BREZTRI AEROSPHERE ®
(Budesonide/Glycopyrronium/Formoterol fumarate dihydrate)

1. NAME OF THE MEDICINAL PRODUCT

BREZTRI AEROSPHERE, budesonide/glycopyrronium/formoterol fumarate dihydrate, 160/7.2/5.0 micrograms/actuation, pressurised inhalation, suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece) contains budesonide 160 micrograms, glycopyrronium bromide 9.0 micrograms, equivalent to 7.2 micrograms of glycopyrronium and formoterol fumarate dihydrate 5.0 micrograms, equivalent to 4.8 micrograms of formoterol fumarate.

This corresponds to a metered dose of 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.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maintenance treatment to relieve symptoms and prevent exacerbations in adult patients with moderate to very severe chronic obstructive pulmonary disease (COPD) (see Section 5.1).

4.2 Posology and method of administration

The recommended and maximum dose is two inhalations of BREZTRI AEROSPHERE 160/7.2/5.0 twice daily, in the morning and in the evening, by the orally inhaled route only.

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.

Children

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

Dosage in patients with renal impairment:

No dosage adjustment is necessary for patients with renal impairment (see section 4.4 and section 5.2).

Dosage in patients with hepatic impairment:

No dosage adjustment is necessary for patients with hepatic impairment (see section 4.4 and section 5.2).

Elderly:

No dosage adjustment is necessary for elderly patients (see section 5.2).

Method of administration

For oral inhalation use.

For detailed instructions, refer to the patient leaflet.

Patients should be instructed 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. BREZTRI AEROSPHERE can be used with spacer devices including the Aerochamber Plus® Flow Vu®.

4.3 Contraindications

Hypersensitivity to the active substances or any of the excipients.

4.4 Special warnings and special precautions for use

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 or antibiotic treatment if an infection is present.

Transfer from oral therapy

Particular care is needed in patients transferring from oral steroids, 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 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. If this occurs, treatment with BREZTRI AEROSPHERE should be stopped and other treatments considered.

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).

Cardiovascular effects

As for all β2-agonists, caution should be observed in patients with thyrotoxicosis and in patients with a severe cardiovascular disorder, such as ischemic heart disease, tachyarrhythmias or severe heart failure. Caution should be observed when treating patients with a prolonged QTc-interval.

Systemic effects

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 section 5.1).

Hypokalaemia and hyperglycaemia

In one clinical trial of 24 weeks that included a 28-week safety extension study, and in one 52-week study evaluating BREZTRI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on potassium. Metabolic effects of hyperglycaemia and hypokalaemia may be observed with high doses of β2-adrenergic agonists. The decrease in serum potassium is usually transient, not requiring supplementation (see section 4.5).

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.

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 (creatinine clearance of <30 mL/min) should be treated with BREZTRI AEROSPHERE only if the expected benefit outweighs the potential risk.

Hepatic impairment

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 section 5.2).

Pneumonia

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

4.5 Interaction with other medicinal products and other forms of interaction

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

COPD medicinal products

Co-administration of BREZTRI AEROSPHERE with other anticholinergic and/or long-acting β2-adrenergic agonist containing medicinal products has not been studied and is not recommended.

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 and section 5.2). 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 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 a limited increase in its total systemic exposure (AUC0-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 (see section 5.2). Budesonide and glycopyrronium do not inhibit or induce CYP450 enzymes at therapeutically relevant concentrations (see section 5.2).

Drug-induced hypokalaemia

Possible initial hypokalaemia may be potentiated by concomitant medications, including non-potassium sparing diuretics.

β-adrenergic blockers

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

Other pharmacodynamic interactions

BREZTRI AEROSPHERE should be administered with caution to patients being treated with medicinal products known to prolong the QTc-interval (see section 4.4).

4.6 Pregnancy and lactation

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 section 5.3).

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

Breast-feeding

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.

Fertility

Studies in rats have shown slight reductions in fertility only at dose levels higher than the maximum human exposure to formoterol (see section 5.3). Budesonide and glycopyrronium individually, did not cause any adverse effects on fertility in rats. It is unlikely that BREZTRI AEROSPHERE administered at the recommended dose will affect fertility in humans.

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, BREZTRI AEROSPHERE is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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.

The safety evaluation of the pivotal program for BREZTRI AEROSPHERE 160/7.2/5.0 included 639 subjects with COPD in one 24-week lung function trial, and a long-term safety extension study of 28 weeks, and 2144 subjects in one 52-week exacerbation trial. In addition, 2137 subjects in the 52-week exacerbation trial received BGF MDI 80/7.2/5.0.

Tabulated summary of adverse reactions

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 Adverse drug reactions by frequency and system order class (SOC)

Frequency	SOC	MedDRA term
Common ≥1% to <10%	*Infections and infestations*	Oral candidiasis Pneumonia
	Metabolism and nutrition disorders	Hyperglycaemia
	Psychiatric disorders	Anxiety, insomnia
	Nervous system disorders	Headache
	Cardiac disorders	Palpitations
	Respiratory, thoracic and mediastinal disorders	Dysphonia, cough
	Gastrointestinal disorders	Nausea
	Renal and urinary disorders	Urinary tract infection

Frequency	SOC	MedDRA term
	Musculoskeletal and connective tissue disorders	Muscle spasms
Uncommon ≥0.1% to <1%	*Immune system disorders*	Hypersensitivity
	Psychiatric disorders	Depression, agitation, restlessness, nervousness
	Nervous system disorders	Tremor, dizziness
	Cardiac disorders	Angina pectoris, Tachycardia, Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles)
	Respiratory, thoracic and mediastinal disorders	Throat irritation, bronchospasm
	Gastrointestinal disorders	Dry mouth
	Skin and subcutaneous tissue disorders	Bruising
	Renal and urinary disorders	Urinary retention
	General disorders and administration site conditions	Chest pain
Very rare <0.01%	*Endocrine disorders:*	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunctions of the adrenal gland
	Psychiatric disorders:	Abnormal behaviour

Description of selected adverse reactions

Pneumonia

In KRONOS (see section 5.1), the incidence of confirmed pneumonia was 1.9% with BREZTRI AEROSPHERE 160/7.2/5.0, 1.9% with budesonide and formoterol fumarate dihydrate [BFF MDI 160/5.0 mcg], and 1.6% with glycopyrronium and formoterol fumarate dihydrate [GFF MDI 7.2/5.0 mcg].

In ETHOS (see section 5.1), the incidence of confirmed pneumonia was 4.2% with BREZTRI AEROSPHERE 160/7.2/5.0, 3.5% with BGF MDI 80/7.2/5, 4.5% with BFF MDI 160/5.0 mcg and 2.3% with GFF MDI 7.2/5.0 mcg.

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 β2-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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

BREZTRI AEROSPHERE contains budesonide, a glucocorticosteroid, and two bronchodilators: glycopyrronium, a long-acting muscarinic antagonist (anticholinergic) and formoterol, a long-acting β2-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 fewer COPD exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids.

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 β2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists are more effective in relaxing central airways and β2-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 efficacy and safety

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) that compared two inhalations twice daily of BREZTRI AEROSPHERE 160/7.2/5.0 micrograms or budesonide/glycopyrronium/formoterol fumarate (BGF MDI) 80/7.2/5.0 micrograms with two inhalations twice daily of glycopyrronium/formoterol fumarate dihydrate (GFF MDI) 7.2/5.0 micrograms, and budesonide/formoterol fumarate dihydrate (BFF MDI) 160/5.0 micrograms.

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

ETHOS was conducted in patients with moderate to very severe COPD (post-bronchodilator FEV1 ≥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 two 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.

KRONOS was a 24-week trial (N=1,896) that compared two inhalations twice daily of BREZTRI AEROSPHERE 160/7.2/5.0 micrograms, with two inhalations twice daily of glycopyrronium and formoterol fumarate dihydrate [GFF MDI 7.2/5.0 micrograms], budesonide and formoterol fumarate dihydrate [BFF MDI 160/5.0 micrograms]) and open-

label active comparator Symbicort Turbuhaler 200/6 micrograms [budesonide/formoterol fumarate dihydrate]. There was a 28-week extension, for up to 52 weeks of treatment, in a subset of patients.

The two primary endpoints in KRONOS were FEV1 area under the curve 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 two 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 less than 26% of patients reported a history of one or more moderate/severe exacerbations in the prior year. The mean CAT score was 18.3 and a total of 72% of subjects were on ICS-containing treatments prior to screening.

Effects on exacerbations - ETHOS

Rate of moderate or severe exacerbations

BREZTRI AEROSPHERE 160/7.2/5.0 and BGF MDI 80/7.2/5.0 significantly reduced the rate of moderate or severe COPD exacerbations over 52 weeks compared with GFF MDI and BFF MDI (see Table 2).

The benefit of BREZTRI AEROSPHERE 160/7.2/5.0 over GFF MDI in reducing the rate of moderate or severe COPD exacerbations was observed in subjects with a baseline blood eosinophil count of ≥150 cells/mm3 and those with a baseline blood eosinophil count of <150 cells/mm3. The magnitude of benefit of BREZTRI AEROSPHERE 160/7.2/5.0 over GFF MDI in reducing the rate of moderate or severe COPD exacerbations increased as blood eosinophil levels increased.

Rate of severe exacerbations

BREZTRI AEROSPHERE 160/7.2/5.0 significantly reduced the rate of severe COPD exacerbations over 52 weeks compared with BFF MDI (see Table 2).

There was a numerical reduction in the rate of severe COPD exacerbations over 52 weeks for BREZTRI AEROSPHERE 160/7.2/5.0 compared with GFF MDI, and for BGF MDI 80/7.2/5.0 compared with GFF MDI and BFF MDI (see Table 2).

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

Table 2 Rates of exacerbations over 52 weeks - ETHOS

	BREZTRI[1] 160/7.2/5.0 (N=2157)	BGF MDI[2] 80/7.2/5.0 (N=2137)	GFF MDI[3] (N=2143)	BFF MDI[4] (N=2151)
Rate of moderate or severe exacerbations over 52 weeks				
Rate	1.08	1.07	1.42	1.24
Rate Ratio: BREZTRI 160/7.2/5.0 vs. comparator	N/A	N/A	0.76	0.87
95% CI			(0.69, 0.83)	(0.79, 0.95)
p-value			p<0.0001	p=0.0027
% reduction			24%	13%
Rate Ratio: BGF MDI 80/7.2/5.0 vs. comparator	N/A	N/A	0.75	0.86
95% CI			(0.69, 0.83)	(0.79, 0.95)
p-value			p<0.0001	p=0.002
% reduction			25%	14%
Rate of severe exacerbations over 52 weeks				
Rate	0.13	0.14	0.15	0.16
Rate Ratio: BREZTRI 160/7.2/5.0 vs. comparator	N/A	N/A	0.84	0.80
95% CI			(0.69, 1.03)	(0.66, 0.97)
p-value			p=0.0944	p=0.0221
% reduction			16%	20%
Rate Ratio: BGF MDI 80/7.2/5.0 vs. comparator	N/A	N/A	0.88	0.83
95% CI			(0.72, 1.08)	(0.69, 1.01)
p-value			p=0.2157	p=0.0647
% reduction			12%	17%

[1]BREZTRI AEROSPHERE abbreviated to BREZTRI
[2]BGF MDI (budesonide, glycopyrronium and formoterol fumarate dihydrate [80/7.2/5 mcg])
[3]GFF MDI (glycopyrronium and formoterol fumarate dihydrate [7.2/5 mcg])
[4]BFF MDI (budesonide and formoterol fumarate dihydrate [160/5 mcg])

Effects on exacerbations - KRONOS

BREZTRI AEROSPHERE 160/7.2/5.0 significantly reduced the rate of moderate/severe COPD exacerbations over 24 weeks compared with GFF MDI. The rate of moderate/severe COPD exacerbations was numerically lower in subjects treated with BREZTRI AEROSPHERE 160/7.2/5.0 compared to BFF MDI and Symbicort TBH (see Table 3).

In a subset of patients treated for up to 52 weeks, the effects of BREZTRI AEROSPHERE 160/7.2/5.0 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 160/7.2/5.0 relative to GFF MDI (rate ratio [95% CI]: 0.36 [0.18, 0.70], unadjusted p=0.0026). The rate of severe COPD exacerbations was numerically lower in subjects treated with BREZTRI AEROSPHERE 160/7.2/5.0 compared to BFF MDI and Symbicort TBH.

Benefits on exacerbations were observed in patients with moderate, severe and very severe COPD. The benefit of BREZTRI AEROSPHERE 160/7.2/5.0 over GFF MDI in reducing the rate of moderate or severe COPD exacerbations was observed in subjects with a baseline blood eosinophil count of ≥150 cells/mm3 and those with a baseline blood eosinophil count of <150 cells/mm3. The magnitude of benefit of BREZTRI AEROSPHERE 160/7.2/5.0 over GFF MDI in reducing the rate of moderate or severe COPD exacerbations increased as blood eosinophil levels increased.

Table 3 Annualised rates of moderate or severe exacerbations over 24 weeks – KRONOS

	BREZTRI AEROSPHERE 160/7.2/5.0 mcg (N=639)	**GFF MDI[1] (N=625)**	**BFF MDI[2] (N=314)**	**Symbicort TBH[3] (N=318)**
Annual rate of moderate/severe COPD exacerbations (adjusted)	0.46	0.95	0.56	0.55
Rate Ratio: BREZTRI 160/7.2/5.0 vs. comparator	N/A	0.48	0.82	0.83
95% CI		(0.37, 0.64)	(0.58, 1.17)	(0.59, 1.18)
p-value		p<0.0001	p=0.2792	p=0.3120
% reduction		52	18	17

[1]GFF MDI (glycopyrronium and formoterol fumarate dihydrate [7.2/5 mcg]).
[2]BFF MDI (budesonide and formoterol fumarate dihydrate [160/5 mcg]).
[3]Symbicort Turbuhaler [TBH] (budesonide and formoterol fumarate dihydrate [200/6 mcg]) (n=318)

Effects on lung function

In both studies, BREZTRI AEROSPHERE provided significant improvements in lung function (FEV1) compared with GFF MDI and BFF MDI (see Table 4). 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 160/7.2/5.0 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 inhaled corticosteroid use.

Table 4 Effects on lung function over 24 weeks

Treatment	n	Trough FEV1 (mL)			FEV_1AUC_{0-4} (mL)			Peak FEV1 (mL		
		Difference from			Difference from			Difference from		
		GFF MDI[1] (95% CI)	BFF MDI[2] (95% CI)	Symbicort TBH[3] (95% CI)	GFF MDI (95% CI)	BFF MDI (95% CI)	Symbicort TBH (95% CI)	GFF MDI (95% CI)	BFF MDI (95% CI)	Symbicort TBH (95% CI)
ETHOS										
BREZTRI AEROSPHERE 160/7.2/5.0 mcg	747	43 mL (25, 60) p<0.0001	76 mL (58, 94) p<0.0001	N/A	49 mL (31, 66) p<0.0001	99 mL (82, 117) p<0.0001	N/A	51 (33, 69) p<0.0001	104 (86, 123) p<0.0001	N/A
KRONOS										
BREZTRI AEROSPHERE 160/7.2/5.0 mcg	**639**	22 mL (4, 39) p=0.0139	74 mL (52, 95) p<0.0001	59 mL (38, 80) p<0.0001	16 mL (-6, 38) p=0.1448	104 mL (77, 131) p<0.0001	91 mL (64, 117) p<0.0001	17 mL (-6, 40) p=0.1425	105 mL (78, 133) p<0.0001	90 mL (62, 118) p<0.0001

[1]GFF MDI (glycopyrronium and formoterol fumarate dihydrate [7.2/5.0 mcg]) (n=625)
[2]BFF MDI (budesonide and formoterol fumarate dihydrate [160/5.0 mcg]) (n=314)
[3]Symbicort Turbuhaler [TBH] (budesonide and formoterol fumarate dihydrate [200/6 mcg]) (n=318)

Effects on symptoms and quality of life outcomes

In ETHOS, BREZTRI AEROSPHERE 160/7.2/5.0 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 and BFF MDI (see Table 5). In patients treated for up to 52 weeks, improvements observed were generally consistent with those observed over 24 weeks.

In KRONOS, BREZTRI AEROSPHERE 160/7.2/5.0 showed numerical improvements in breathlessness (assessed by the Transition Dyspnoea Index [TDI]), numerical reductions in the use of rescue medication and numerical improvements in disease-specific health status (as assessed by the St. George's Respiratory Questionnaire [SGRQ]) compared to GFF MDI and BFF MDI (See Table 5). In patients treated for up to 52 weeks, the improvements observed were generally consistent with those observed over 24 weeks.

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 AEROPSHERE 160/7.2/5 (52.2%) versus GFF MDI (42.2%) and BFF MDI (45.0%).
In KRONOS, a SGRQ responder analysis showed that there was a significantly greater percentage of responders over 24 weeks with BREZTRI AEROSPHERE 160/7.2/5.0 (47.3%) versus GFF MDI (41%; unadjusted p=0.0348), BFF MDI (39.5%; unadjusted p=0.0339) and Symbicort TBH (39.5%; unadjusted p=0.0321).

Table 5 Symptoms and Quality of Life outcomes over 24 weeks

Treatment	n	TDI (units) Difference from[5] GFF MDI[1] (95% CI)	TDI (units) Difference from BFF MDI[2] (95% CI)	TDI (units) Difference from Symbicort TBH[3] (95% CI)	Rescue Medication Usage[6] (puffs/day) Difference from GFF MDI (95% CI)	Rescue Medication Usage[6] (puffs/day) Difference from BFF MDI (95% CI)	Rescue Medication Usage[6] (puffs/day) Difference from Symbicort TBH (95% CI)	SGRQ (units)[4] Difference from GFF MDI (95% CI)	SGRQ (units)[4] Difference from BFF MDI (95% CI)	SGRQ (units)[4] Difference from Symbicort TBH (95% CI)
ETHOS										
BREZTRI AEROSPHERE 160/7.2/5.0 mcg	2137	0.40 (0.24, 0.55) p<0.0001	0.31 (0.15, 0.46) p<0.0001	N/A	-0.51 (-0.68, -0.34) p<0.0001	-0.37 (-0.54, -0.20) p<0.0001	N/A	-1.62 (-2.27, -0.97) p<0.0001	-1.38 (-2.02, -0.73) p<0.0001	N/A
KRONOS										
BREZTRI AEROSPHERE 160/7.2/5.0 mcg	639	0.18	0.24	0.46	-0.25	-0.24	0.23	-1.22	-0.45	-1.26
		(-0.071, 0.43)	(-0.068, 0.54)	(0.16, 0.77)	(-0.60, 0.09)	(-0.65, 0.18)	(-0.17, 0.63)	(-2.30, -0.15)	(-1.78, 0.87)	(-2.58, 0.06)
		p=0.1621	p=0.1283	p=0.0031	p=0.1446	p=0.2661	p=0.2667	p=0.0259	p=0.5036	p=0.0617

[1]GFF MDI (glycopyrronium and formoterol fumarate dihydrate [7.2/5.0 mcg]) (n=625)
[2]BFF MDI (budesonide and formoterol fumarate dihydrate [160/5.0 mcg]) (n=314)
[3]Symbicort Turbuhaler [TBH] (budesonide and formoterol fumarate dihydrate [200/6 mcg]) (n=318)
[4]defined as an improvement in score of 4 or more as threshold
[5]Baseline dyspnea index (BDI) was similar across the treatment groups (range: 6.330 to 6.496)
[6]Evaluated in a subset of subjects from ITT population with mean baseline Rescue Ventolin use of ≥1.0 puff/day. In ETHOS, BREZTRI AEROSPHERE 160/7.2/5.0 (n=1430)

Time to clinically important deterioration (CID)

In KRONOS, the median time to a CID event was longer during treatment with BREZTRI AEROSPHERE 160/7.2/5.0 (13.5 weeks) relative to GFF MDI (12.2 weeks), BFF MDI (12.2 weeks) and Symbicort TBH (12.2 weeks).

The risk of a CID event was significantly lower during treatment with BREZTRI AEROSPHERE 160/7.2/5.0 relative to BFF MDI (HR: 0.831; unadjusted p=0.0276) and Symbicort TBH (HR: 0.811; unadjusted p=0.0119); a numerically lower risk of a CID event was observed during treatment with BREZTRI AEROSPHERE 160/7.2/5.0 relative to GFF MDI (HR: 0.877; p=0.0593).

Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

In ETHOS, BREZTRI AEROSPHERE 160/7.2/5.0 demonstrated a significant improvement in LS mean change from baseline in EXACT total score over 52 weeks compared with GFF MDI (LS mean difference of -1.14 units; p<0.0001) and BFF MDI (LS mean difference of -1.04 units; p<0.0001).

Evaluating Respiratory Symptoms in COPD (E-RS)

In KRONOS, BREZTRI AEROSPHERE 160/7.2/5.0 demonstrated a significant improvement in LS mean change from baseline in RS Total score over 24 weeks compared with GFF MDI (-0.38; unadjusted p=0.0430); numerical improvements were observed for BREZTRI AEROSPHERE 160/7.2/5.0 compared with BFF MDI (0.16; p=0.4790) and Symbicort TBH (-0.16; p=0.4923).

Bone mineral density and ocular endpoints

In a subset of patients treated for up to 52 weeks in KRONOS, BREZTRI AEROSPHERE 160/7.2/5.0 was non-inferior to GFF MDI for the primary bone mineral density and ocular endpoints.

5.2 Pharmacokinetic properties

Lung deposition

A lung deposition study with BREZTRI AEROSPHERE 160/7.2/5.0 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 Cmax 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.

The use of BREZTRI AEROSPHERE with the Aerochamber Plus® Flow-Vu® spacer in healthy volunteers increased the total systemic exposure (as measured by AUC0-t) to budesonide and glycopyrronium by 33% and 55%, respectively, while exposure to formoterol was unchanged. However, the highest increases in exposure with spacer were observed in subjects showing low exposure without spacer (most probably due to poor inhalation technique).

Distribution

Budesonide

The estimated budesonide apparent volume of distribution at steady-state is 1200 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 5500 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 2400 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 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 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 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 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.

Elderly patients

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 included 343 subjects aged 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

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 (AUC0-12) 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

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.

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 (see section 4.6). 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.

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. 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 β2-adrenoreceptor agonists.

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. No evidence of carcinogenicity was seen in 2-year studies in rats and mice.

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 pressurised 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrofluoroalkane (HFA-134a)
1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]
Calcium chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

As packaged for sale: Refer to the outer carton and/or inner product label for expiration date.

After removal from the foil pouch: 3 months (120 actuation pack size).

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

A pressurised metered dose inhaler, comprising a coated aluminium 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.

6.6 Instructions for use, handling and disposal

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 50ºC.
The actuator should be rinsed weekly.
Store in a dry place.

Product Owner

AstraZeneca AB
Sodertalje, Sweden

Date of revision of text:
February 2023

02/BC/SG/Doc ID-004709012 V3.0

Read prior to using inhaler

INSTRUCTIONS FOR USE

BREZTRI AEROSPHERE
(budesonide, glycopyrronium, and formoterol fumarate dihydrate)
Pressurised inhalation, suspension
For oral inhalation use

Please read these instructions carefully.
Your Breztri Aerosphere (called "inhaler" in this leaflet) may be different from inhalers you have used before.

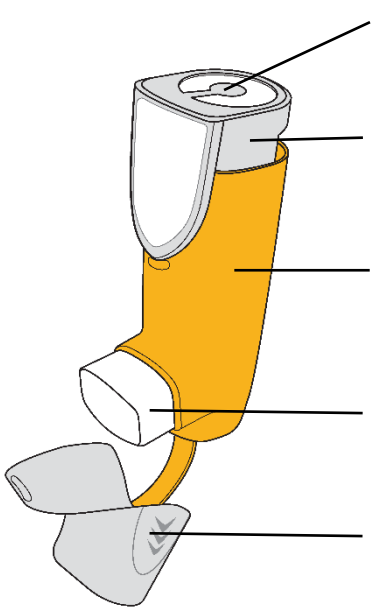
Important information

- **For oral inhalation use only**
- **Prepare your inhaler for its first time use by priming it**
- **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 below 30°C
- **Do not store in a humid environment, such as a bathroom**
- Keep your inhaler and all medicines out of the reach of children

Parts of your inhaler



Puff indicator
Attached to the top of the pressurised canister.

Pressurised Canister (inside)
Holds the medicine.

Actuator
Contains the pressurised canister.

Mouthpiece
Sprays the medicine.

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

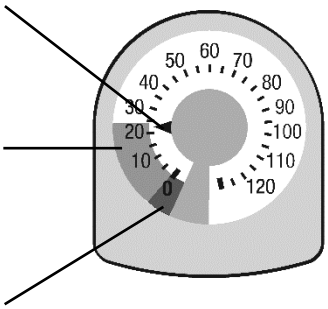
Reading the puff indicator

ⓘ **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.
ⓘ **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:

- puff indicator shows 0

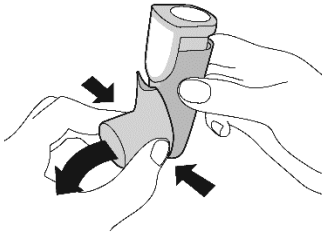
or

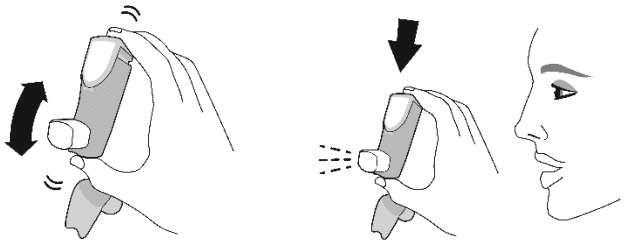
- **3 months** (for the 30-day inhaler) after your inhaler has been removed from the foil pouch

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. 

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:**

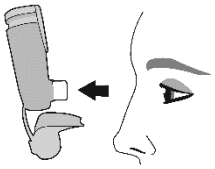
- after rinsing the actuator
- if dropped
- if not used for more than 7 days

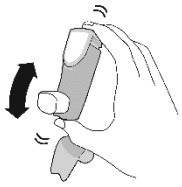
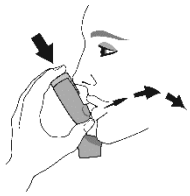
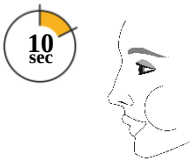
To re-prime, spray **2 Test-puffs**, shaking before each Test-puff.

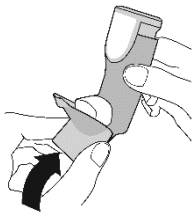
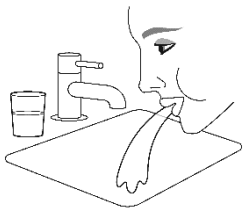
x2 total
Shake and Test-puffs

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.

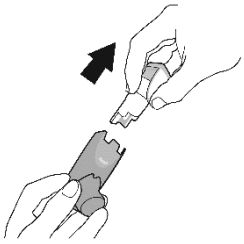
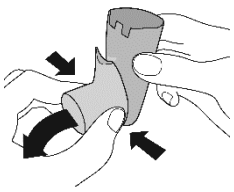
Step 1
Remove mouthpiece cover. **Check the mouthpiece for foreign objects and remove objects before use.** 

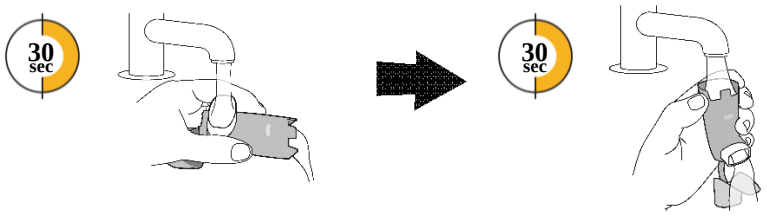
Step 2				
Shake the inhaler well before each puff. 	Breathe out fully. 	Place mouthpiece into mouth and close lips around the mouthpiece. 	Start to breathe in deeply and slowly while spraying **1 puff**. Continue breathing in until you cannot any more. 	Hold breath for as long as you can, up to **10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

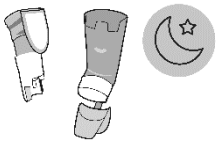
Step 3	Step 4	Step 5
Repeat Step 2 for a second puff	Put mouthpiece cover back on. 	Rinse mouth with water. Spit out water. **Do not swallow.** 

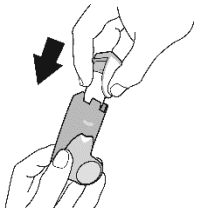
WEEKLY RINSE – Rinse your actuator once a week

- **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**