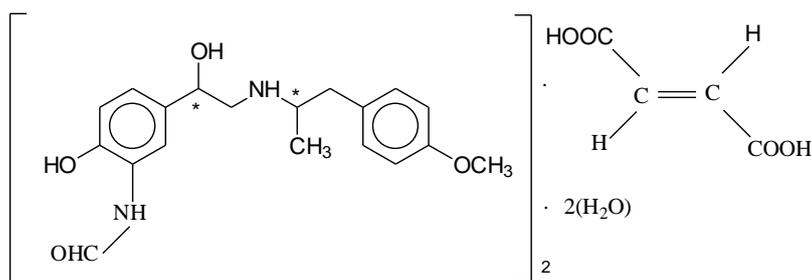
16 α , 17 α -22 R, S-propylmethylenedioxyprogna-1, 4-diene-1 β , 21-diol-3, 20-dione

Glycopyrronium (as glycopyrronium bromide (glycopyrrolate))



3[(cyclopentylhydroxyphenylacetyl) oxy]-1,1-dimethyl pyrrolidinium bromide.

Formoterol (eformoterol) fumarate dihydrate



(R*R*)-(\pm)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate.

CAS number

Budesonide	51333-22-3
Glycopyrronium (as glycopyrronium bromide (glycopyrrolate))	596-51-0
Formoterol (eformoterol) fumarate dihydrate	183814-30-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 July 2021

10 DATE OF REVISION

05 March 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Editorials on Table 2 footnote

BREZTRI, AEROSPHERE, and Turbuhaler are registered trade marks of the AstraZeneca group of companies.

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