Proposed packaging material		
Code	BREZTRI AEROSPHERE-PI-02.01	
Submission	☐NDA ☐Renewal ☒ Variation change detail no.: RO-Change Event-0039659	
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Name & Date	ADR, 19 Mar 24	

BREZTRI AEROSPHERE®
formoterol fumarate dihydrate / glycopyrronium bromide / budesonide
pressurised inhalation, suspension

1. NAME OF THE MEDICINAL PRODUCT
BREZTRI AEROSPHERE 5 micrograms/9 micrograms/160 micrograms pressurised inhalation, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each single actuation (delivered dose, ex-actuator) contains 5 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 9 micrograms, and budesonide 160 micrograms.

This corresponds to a metered dose of 5.3 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 9.6 micrograms, and budesonide 170 micrograms.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Pressurised inhalation, suspension (pressurized inhalation). White suspension.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
BREZTRI AEROSPHERE is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

4.2. Posology and method of administration
Posology
The recommended and maximum dose is two inhalations twice daily (two inhalations in the morning and two inhalations in the evening).

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.

Special populations

Elderly

No dose adjustments are required in elderly patients (see section 5.2).

Renal impairment

BREZTRI AEROSPHERE can be used at the recommended dose in patients with mild to moderate renal impairment. It can also be used at the recommended dose in patients with severe renal impairment or end-stage renal disease requiring dialysis, only if the expected benefit outweighs the potential risk (see sections 4.4 and 5.2).

Hepatic impairment

BREZTRI AEROSPHERE can be used at the recommended dose in patients with mild to moderate hepatic impairment. It can also be used at the recommended dose in patients with severe hepatic impairment, only if the expected benefit outweighs the potential risk (see sections 4.4 and 5.2).

Paediatric population

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

Method of administration

For inhalation use.

Instructions for use

To ensure proper administration of BREZTRI AEROSPHERE, the patient should be shown how to use the inhaler correctly by a physician or other healthcare professional, who should also regularly check the adequacy of the patient's inhalation technique. The patient should be advised to read the Package Leaflet carefully and follow the instructions for use as given in the leaflet.

Note: It is important to instruct the patients to:

- Not use the inhaler if the drying agent, which is inside the foil pouch, has leaked out of its packet. For best results the inhaler should be at room temperature before use.
- Prime the inhaler by shaking it and actuating into the air four times before first use or two times when the inhaler has not been used for more than seven days, after weekly washing or if it has been dropped.
- Rinse their mouth out with water after inhaling the dose to minimise the risk of oropharyngeal thrush. Do not swallow.

On actuation of BREZTRI AEROSPHERE, a volume of the suspension is expelled from the pressurized container. When the patient inhales through the mouthpiece at the same time as actuating the inhaler, the substance will follow the inspired air into the airways.

Patients who find it difficult to coordinate 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 (see section 5.2).

4.3. Contraindication

Hypersensitivity to the active substances or any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Not for acute use

BREZTRI AEROSPHERE is not indicated for the treatment of acute episodes of bronchospasm, i.e. as a rescue therapy.

Paradoxical bronchospasm

Administration of formoterol/glycopyrronium bromide/budesonide may produce paradoxical bronchospasm with an immediate wheezing and shortness of breath after dosing and may be life-threatening.

Treatment with BREZTRI AEROSPHERE should be discontinued immediately if paradoxical bronchospasm occurs. The patient should be assessed, and alternative therapy instituted if necessary.

Deterioration of disease

It is recommended that treatment with BREZTRI AEROSPHERE should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment, but medical attention must be sought. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden and progressive deterioration in the symptoms of COPD is potentially life-threatening and the patient should undergo urgent medical assessment.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including glycopyrronium bromide and formoterol. BREZTRI AEROSPHERE should be used with caution in patients with clinically significant uncontrolled and severe cardiovascular disease such as unstable 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 (QTc > 450 milliseconds for males, or > 470 milliseconds for females), either congenital or induced by medicinal products.

Systemic corticosteroid 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 inhalation treatment 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.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids (see section 4.8).

Transfer form 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.

Pneumonia in patients with COPD
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. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections 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.

Hypokalaemia
Potentially serious hypokalaemia may result from β2-agonist therapy. This has the potential to produce adverse cardiovascular effects. Particular caution is advised in severe COPD as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see section 4.5).

Hyperglycaemia
Inhalation of high doses of β2-adrenergic agonists may produce increases in plasma glucose. Therefore, blood glucose should be monitored during treatment following established guidelines in patients with diabetes.

Co-existing conditions
BREZTRI AEROSPHERE should be used with cautions in patients with thyrotoxicosis.

Anticholinergic activity
Due to its anticholinergic activity, BREZTRI AEROSPHERE should be used with caution in patients with symptomatic prostatic hyperplasia, urinary retention or with narrow-angle glaucoma. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using BREZTRI AEROSPHERE and to contact their doctor immediately should any of these signs or symptoms develop.

Co-administration of BREZTRI AEROSPHERE with other anticholinergic containing medicinal products is not recommended (see section 4.5).

Renal impairment
As glycopyrronium bromide is predominantly renally excreted, patients with severe renal impairment (creatinine clearance of <30 mL/min), including those with end-stage renal disease requiring dialysis, should only be treated with Breztri Aerosphere if the expected benefit outweighs the potential risk (see section 5.2).

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). These patients should be monitored for potential adverse reactions.

4.5. Interaction with other medicinal product and other forms of interaction

Pharmacokinetic interactions

Clinical drug-drug interaction studies have not been conducted with BREZTRI AEROSPHERE, however, the potential for metabolic interactions is considered to be low based on in-vitro studies (see section 5.2).

Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations (see section 5.2). Budesonide and glycopyrronium bromide do not inhibit or induce CYP450 enzymes at therapeutically relevant concentrations.

The metabolism of budesonide is primarily mediated by CYP3A4 (see section 5.2). 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, and should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid adverse reactions, in which case patients should be monitored for systemic corticosteroid adverse reactions. This is of limited clinical importance for short-term (1-2 weeks) treatment.

Limited data about this interaction for high-dose inhaled budesonide indicates that marked increases in plasma levels (on average four-fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 micrograms).

Since glycopyrronium bromide is eliminated mainly by the renal route, drug interaction could potentially occur with medicinal products affecting renal excretion mechanisms. In vitro, glycopyrronium bromide 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 bromide 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.

Pharmacodynamic interactions

Other antimuscarinics and sympathomimetics

Co-administration of BREZTRI AEROSPHEREwith 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 beta2-adrenergic agonist adverse reactions (see section 4.4 and section 4.9).

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.

Medicinal product-induced hypokalaemia

Possible initial hypokalaemia may be potentiated by concomitant medicinal products, including xanthine derivatives, steroids and non-potassium sparing diuretics (see section 4.4). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

β-adrenergic blockers

β-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol. Concurrent use of β-adrenergic blockers should be avoided unless the expected benefit outweighs the potential risk. If β-adrenergic blockers are required, cardio-selective β-adrenergic blockers are preferred.

Other pharmacodynamic interactions
Concomitant treatment with quinidine, disopyramide, procainamide, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants and phenothiazines can prolong the QT interval and increase the risk of ventricular arrhythmias. In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including medicinal products with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of budesonide, glycopyrronium bromide and formoterol in pregnant women.

Data on the use of inhaled budesonide in more than 2,500 exposed pregnancies indicate no increased teratogenic risk associated with budesonide. Single-dose studies in humans found that very small amounts of glycopyrronium bromide passed the placental barrier.

There is no experience with or evidence of safety issues on the use of the propellant norflurane (HFA134a) during human pregnancy or lactation. However, studies on the effect of HFA134a on the reproductive function and embryofoetal development in animals revealed no clinically relevant adverse effects.

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 glycopyrronium bromide had no significant effects on reproduction (see section 5.3).

Administration of BREZTRI AEROSPHERE to pregnant women should only be considered if the expected benefit to the mother justifies the potential risk to the foetus.

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 bromide or formoterol are excreted in human milk. Evidence of transfer of glycopyrronium bromide 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 adverse effects on fertility only at dose levels higher than the maximum human exposure to formoterol (see section 5.3). Budesonide and glycopyrronium bromide 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

BREZTRI AEROSPHERE has no or negligible influence on the ability to drive and use machines. However dizziness is an uncommon side effects which should be taken into account when driving or using machines.

4.8. Undesirable effects

Summary of the safety profile
The safety profile is characterised by corticosteroid, anticholinergic and β2-adrenergic class effects

related to the individual components of the combination. The most commonly reported adverse reactions in patients receiving BREZTRI AEROSPHERE were pneumonia (4.6%), headache (2.7%) and urinary tract infection (2.7%).

Tabulated list of adverse reactions
The tabulated list of adverse reactions is based on the experience with BREZTRI AEROSPHERE in clinical trials and experience with the individual components.

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 reactions by frequency and system organ class (SOC)

System Organ Class	**Preferred term**	**Frequency**
Infections and infestations	Oral candidiasis Pneumonia	Common
Immune system disorders	Hypersensitivity	Uncommon
	Angioedema	Not known
Endocrine disorders	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland	Very rare
Metabolism and nutrition disorders	Hyperglycaemia	Common
Psychiatric disorders	Anxiety Insomnia	Common
	Depression Agitation Restlessness Nervousness	Uncommon
	Abnormal behaviour	Very rare
Nervous system disorders	Headache	Common
	Dizziness Tremor	Uncommon

Eye disorder	Vision blurred (see section 4.4) Cataract Glaucoma	Not known
Cardiac disorders	Palpitations	Common
	Angina pectoris Tachycardia Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles)	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough	Common
	Throat irritation Bronchospasm	Uncommon
Gastrointestinal disorders	Dry mouth	Common
	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Bruising	Uncommon
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
Renal and urinary disorders	Urinary tract infection	Common
	Urinary retention	Uncommon
General disorders and administration site conditions	Chest pain	Uncommon

Description of selected adverse reactions

Pneumonia

KRONOS was a 24-week study in a total of 1,896 patients with moderate to very severe COPD (mean post-bronchodilator screening FEV1 50% of predicted, standard deviation [SD] 14%), 26% of whom had experienced a COPD exacerbation in the year prior to study entry. The incidence of confirmed pneumonia events reported up to 24 weeks was 1.9% (12 patients) for BREZTRI AEROSPHERE (n=639), 1.6% (10 patients) for formoterol fumarate dihydrate/glycopyrronium bromide (FOR/GLY) MDI 5/9 micrograms (n=625), 1.9% (6 patients) for formoterol fumarate dihydrate/budesonide (FOR/BUD) MDI 5/160 micrograms (n=314) and 1.3% (4 patients) for open- labelled formoterol fumarate dihydrate/budesonide Turbuhaler (FOR/BUD) TBH 6/200 micrograms (n=318). In KRONOS, there were no fatal cases of pneumonia with Breztri Aerosphere.

ETHOS was a 52-week study in a total of 8,529 patients (in the safety population) with moderate to very severe COPD and a history of moderate or severe exacerbations within the prior 12 months (mean post-bronchodilator screening FEV1 43% of predicted, SD 10%). The incidence of confirmed pneumonia was 4.2% (90 patients) for BREZTRI AEROSPHERE (n=2144), 3.5% (75 patients) for formoterol fumarate dihydrate/glycopyrronium bromide/budesonide (FOR/GLY/BUD) MDI 5/9/80 micrograms (n=2124), 2.3% (48 subjects) for FOR/GLY MDI 5/9 micrograms (n=2125) and 4.5% (96 subjects) FOR/BUD MDI 5/160 micrograms (n=2136). In ETHOS, there were five fatal cases of pneumonia during the treatment phase of the study (two with FOR/GLY/BUD MDI 5/9/80, three with FOR/GLY MDI and none with BREZTRI AEROSPHERE).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of BREZTRI AEROSPHERE is important. It allows continued monitoring of the benefit/risk balance of the BREZTRI AEROSPHERE.

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9. Overdose

An overdose 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. When used chronically in excessive doses, systemic glucocorticosteroid effects may appear.

There is no specific treatment for an overdose with BREZTRI AEROSPHERE. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases: adrenergics in combination with anticholinergics including triple combinations with corticosteroids, ATC code: R03AL11.

Mechanism of action

BREZTRI AEROSPHERE contains budesonide, a glucocorticosteroid, and two bronchodilators: glycopyrronium bromide, a long-acting muscarinic antagonist (anticholinergic) and formoterol, a long-acting β2-adrenergic agonist.

Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose dependent anti-inflammatory action in the airways.

Glycopyrronium bromide is a long-acting, muscarinic antagonist, which is often referred to as an anticholinergic. The major targets for anticholinergic drugs are muscarinic receptors located in the respiratory tract. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. Antagonism is competitive and reversible. Prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose dependent and lasted more than 12 hours.

Formoterol is a selective β2-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy

The efficacy and safety of BREZTRI AEROSPHERE was evaluated in patients with moderate to very severe COPD in two randomised, parallel-group trials, ETHOS and KRONOS. Both studies were multicentre, double-blind studies. Patients were symptomatic with a COPD Assessment Test (CAT) score ≥10 while receiving two or more daily maintenance therapies for at least 6 weeks prior to screening.

ETHOS was a 52-week trial (N=8,588 randomised; 60% male, mean age of 65) that compared two inhalations twice daily of BREZTRI AEROSPHERE, formoterol fumarate dihydrate/glycopyrronium bromide (FOR/GLY) MDI 5/9 micrograms, and formoterol fumarate dihydrate/budesonide

(FOR/BUD) MDI 5/160 micrograms. Patients had moderate to very severe COPD (post-bronchodilator FEV1
≥25% to <65% predicted) and were required to have a history of one or more moderate or severe COPD exacerbations in the year prior to screening. The proportion of patients with moderate, severe and very severe COPD was 29%, 61% and 11% respectively. The mean baseline FEV1 across all groups was 1,021-1,066 mL, and during screening the mean post-bronchodilator percent predicted FEV1 was 43% and mean CAT score was 19.6. The primary endpoint of the ETHOS trial was the rate of on-treatment moderate or severe COPD exacerbations for BREZTRI AEROSPHERE compared with FOR/GLY MDI and FOR/BUD MDI.

KRONOS was a 24-week trial (N=1,902 randomised; 71% male, mean age of 65) that compared two inhalations twice daily of BREZTRI AEROSPHERE, FOR/GLY MDI 5/9 micrograms, FOR/BUD MDI 5/160 micrograms and open-label active comparator formoterol fumarate dihydrate/budesonide Turbuhaler (FOR/BUD TBH) 6/200 micrograms. Patients had moderate to very severe COPD (postbronchodilator FEV1 ≥25% to <80% predicted). The proportion of patients with moderate, severe and very severe COPD was 49%, 43% and 8% respectively. The mean baseline FEV1 across all groups was 1,050-1,193 mL, and during screening the mean post-bronchodilator percent predicted FEV1 was 50%, over 26% of patients reported a history of one or more moderate or severe COPD exacerbation in the past year and the mean CAT score was 18.3. There was a 28-week extension, for up to 52 weeks of treatment, in a subset of subjects. The primary endpoints of the KRONOS trial were the on-treatment FEV1 area under the curve from 0-4 hours (FEV1 AUC0-4) over 24 weeks for BREZTRI AEROSPHERE compared to FOR/BUD MDI and the on-treatment change from baseline in morning pre-dose trough FEV1 over 24 weeks for Breztri Aerosphere compared to FOR/GLY MDI.

At study entry, the most common COPD medications reported in the ETHOS and KRONOS studies were ICS+LABA+LAMA (39%, 27% respectively), ICS+LABA (31%, 38% respectively) and LAMA+LABA (14%, 20% respectively).

Effect on exacerbations
Moderate or severe exacerbations:
In the 52-week ETHOS study, BREZTRI AEROSPHERE significantly reduced the annual rate of on-treatment moderate/severe exacerbations by 24% (95% CI: 17, 31; p<0.0001) compared with FOR/GLY MDI (rate; 1.08 vs 1.42 events per patient year) and by 13% (95% CI: 5, 21; p=0.0027) compared with FOR/BUD MDI (rate; 1.08 vs 1.24 events per patient year).

The benefits observed on annualised rate of moderate/severe COPD exacerbations over 24 weeks in KRONOS were generally consistent with those observed in ETHOS. Improvements compared with FOR/GLY MDI were statistically significant; however improvements compared with FOR/BUD MDI and FOR/BUD TBH did not reach statistical significance.

Severe exacerbations (resulting in hospitalisation or death):
In ETHOS, BREZTRI AEROSPHERE numerically reduced the annual rate of on-treatment severe exacerbations by 16% (95% CI: -3, 31; p=0.0944) compared with FOR/GLY MDI (rate; 0.13 vs 0.15 events per patient year) and significantly reduced the annual rate of on-treatment severe exacerbations by 20% (95% CI: 3, 34; p=0.0221) compared with FOR/BUD MDI (rate; 0.13 vs 0.16 events per patient year).

In both studies, benefits on exacerbations were observed in patients with moderate, severe and very severe COPD.

Effect on lung function

In ETHOS and KRONOS, BREZTRI AEROSPHERE improved on-treatment lung function (FEV1) compared with FOR/GLY MDI and FOR/BUD MDI (see Table 2 for ETHOS and Table 3 for KRONOS). There as a sustained effect over the 24-week treatment period in both studies, and over 52 weeks in ETHOS.

Table 2: Lung function analysis - ETHOS (spirometric sub-study)

	Breztri Aerosphere (N=747)	**FOR/GLY MDI (N=779)**	**FOR/BUD MDI (N=755)**	**Treatment difference 95% CI**	
				Breztri Aerosphere vs. FOR/GLY MDI	**Breztri Aerosphere vs. FOR/BUD MDI**
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	129 (6.5)	86 (6.6)	53 (6.5)	43 mL (25, 60) p<0.0001	76 mL (58, 94) p<0.0001#
FEV_1 AUC_{0-4} over 24 weeks; LS mean change from baseline (SE)	294 (6.3)	245 (6.5)	194 (6.3)	49 mL (31, 66) p<0.0001#	99 mL (82, 117) p<0.0001

# p-value not adjusted for multiplicity in hierarchical testing plan
LS = least square, SE = standard error, CI = confidence intervals, N = number in Intent-to-Treat population

Table 3: Lung function analyses - KRONOS

	Breztri Aero-sphere (N=639)	**FOR/ GLY MDI (N=625)**	**FOR/ BUD MDI (N=314)**	**FOR/ BUD TBH (N=318)**	**Treatment difference 95% CI**		
					Breztri Aerosphere vs. FOR/GLY MDI	**Breztri Aerosphere vs. FOR/BUD MDI**	**Breztri Aerosphere vs. FOR/BUD TBH**
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	147 (6.5)	125 (6.6)	73 (9.2)	88 (9.1)	22 mL (4, 39) p=0.0139	74 mL (52, 95) p<0.0001	59 mL (38, 80) p<0.0001#
FEV_1 AUC_{0-4} over 24	305 (8.4)	288 (8.5)	201 (11.7)	215 (11.5)	16 mL (-6, 38) p=0.1448#	104 mL (77, 131) p<0.0001	91 mL (64, 117) p<0.0001

weeks; LS mean change from baseline (SE)							

# p-value not adjusted for multiplicity in hierarchical testing plan
LS = least square, SE = standard error, CI = confidence intervals, N = number in Intent-to-Treat population

Symptom relief

In ETHOS, the baseline average dyspnoea scores ranged from 5.8 – 5.9 across the treatment groups. BREZTRI AEROSPHERE significantly improved breathlessness (measured using the Transition Dyspnoea Index (TDI) focal score over 24 weeks) compared with FOR/GLY MDI (0.40 units; 95% CI: 0.24, 0.55; p<0.0001) and compared with FOR/BUD MDI (0.31 units; 95% CI: 0.15, 0.46; p<0.0001). Improvements were sustained over 52 weeks. In KRONOS, the baseline average dyspnoea scores ranged from 6.3 – 6.5 across the treatment groups. Breztri Aerosphere significantly improved breathlessness over 24 weeks compared with FOR/BUD TBH (0.46 units; 95% CI: 0.16, 0.77; p=0.0031). Improvements compared with FOR/GLY MDI, and FOR/BUD MDI did not reach statistical significance.

Health-related quality of life

In ETHOS, BREZTRI AEROSPHERE significantly improved disease-specific health status (as assessed by the St. George's Respiratory Questionnaire [SGRQ] total score) over 24 weeks compared with FOR/GLY MDI (improvement -1.62; 95% CI: -2.27, -0.97; p<0.0001) and compared with FOR/BUD MDI (improvement -1.38, 95% CI: -2.02, -0.73; p<0.0001). Improvements were sustained over 52 weeks. In KRONOS, improvements compared with FOR/GLY MDI, FOR/BUD MDI and FOR/BUD TBH did not reach statistical significance.

Use of rescue medication

In ETHOS, BREZTRI AEROSPHERE significantly reduced the on-treatment use of rescue medication over 24 weeks compared with FOR/GLY MDI (treatment difference -0.51 puffs/day; 95% CI: -0.68, - 0.34; p<0.0001) and FOR/BUD MDI (treatment difference -0.37 puffs/day; 95% CI: -0.54, -0.20; p<0.0001). Reductions were sustained over 52 weeks. In KRONOS, differences compared with FOR/GLY MDI, FOR/BUD MDI and FOR/BUD TBH were not statistically significant.

5.2. Pharmacokinetic properties

Following inhalation of the formoterol, glycopyrronium bromide and budesonide combination, the pharmacokinetics of each component was similar to those observed when each active substance was administered separately.

Effect of a spacer
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 bromide by 33% and 55%, respectively, while exposure to formoterol was unchanged. In patients with good inhalation technique, systemic exposure was not increased with the use of a spacer.

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 this BREZTRI AEROSPHERE and the extent of exposure is approximately 1.3 times higher than after the first dose.

Glycopyrronium bromide
Following inhaled administration of BREZTRI AEROSPHERE in subjects with COPD, glycopyrronium bromide 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 1200 L, via population pharmacokinetic analysis. Plasma protein binding is approximately 90% for budesonide.

Glycopyrronium bromide
The estimated glycopyrronium bromide 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 bromide 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%.

Biotransformation

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 β-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide.

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

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 bromide
After IV administration of a 0.2 mg dose of radiolabelled glycopyrronium bromide, 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 bromide 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
Dose adjustments are not necessary based on the effect of age, gender or weight on the pharmacokinetic parameters of budesonide, glycopyrronium bromide and formoterol. There were no major differences in total systemic exposure (AUC) for all compounds between healthy Japanese, Chinese and Western subjects. Insufficient pharmacokinetic data is available for other ethnicities or races.

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 bromide is primarily cleared from the systemic circulation by renal excretion and hepatic impairment would therefore not be expected to affect systemic exposure.

Renal impairment
Studies evaluating the effect of renal impairment on the pharmacokinetics of budesonide, glycopyrronium bromide and formoterol were not conducted.

The effect of renal impairment on the exposure to budesonide, glycopyrronium bromide 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 bromide 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. Subjects with COPD with both low body weight and moderate-severe impaired renal function may have an approximate doubling of systemic exposure to glycopyrronium bromide.

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.

No studies have been conducted with the combination of budesonide, glycopyrronium bromide and formoterol in respect of genotoxicity, carcinogenic potential and toxicity to reproduction and development.

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 bromide have shown reduced rat and rabbit foetal weights, and low body weight gain of rat offspring before weaning at considerably higher systemic exposure than those reached during clinical use. No evidence of carcinogenicity was seen in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Norflurane
1,2-distearoyl-sn-glycero-3-phosphocholine
Calcium chloride

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months
To be used within 3 months of opening the pouch.

6.4. Special precautions for storage

Do not store above 30^{o}C.
Do not expose to temperatures higher than 50°C. Do not pierce the pressurised container.
Store in dry place

6.5. Nature and contents of container

BREZTRI AEROSPHERE is a pressurised metered dose inhaler, comprising a coated aluminium canister, a yellow plastic actuator and white mouthpiece with an attached grey plastic dust cap, and a dose indicator. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed in to a carton.

Pack size of 1 container of 120 actuations.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The pressurised container should not be broken, punctured or burnt, even when apparently empty.

Date of revision of text

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HARUS DENGAN RESEP DOKTER

Manufactured by

AstraZeneca Dunkerque Production
224 Avenue de la Dordogne
Dunkerque - France

Imported by

PT AstraZeneca Indonesia Cikarang, Bekasi – Indonesia

Proposed packaging material		
Code	BREZTRI AEROSPHERE-PIL-02.01	
Submission	☐NDA ☐Renewal ☒ Variation change detail no.: TBC	
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Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: 09 Dec 2020 ☐GRL approval:
Name & Date	ADR, 05 Feb 24	

Leaflet Informasi Pasien

Breztri Aerosphere 5 mikrogram/9 mikrogram/160 mikrogram, suspensi inhalasi bertekanan

Formoterol fumarat dihidrat/Glikopironium bromida/Budesonide

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker, atau perawat Anda.
- Obat ini diresepkan khusus hanya untuk Anda. Jangan berikan obat ini kepada orang lain karena dapat membahayakan mereka meskipun tanda dan gejala penyakitnya sama dengan yang Anda miliki.
- Jika Anda mengalami efek samping, beri tahu dokter, apoteker, atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Informasi yang terkandung pada leaflet ini

1. Breztri Aerosphere dan kegunaannya

Breztri Aerosphere mengandung tiga bahan aktif, yaitu formoterol fumarat dihidrat, glikopironium bromida, dan budesonid.

- Formoterol fumarat dihidrat dan glikopironium bromida termasuk dalam kelompok

obat yang disebut bronkodilator. Formoterol fumarat dihidrat dan glikopironium bromida bekerja dengan cara yang berbeda dalam mencegah otot-otot sekitar saluran napas menyempit, sehingga memudahkan udara masuk dan keluar dari paru-paru.
- Budesonid termasuk dalam kelompok obat 'kortikosteroid'. Kortikosteroid bekerja dengan mengurangi peradangan pada paru-paru.

Breztri Aerosphere adalah suatu inhaler yang digunakan untuk pasien Penyakit Paru Obstruktif Kronik (PPOK) dewasa derajat sedang sampai berat, yang merupakan suatu penyakit jangka panjang pada saluran napas di paru-paru. Breztri Aerosphere inhaler digunakan untuk pasien PPOK yang tidak dapat diobati dengan menggunakan kombinasi inhalasi kortikosteroid dan Long-acting beta2-agonist (LABA) atau kombinasi Long-acting beta2-agonist (LABA) dan long-acting muscarinic antagonist (LAMA)

Bahan aktif Breztri Aerosphere akan langsung menuju saluran napas di paru-paru saat Anda bernapas. Jika Anda menggunakan Breztri Aerosphere secara teratur dua kali sehari, hal tersebut akan membantu mengurangi gejala PPOK.

2. **Hal yang perlu diketahui sebelum menggunakan Breztri Aerosphere**

Jangan gunakan Breztri Aerosphere jika
- Anda memiliki alergi terhadap formoterol fumarat dihidrat, glikopironium bromida, budesonid, atau salah satu bahan lainnya dari obat ini (tercantum di Bagian 6).

Peringatan dan pencegahan

Breztri Aerosphere digunakan sebagai terapi pemeliharaan PPOK jangka panjang. **Jangan gunakan obat ini untuk mengobati serangan sesak napas atau mengi yang mendadak.**

Kesulitan bernapas yang tiba-tiba

Jika Anda merasakan dada sesak, batuk, mengi atau sesak napas sesaat setelah menggunakan Breztri Aerosphere, **hentikan penggunaan Breztri Aerosphere dan segera hubungi dokter** (untuk informasi lebih lanjut, lihat 'Efek Samping Serius' pada Bagian 4).

Jika sesak napas, dada sesak, mengi atau batuk yang Anda rasakan memburuk saat menggunakan Breztri Aerosphere, sebaiknya Anda lanjutkan penggunaan Breztri Aerosphere namun tetap hubungi dokter Anda karena mungkin Anda memerlukan terapi tambahan.

Hubungi dokter Anda sebelum menggunakan Breztri Aerosphere, jika:
- Anda memiliki tekanan darah tinggi atau gangguan jantung
- Anda memiliki diabetes
- Anda memiliki infeksi saluran napas
- Anda memiliki gangguan pada kelenjar tiroid

- Kadar kalium dalam darah yang rendah
- Anda memiliki gangguan prostat atau kesulitan buang air kecil
- Anda memiliki gangguan mata yang disebut ‘glaukoma sudut tertutup’
- Anda memiliki gangguan ginjal atau hati

Hubungi dokter Anda, jika Anda memiliki salah satu atau beberapa kondisi tersebut.

Anak-anak dan remaja

Belum terdapat penelitian terkait penggunaan Breztri Aerosphere pada anak-anak dan remaja. Jangan berikan Breztri Aersphere pada anak-anak atau remaja di bawah usia 18 tahun.

Obat-obatan lain dan Breztri Aerosphere

Beri tahu dokter atau apoteker Anda jika Anda sedang menggunakan/baru-baru ini menggunakan/akan menggunakan obat-obatan lain, termasuk obat bebas (obat yang diperoleh tanpa resep) atau obat herbal. Hal ini dikarenakan Breztri Aerosphere dapat memengaruhi kerja dari beberapa obat-obatan. Beberapa obat-obatan juga dapat memengaruhi kerja dari Breztri Aerosphere, atau cenderung menimbulkan efek samping.

Beri tahu dokter atau apoteker Anda jika anda menggunakan obat-obatan seperti:

- obat-obatan yang disebut beta-bloker atau obat-obatan penghambat beta (seperti atenolol atau propranolol), yang digunakan untuk mengobati tekanan darah tinggi atau gangguan jantung, atau untuk mengobati glaucoma (seperti timolol).
- obat-obatan yang digunakan untuk mengobati infeksi jamur – seperti ketokonazol atau itrakonazol
- obat-obatan yang digunakan untuk mengobati infeksi HIV – seperti ritonavir atau *cobicistat*
- obat-obatan yang digunakan untuk menurunkan kadar kalium dalam darah, seperti:
    - kortikosteroid oral (seperti prednisolon),
    - diuretik – obat yang digunakan untuk meningkatkan produksi urin (seperti furosemide atau hidroklortiazid), yang dapat digunakan untuk mengobati tekanan darah tinggi,
    - obat-obatan yang digunakan untuk mengobati gangguan napas (seperti teofilin) – yang disebut dengan metilxantin,
- obat-obatan yang memiliki cara kerja sama seperti Breztri Aerosphere – seperti tiotropoum, ipratropium, aclidinium, umeclidinium atau salmeterol, arformoterol, vilanterol, olodaterol atau indacaterol. Jangan gunakan Breztri Aerosphere jika Anda telah menggunakan obat-obatan tersebut.
- obat-obatan yang digunakan untuk mengobati gangguan irama jantung – seperti amiodaron
- obat-obatan yang dapat memengaruhi aktivitas jantung (disebut dengan “interval QT”) – seperti obat-obatan untuk:
    - depresi (seperti inhibitor monoamin oksidase atau antidepresan trisiklik),
    - infeksi bakteri (seperti eritromisin, klaritromisin, telitromisin),
    - reaksi alergi (anti-histamin).

Apabila Anda mengalami salah satu gejala diatas, atau jika Anda tidak yakin, konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan Breztri Aerosphere.

Kehamilan dan menyusui
Jika Anda sedang hamil atau menyusui, kemungkinan hamil, atau berencana memiliki bayi, beri tahu dokter atau apoteker Anda sebelum menggunakan Breztri Aerosphere.

Jangan gunakan Breztri Aerosphere jika Anda sedang hamil, kecuali atas izin dokter Anda. Jangan gunakan Breztri Aerosphere jika Anda sedang menyusui, kecuali atas izin dokter Anda.

Mengemudi dan mengoperasikan mesin
Kecil kemungkinan Breztri Aerosphere dapat memengaruhi kemampuan mengemudi atau mengoperasikan mesin. Namun, pusing merupakan efek samping yang jarang terjadi sehingga Anda harus berhati-hati saat mengemudi atau mengoperasikan mesin.

3. Cara menggunakan Breztri Aerosphere

Selalu gunakan obat ini sesuai dengan yang diinstruksikan oleh dokter Anda. Tanyakan kembali kepada dokter atau apoteker Anda jika Anda tidak yakin.

Dosis penggunaan
Dosis yang dianjurkan adalah dua *puff* dua kali sehari – dua *puff* pada pagi hari dan dua *puff* pada malam hari. Penting untuk menggunakan Breztri Aerosphere setiap hari meskipun Anda tidak memiliki gejala PPOK.

Ingat: Selalu berkumur dengan air setelah menggunakan Breztri Aerosphere. Hal ini bertujuan untuk membersihkan kemungkinan obat yang tertinggal dalam mulut. Buang air kumur tersebut, jangan ditelan.

Cara penggunaan
Breztri Aerosphere digunakan untuk penggunaan inhalasi.
Bacalah petunjuk “Instruksi Penggunaan” di akhir leaflet ini. Jika Anda tidak yakin tentang cara menggunakan Breztri Aerosphere, hubungi dokter atau apoteker Anda.

Menggunakan Breztri Aerosphere dengan *spacer*
Jika Anda kesulitan untuk bernapas sambil menekan inhaler secara bersamaan, konsultasikan dengan dokter atau apoteker Anda. Anda dapat memasang alat bantu yang disebut '*spacer*' pada inhaler Anda.

Jika Anda menggunakan Breztri Aerosphere lebih banyak dari yang seharusnya
Jika Anda telah menggunakan Breztri Aerosphere lebih dari yang seharusnya, segera konsultasikan dengan dokter atau apoteker. Anda mungkin memerlukan pertolongan medis. Anda mungkin merasakan detak jantung yang lebih cepat dari biasanya, merasa gemetar, gangguan penglihatan, mulut kering, sakit kepala atau mual (tidak enak badan).

Jika Anda lupa menggunakan Breztri Aerosphere
Jangan mengonsumsi dosis ganda untuk mengganti dosis yang terlewat. Gunakan segera saat ingat. Namun, jika sudah mendekati waktu untuk dosis berikutnya, abaikan dosis yang terlewat. Jangan menggunakan lebih dari dua *puff* dua kali sehari pada hari yang sama.

Jika Anda berhenti menggunakan Breztri Aerosphere
Breztri Aerosphere digunakan untuk penggunaan jangka panjang. Gunakan Breztri Aerosphere seperti yang diinstruksikan oleh dokter. Breztri Aerosphere hanya akan efektif selama Anda menggunakannya.

Jangan berhenti menggunakan Breztri Aerosphere kecuali atas anjuran dokter, meskipun Anda merasa lebih baik, bisa jadi gejala Anda bertambah buruk. Jika Anda ingin menghentikan pengobatan, konsultasikan dengan dokter Anda terlebih dahulu.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, konsultasikan dengan dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi
Seperti obat-obatan lainnya, obat ini dapat menyebabkan efek samping meskipun tidak semua orang dapat mengalaminya.

Efek samping serius
Jarang (dapat dialami 1 dari 100 orang)

Kesulitan bernapas yang tiba-tiba
- jika Anda merasa sulit bernapas sesaat setelah menggunakan Breztri Aerosphere, seperti dada sesak, batuk, mengi atau sesak napas, **segera hentikan penggunaan Breztri Aerosphere dan segera hubungi dokter.**

Reaksi alergi:
- bengkak pada wajah, terutama di area sekitar mulut (pembengkakan lidah atau tenggorokan dapat membuat Anda sulit menelan);
- ruam atau gatal-gatal disertai kesulitan bernapas

- tiba-tiba merasa lemas.

Gejala tersebut merupakan tanda-tanda terjadinya reaksi alergi yang dapat menjadi serius. Hentikan penggunaan Breztri Aerosphere dan segera cari pertolongan medis jika Anda menyadari salah satu dari gejala reaksi alergi.

Efek samping lainnya

Beri tahu dokter atau apoteker Anda jika ada merasakan gejala-gejala dari efek samping:

Umum (dapat dialami 1 dari 10 orang)
- sariawan di mulut (infeksi jamur). Segera berkumur dengan air sesaat setelah menggunakan Breztri Aerosphere untuk mencegah terjadinya sariawan merasa gelisah
- sulit tidur
- tidak enak badan (mual)
- sakit kepala
- batuk atau suara serak
- kram otot
- jantung berdebar (palpitasi)
- kadar gula darah tinggi (ditunjukkan dengan hasil uji)
- sering buang air kecil dan terasa nyeri (mungkin merupakan tanda infeksi saluran kencing)
- pneumonia (infeksi saluran napas)

Hubungi dokter jika Anda merasakan gejala berikut saat menggunakan Breztri Aerosphere.

Gejala-gejala berikut dapat menunjukkan terjadinya infeksi saluran napas:
- demam atau menggigil
- produksi mukus meningkat, warna mukus berubah
- batuk menjadi lebih parah atau kesulitan bernapas

Jarang (dapat dialami 1 dari 100 orang)
- gemetar, tremor atau pusing
- mulut kering atau iritasi tenggorokan sedang
- memar pada kulit
- gelisah, gugup atau agitasi
- depresi
- denyut jantung berdetak cepat atau denyut jantung yang tidak beraturan
- nyeri dada atau dada terasa sesak (angina pektoris)

Sangat jarang (dapat dialami 1 dari 10.000 orang)
- perubahan perilaku
- terjadi perubahan pada kelenjar adrenal

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
- pandangan kabur
- kekeruhan pada lensa mata (tanda-tanda katarak)
- tekanan pada mata meningkat (glaucoma)
- bengkak pada wajah, terutama di sekitar mulut (pembengkakkan pada lidah atau

tenggorokan yang menyebabkan kesulitan menelan)

Pelaporan efek samping

Jika Anda mengalami efek samping, komunikasikan kepada dokter atau apoteker Anda. Termasuk efek samping yang mungkin terjadi yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda membantu memberikan informasi lebih lanjut mengenai
keamanan obat ini.

5. Cara penyimpanan Breztri Aeroshere

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan Breztri Aerosphere jika telah lewat tanggal kedaluwarsa yang tertera pada karton, kantong, dan tabung *canister* setelah tanda 'EXP'. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.

Inhaler dapat digunakan hingga **3 bulan** setelah pertama kali kantong dibuka.

Inhaler harus selalu tersimpan dalam kantong tertutup. Inhaler hanya dikeluarkan dari kantong jika akan digunakan saja. Saat kantong pertama kali dibuka, tulis tanggal kantong dibuka pada label inhaler di tempat yang tersedia.

Jangan disimpan di atas suhu 30°C. Simpan pada tempat yang kering.

Untuk mendapatkan hasil seperti yang diharapkan, sebaiknya inhaler disimpan pada suhu ruang sebelum digunakan.

Jangan merusak, menusuk, atau membakar tabung *canister*, meskipun tampaknya kosong. Jangan digunakan atau disimpan dekat panas atau api.

Jangan membuang obat ini ke saluran pembuangan air atau limbah rumah tangga. Tanyakan pada apoteker Anda mengenai cara membuang sisa obat yang sudah tidak digunakan lagi. Hal ini dapat membantu melindungi lingkungan hidup

6. Isi kemasan dan informasi lain

Kandungan Breztri Aerosphere

Bahan aktif Breztri Aerosphere terdiri atas formoterol fumarat dihidrat, glikopironium bromida dan budesonide.

Tiap satu kali inhalasi (*puff*) memberikan dosis (dosis yang keluar dari *mouthpiece*) 5 mikrogram formoterol fumarat dihidrat, 9 mikrogram glikopironium bromida dan 160 mikrogram budesonide.

Bahan lainnya adalah norfluran, 1,2- distearoyl-sn-glycero-3-phosphocholine dan kalsium klorida.

Bentuk dan isi kemasan Breztri Aerosphere

Breztri Aerosphere adalah suspensi inhalasi bertekanan.

Breztri Aerosphere tersedia dalam bentuk tabung *canister* dengan indikator dosis, dilengkapi dengan badan aktuator plastik berwarna kuning dan corong mulut (*mouthpiece*) berwarna putih. *Mouthpiece* dilengkapi tutup pelindung berwarna abu-abu.

Breztri Aerosphere tersedia dalam kantong berbahan foil yang berisi bahan pengering (desikan) dan dikemas dalam kemasan karton.

Tiap inhaler mengandung 120 *puff*

Breztri Aerosphere tersedia dalam kemasan yang berisi 1 inhaler dengan 120 dosis

HARUS DENGAN RESEP DOKTER

Diimpor oleh:
PT. AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Produsen
AstraZeneca Dunkerque Production
224 Avenue de la Dordogne
Dunkerque – France

Leaflet terakhir direvisi :05 Februari 2024
Nomor izin edar : DKI2304900468A1
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7. PETUNJUK PENGGUNAAN

Breztri Aerosphere

(formoterol fumarat dihidrat/glikopironium bromida/budesonide) Suspensi inhalasi bertekanan

Untuk penggunaan inhalasi oral

Bacalah petunjuk penggunaan berikut dengan seksama

Breztri Aerosphere (yang disebut 'inhaler' dalam leaflet ini) mungkin berbeda dengan inhaler yang Anda pernah gunakan sebelumnya.

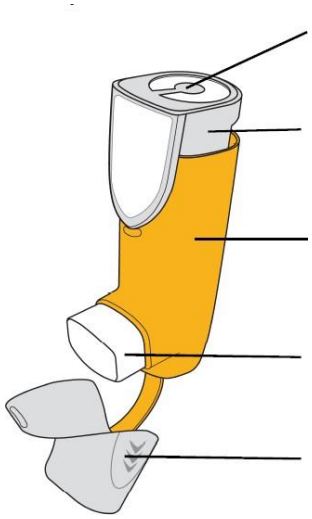
Informasi penting

- **Hanya untuk penggunaan inhalasi oral**
- **Persiapkan inhaler Anda untuk penggunaan pertama kali dengan cara *priming* (persiapan awal)**
- **Bilas badan aktuator plastik yang berwarna kuning setiap minggu**
- **Gunakan 2 *puff* di pagi hari dan 2 *puff* di malam hari**

Cara penyimpanan inhaler Anda

- Jangan disimpan pada suhu di atas 30°C. Simpan di tempat yang kering
- Jangan disimpan pada lingkungan yang lembab, seperti kamar mandi
- Simpan inhaler dan obat-obatan lainnya jauh dari pandangan dan jangkauan anak-anak

Bagian-bagian inhaler



Indikator *puff*

Terletak di atas dari tabung *canister* bertekanan

Tabung *canister* bertekanan (di dalam)

Berisi bahan aktif yang terkandung

Aktuator

Mengandung *canister* bertekanan

Mouthpiece

Menyemprotkan bahan aktif yang terkandung

Penutup *mouthpiece*

Melindungi *mouthpiece* saat inhaler tidak digunakan

Cara membaca indikator *puff*/dosis

***Indikator *puff* akan berkurang 1 (satu) setiap kali Anda menggunakan 1 (satu) *puff*/dosis**

Garis Petunjuk

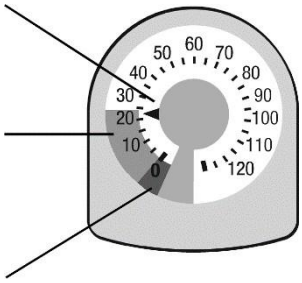
Menunjukkan jumlah *puff* yang tersisa

Zona kuning

Segera ganti dengan inhaler baru saat garis petunjuknya berada pada zona kuning

Zona merah

Buang inhaler saat garis petunjuknya berada di angka 0 pada zona merah



Jangan mengisap saat garis petunjuk menunjukkan angka 0 karena Anda tidak akan mendapatkan dosis penuh.

Ganti inhaler baru

Ganti inhaler dengan yang baru saat petunjuk pada indikator *puff* berada pada bagian kuning

Buang inhaler

Buang inhaler dengan mengikuti langkah-langkah yang sesuai, saat:

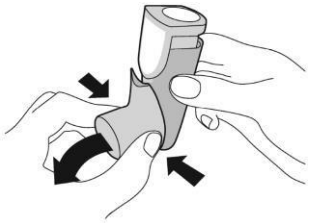
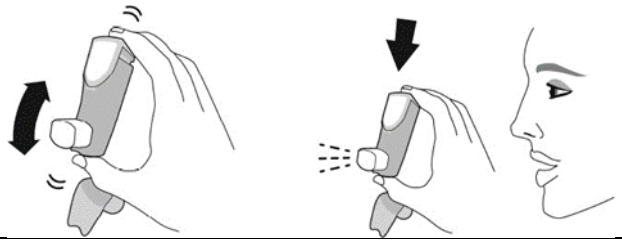
- Indikator *puff*/dosis menunjukkan 0, atau
- **3 bulan** setelah inhaler Anda dikeluarkan dari dalam kantong berbahan foil

Aktuator jangan digunakan kembali dengan *canister* yang berisi obat dari inhaler lain

Jangan menusuk atau membuang *canister* ke dalam api atau insenerator

SEBELUM PENGGUNAAN PERTAMA KALI – Inhaler disiapkan dengan cara *priming* sebanyak 4 kali sebelum pertama kali digunakan

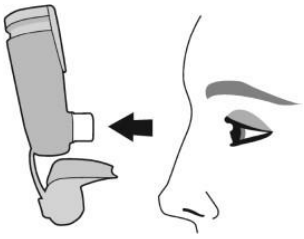
- Sebelum menggunakan inhaler untuk pertama kali, Anda harus menyiapkan inhaler dengan cara *priming* sehingga Anda akan mendapatkan jumlah obat yang tepat saat Anda menggunakan Breztri Aerosphere.

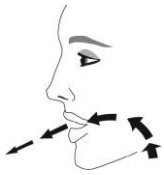
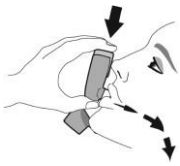
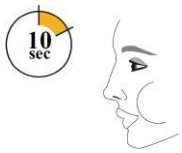
***Priming* 1**
Lepaskan penutup *mouthpiece* 
***Priming* 2**
Kocok inhaler dengan baik dan semprotkan 1 *puff* uji ke udara dengan mengarah jauh dari Anda. Ulangi sebanyak empat (4) kali *puff* uji (*priming)*, kocok setiap sebelum menyemprotkan *puff* uji. **Total 4x** **Kocok dan semprotkan puff uji** 
Puff ekstra disediakan untuk *priming.* **Jangan lewatkan tahapan *priming***

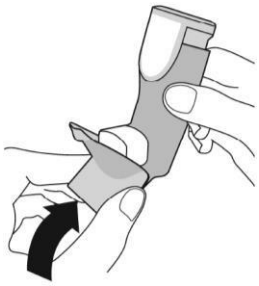
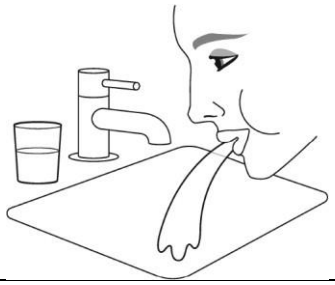
Lakukan *priming* ulang inhaler Anda: • Setelah membilas actuator • Bila terjatuh • Bila tidak digunakan lebih dari 7 hari	Untuk melakukan *priming* ulang, semprotkan 2 *puff* uji, kocok sebelum menyemprotkan setiap *puff* uji **Total 2x** **Kocok dan semprotkan puff uji**

PENGGUNAAN SEHARI-HARI, pagi dan malam – Isap obat Anda (Breztri Aerosphere)

- Dosis harian: 2 *puff/*dosis di pagi hari dan 2 *puff/*dosis di malam hari
- Berkumurlah dengan air setelah menggunakan 2 *puff/*dosis untuk mencegah infeksi jamur

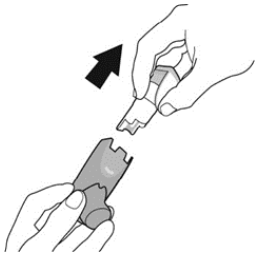
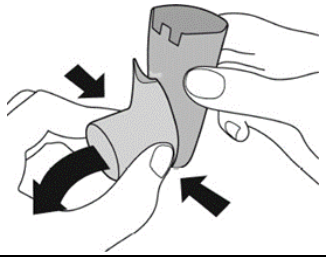
Langkah 1
Lepaskan penutup *mouthpiece.* **Periksa bagian *mouthpiece,* dan pastikan tidak ada benda asing di dalam *mouthpiece* tersebut sebelum digunakan.** 

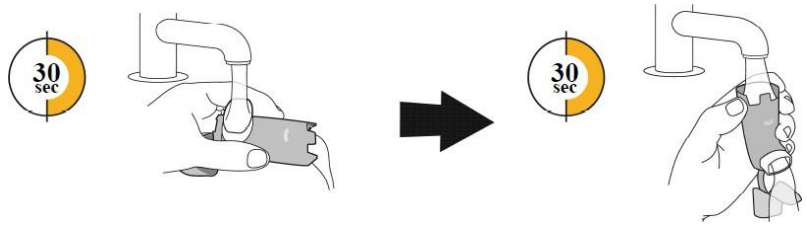
Langkah 2				
Kocok inhaler terlebih dahulu setiap hari sebelum digunakan	Hembuskan napas secara dalam	Letakkan *mouthpiece* pada mulut Anda dan rapatkan bibir Anda di sekitar *mouthpiece*. Kepala Anda ditengadahkan ke atas, posisikan lidah Anda di bawah *mouthpiece*	Tarik napas dalam- dalam dan perlahan sambil menyemprotkan 1 puff. Lanjutkan menarik napas secara maksimal	Tahan napas selama mungkin yang Anda bisa hingga **10 detik**
				

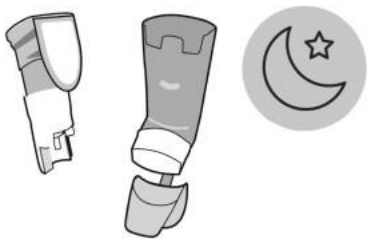
Langkah 3	Langkah 4	Langkah 5
Ulangi Langkah 2 untuk *puff* kedua	Letakkan kembali penutup *mouthpiece.* 	Berkumurlah dengan air. Buang air kumur tersebut. **Jangan ditelan.** 

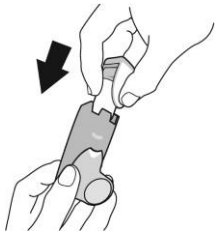
BILAS MINGGUAN – Bilas aktuator Anda 1 (satu) kali seminggu

- Bilas badan aktuator plastik berwarna kuning setiap minggu, agar obat tidak menumpuk dan menghalangi semprotan *mouthpiece*
- Jangan sampai *canister* menjadi basah
- Lakukan *priming* kembali setelah dibilas

Pembilasan 1	Pembilasan 2
Lepaskan *canister* dan sisihkan. Jangan sampai *canister* menjadi basah 	Lepaskan penutup *mouthpiece.* 

Pembilasan 3	Pembilasan 4
Alirkan air hangat melewati *mouthpiece* selama 30 detik, kemudian melalui bagian atas badan aktuator plastik berwarna kuning selama 30 detik. **Secara keseluruhan, bilas selama 60 detik** 	**Kocok aktuator plastik berwarna kuning untuk mengeluarkan air bilasan dari dalam aktuator**  **Jangan dikeringkan menggunakan handuk atau tisu**

Pembilasan 5	Pembilasan 6
Periksa dan lihat badan aktuator plastik berwarna kuning apakah masih tersisa tumpukan obat, ulangi Langkah pembilasan 3 hingga 5. Pastikan hingga tidak ada tumpukan obat. 	Biarkan aktuator hingga mengering (*air-dry*), lebih baik semalaman. **Jangan** simpan *canister* ke dalam aktuator jika masih basah. 

Pembilasan 7	Pembilasan 8
Setelah kering, **lepaskan penutup *mouthpiece* terlebih dahulu** lalu tekan *canister* ke dalam tabung aktuator secara perlahan. 	Lakukan *priming* ulang pada inhaler dengan menyemprotkan 2 *puff* uji, kocok sebelum menyemprotkan setiap *puff* uji. **Total 2x** **Kocok dan semprotkan puff uji**