Proposed packaging material		
Code	BEVESPI AEROSPHERE SPI-PI-01.01	
Submission	☒NDA ☐Renewal ☐Variation change detail no.: RO-Primary Event-0002578-0019	
Code of previous version	N/A	
Changes	MAA for Bevespi 7.2 ug + 5.0 ug - Stage 2 of 2	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: EMA SmPC 18 December 2018 ☒GRL approval: Vikram Soundale 17 April 2023
Name & Date	ADR, 17 April 2023	

BEVESPI AEROSPHERE® 7.2/5 mcg
Glycopyrronium bromide / Formoterol Fumarate Dihydrate
Pressurised inhalation, Suspension

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation (delivered dose, ex-actuator) contains glycopyrronium bromide 9 micrograms and 5 micrograms of formoterol fumarate dihydrate.

This corresponds to a metered dose of glycopyrronium bromide 10.4 micrograms and formoterol fumarate dihydrate 5.8 micrograms.

For the full list of excipients, see section 5.1.

2. PHARMACEUTICAL FORM

Pressurised inhalation, suspension (pressurized inhalation). White suspension.

3. CLINICAL PARTICULARS

3.1 Therapeutic indications

Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) (see section 4.1).

3.2 Posology and method of administration

Posology

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

Patients should be advised not to take more than 2 inhalations twice daily.

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 4.2).

Renal impairment

Bevespi Aerosphere can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk (see sections 3.4 and 4.2).

Hepatic Impairment
Bevespi Aerosphere can be used at the recommended dose in patients with mild to moderate hepatic impairment. There are no relevant data on the use of Bevespi Aerosphere in patients with severe hepatic impairment and the medicinal product should be used with caution in these patients (see sections 3.4 and4.2).

Paediatric population
There is no relevant use of Bevespi Aerosphere in children and adolescents (under 18 years of age) for the indication of COPD.

Method of administration
For inhalation use.

Instructions for use
On actuation of Bevespi Aerosphere, a volume of the suspension is expelled from the pressurised container at high velocity. 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.
Note: Patients should be instructed on the correct inhalation technique. It is important to instruct the patient to:

- Carefully read the instructions for use in the patient information leaflet, which is packed together with each inhaler.
- Not use the inhaler if the drying agent, which is inside the foil pouch, has leaked out of its packet.
- 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, has been exposed to low temperatures, or has been dropped.

To get adequate lung deposition of the active substances actuation must be co-ordinated with inhalation.

Patients who find it difficult to co-ordinate actuation with inspiration of breath may use Bevespi Aerosphere with a spacer to ensure proper administration of the product. Compatibility with the Aerochamber Plus Flow-Vu spacer device has been demonstrated (see section 4.2).

3.3 Contraindications
Hypersensitivity to the active substances or any of the excipients listed in section 5.1.

3.4 Special warnings and precautions for use
Asthma
Bevespi Aerosphere should not be used to treat asthma.

Paradoxical bronchospasm
In clinical studies, paradoxical bronchospasm was not observed with Bevespi Aerosphere at its recommended dose. If paradoxical bronchospasm does occur, treatment with the medicinal product should be stopped and other treatments considered.

Not for acute use

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

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 or formoterol. Patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Bevespi Aerosphere should be used with caution in patients with severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Caution should also be exercised in patients with thyrotoxicosis or known or suspected prolongation of the QTc interval (see section 3.5).

Hypokalaemia

β2-adrenergic agonists may produce significant hypokalaemia, which may increase the susceptibility to cardiac arrhythmias. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 3.5).

Hyperglycaemia

Inhalation of high doses of β2-adrenergic agonists may produce increases in plasma glucose.

Anticholinergic activity

Due to its anticholinergic activity, Bevespi Aerosphere should be used with caution in patients with symptomatic prostatic hyperplasia, urinary retention or with narrow-angle glaucoma (see section 3.8).

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 Bevespi Aerosphere if the expected benefit outweighs the potential risk (see section 4.2).

Hepatic impairment

In patients with severe hepatic impairment, Bevespi Aerosphere should be used only if the expected benefit outweighs the potential risk (see section 4.2). These patients should be monitored for potential adverse reactions.

3.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Clinical drug-drug interaction studies have not been conducted with Bevespi Aerosphere, however, the potential for metabolic interactions is considered to be low based on *in-vitro* studies (see section 4.2).

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 sympatomimetics
Co-administration of Bevespi Aerosphere with other anticholinergic and/or long-acting β2-adrenergic agonist containing medicinal products has not been studied and is not recommended as it may potentiate known inhaled muscarinic antagonist or beta2-adrenergic agonist adverse reactions (see section 3.4 and section 3.9).

Although no formal *in-vivo* drug interaction studies have been performed with Bevespi Aerosphere, studies indicate no clinical evidence of interactions when used concomitantly with other COPD medicinal products including short-acting β2-adrenergic bronchodilators, methylxanthines, and oral and inhaled steroids.

Drug-induced hypokalaemia
Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible initial hypokalaemic effect of β2-adrenergic agonists, therefore, caution is advised in their concomitant use (see section 3.4).

β-adrenergic blockers
β-adrenergic blockers (including eye drops) can weaken or inhibit the effect of β2-adrenergic agonists, such as formoterol. Concurrent use of either non-selective or selective β-adrenergic blockers should be avoided unless there are compelling reasons for their use. If β-adrenergic blockers are required (including eye drops), cardioselective β-adrenergic blockers are preferred, although they should also be administered with caution.

Other pharmacodynamic interactions
Bevespi Aerosphere should be administered with caution to patients being treated with medicinal products known to prolong the QTc interval (see section 3.4).

3.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of Bevespi Aerosphere in pregnant women.
Single-dose studies in humans found that very small amounts of glycopyrronium bromide passed the placental barrier. In animal studies formoterol and glycopyrronium bromide , individually, have caused adverse effects in reproduction studies at very high doses/systemic exposure levels (see section 4.3).

Bevespi Aerosphere should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding
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 Bevespi 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 infant (see section 4.3).

Fertility

Studies in rats have shown adverse effects on fertility only at dose levels higher than the maximum human exposure to formoterol (see section 4.3). Glycopyrronium bromide did not cause any adverse effects on fertility in rats. It is unlikely that Bevespi Aerosphere administered at the recommended dose will affect fertility in humans.

3.7 Effects on ability to drive and use machines

Bevespi Aerosphere has no or negligible influence on the ability to drive and use machines. However dizziness and nausea are common side effects which should be taken into account when driving or using machines.

3.8 Undesirable effects

Summary of the safety profile

The safety profile is characterised by anticholinergic and β2-adrenergic class effects related to the individual components of the combination. The most common adverse reactions reported in the clinical development program (comprised of 1,588 patients receiving Bevespi Aerosphere) were headache (1.9%), nausea (1.4%), muscle spasms (1.4%), and dizziness (1.3%).

Tabulated list of adverse reactions

The tabulated list of adverse reactions is based on the experience with Bevespi Aerosphere in clinical trials and experience with the individual components and related products.

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
Immune system disorders	Hypersensitivity reactions including rash and pruritus	Uncommon
Metabolism and nutrition disorders	Hyperglycaemia[1]	Uncommon
Psychiatric disorders	Anxiety	Common
	Agitation Restlessness Insomnia	Uncommon
Nervous system disorders	Headache[1] Dizziness	Common
	Tremor[1]	Uncommon
Cardiac disorders	Tachycardia Palpitations Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles)	Uncommon
Gastrointestinal disorders	Dry mouth[2], Nausea	Common
Musculoskeletal and connective tissue disorders	Muscle spasms[1]	Common
Renal and urinary disorders	Urinary tract infection	Common
	Urinary retention[2]	Uncommon

General disorders and administration site conditions	Chest pain	Common

[1]adverse reaction relates to formoterol
[2]adverse reaction relates to glycopyrronium bromide

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

3.9 Overdose
An overdose of Bevespi 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.

If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

4. PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for obstructive airway diseases: adrenergics in combination with anticholinergics, ATC code: R03AL07.

Mechanism of action
Bevespi Aerosphere contains two bronchodilators: glycopyrronium bromide a long-acting muscarinic antagonist (also referred to as an anticholinergic) and formoterol a long-acting β2-adrenergic agonist with a rapid onset of action.

Glycopyrronium bromide has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. Formoterol causes direct relaxation of airway smooth muscle as a consequence of the increase in cyclic AMP through activation of adenylate cyclase. The combination of these substances with different mechanisms of action results in additive efficacy compared to use with either component alone.

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.

Pharmacodynamic effects
In three Phase III, 24-week studies (PINNACLE 1, PINNACLE 2 and PINNACLE 4) Bevespi Aerosphere provided improvements over placebo in lung function (as measured by morning pre-dose trough forced expiratory volume in 1 second [FEV1]), with a demonstrated onset of action at 5 minutes following administration of the first dose on Day 1 (improvement over placebo by 187 mL, 186 mL and 179 mL in PINNACLE 1, PINNACLE 2 and PINNACLE 4, respectively [$p < 0.001$]). The mean bronchodilator effect derived from serial FEV1 measurements at Day 1 and Week 12 from PINNACLE 1 are shown in Figure 1. In PINNACLE 2, the results were similar to those observed in PINNACLE 1.

Figure 1 - Mean Change from Baseline in FEV1 over Time on Day 1 and at Week 12

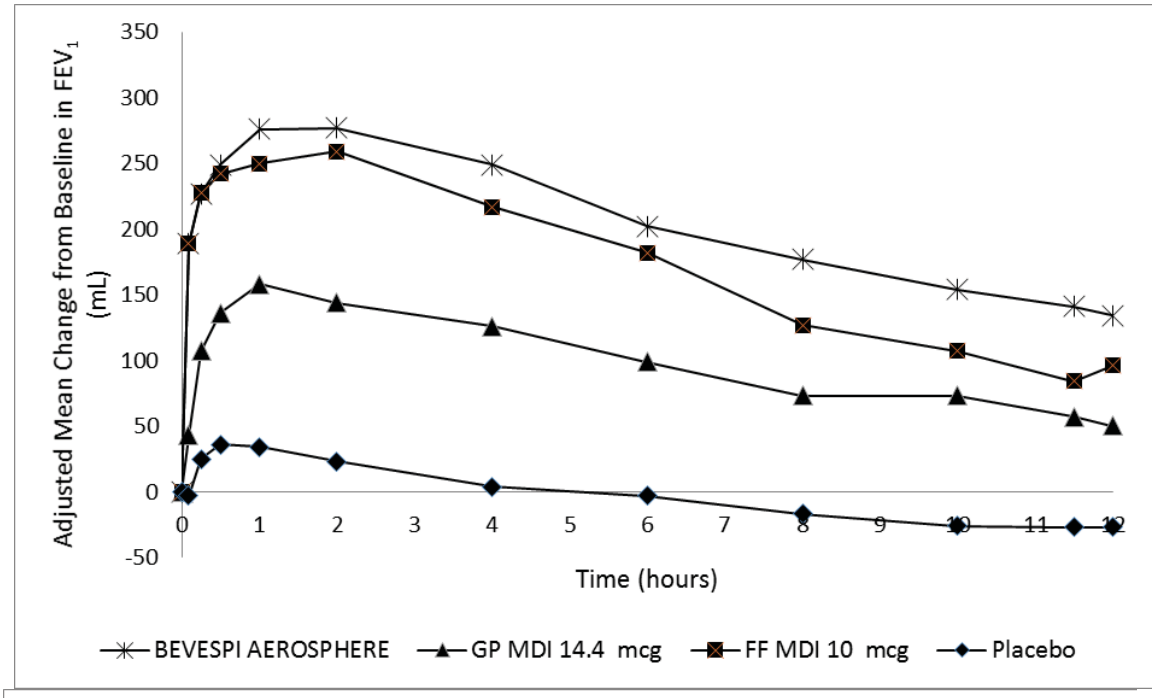

Figure 1a. DAY 1

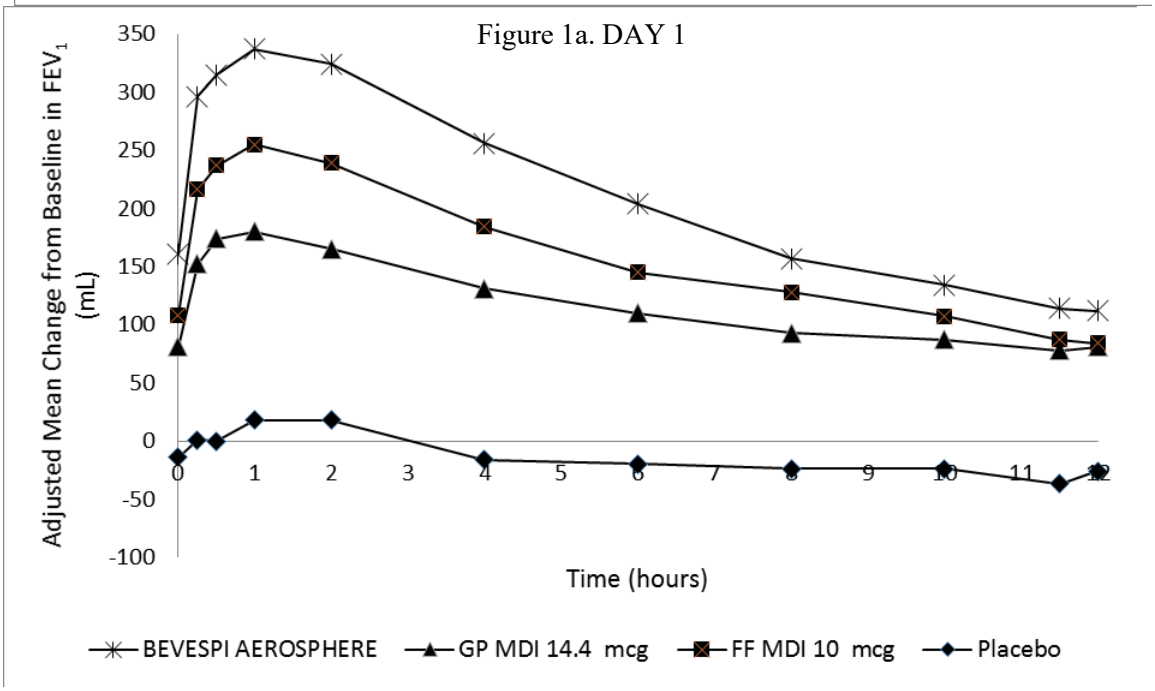

Figure 1b. WEEK 12

Cardiac electrophysiology

A placebo- and active-controlled (moxifloxacin) thorough QT study in 69 healthy subjects did not demonstrate a clinically relevant effect on the QT interval, using a threshold of 10 ms. The largest mean (90% upper confidence bound) differences from placebo in baseline- and

individually corrected QT was 3.1 (4.7) ms for Bevespi Aerosphere (14.4 /10 micrograms) and 7.6 (9.2) ms for glycopyrronium bromide /formoterol with eight times the recommended dose of glycopyrronium bromide and four times the recommended dose of formoterol.

Clinical efficacy

The clinical development program for Bevespi Aerosphere included three 24-week, randomised, double-blind, placebo-controlled, parallel-group pivotal Phase III studies in 5,433 patients with moderate to very severe COPD (PINNACLE 1, PINNACLE 2 and PINNACLE 4).

Effects on lung function

In studies PINNACLE 1, PINNACLE 2 and PINNACLE 4, Bevespi Aerosphere showed improvements in trough FEV1 over 24 weeks relative to placebo, glycopyrronium bromide and formoterol ($p<0.0001$) [see Table 2]. There was no attenuation of the bronchodilator effect over time. Bevespi Aerosphere also showed improvements in peak FEV1 within 2 hours post- dose over 24 weeks relative to placebo, glycopyrronium bromide and formoterol ($p<0.0001$) [see Table 2].

There were improvements in trough FEV1 irrespective of age, sex, degree of airflow limitation, baseline symptoms, smoking status, or inhaled corticosteroid use.

Symptomatic outcomes

Breathlessness:

In PINNACLE 1 and PINNACLE 2, Bevespi Aerosphere provided improvements in breathlessness as demonstrated by Self-administered Computerised Transitional Dyspnoea Index (SAC TDI) focal score over 24 weeks compared to placebo and glycopyrronium bromide (see Table 2). Improvements compared to formoterol were observed in PINNACLE 2 (see Table 2). In PINNACLE 4, Bevespi Aerosphere provided improvements in breathlessness as demonstrated by TDI focal score over 24 weeks compared to placebo and glycopyrronium bromide (see Table 2).

Health-related quality of life:

In PINNACLE 1, PINNACLE 2 and PINNACLE 4, Bevespi Aerosphere provided an improvement in disease-specific health-related quality of life, as indicated by a reduction in the St George's Respiratory Questionnaire (SGRQ) total score over 24 weeks compared to placebo and glycopyrronium bromide [see Table 2]. There were improvements compared to formoterol in PINNACLE 1 and PINNACLE 2.

Table 2. Lung function, symptomatic and health related quality of life outcomes over 24 weeks

Treatmen comparison with Bevespi Aerosphere	Treatment difference (95% confidence intervals, p-value)				
	Throygh FEVI (ml)[a]	Peak FEVI (ml)	SAC-TDI/TDI Focal Score[b]	SGRQ total score	Daily rescue Ventolin (inhalation/day)[C]
PINNACLE 1					
Bevespi Aerosphere (N=526) vs placebo (N=219)	158 (132, 183) p<0.0001	288 (259, 317) p<0.0001#	0.47 (0.21, 0.72) p=0.0003	-2.39 (-4.07, -0.71) p=0.0053#	-1.08 (-1.43, -0.73) p<0.0001#
Bevespi Aerosphere (N=526) vs Glycopyrronium (N=451)	60 (39, 80) p<0.0001	123 (100, 146) p<0.0001#	0.27 (0.07, 0.47) p=0.0086#	-1.90 (-3.24, 0.57) p=0.0052#	-0.26 (-0.53, 0.01) p=0.0619
Bevespi Aerosphere (N=526) vs formoterol fumarate (N=449)	64 (44, 84) p<0.0001	81 (59, 104) p<0.0001#	0.16 (-0.03, 0.36) p=0.1060	-0.75 (-2.08, 0.57) p=0.2640	-0.01 (-0.27, 0.26) p=0.9683
PINNACLE 2					
Bevespi Aerosphere (N=510) vs placebo (N=223)	129 (103, 155) p<0.0001	278 (249, 308) p<0.0001	0.33 (0.11, 0.56) p=0.0041	-1.66 (-3.34, 0.02) p=0.0534	-1.04 (-1.37, -0.72) p<0.0001
Bevespi Aerosphere (N=510) vs Glycopyrronium (N=439)	55 (34, 76) p<0.0001	129 (106, 153) p<0.0001	0.21 (0.03, 0.40) p=0.0199	-1.28 (-2.62, 0.06) p=0.0605	-0.57 (-0.83, -0.31) p<0.0001
Bevespi Aerosphere (N=510) vs formoterol fumarate (N=437)	57 (36, 78) p<0.0001	76 (52, 99) p<0.0001	0.28 (0.10, 0.46) p=0.0028	-1.22 (-2.56, 0.13) p=0.0760	-0.29 (-0.55, -0.03) p=0.0274#
PINNACLE 4					
Bevespi Aerosphere (N=551)	155 (129, 180)	293 (265, 321)	0.80 (0.47, 1.13)	-3.50 (-5.18, -1.82)	-0.98 (-1.47, -0.49)

vs placebo (N=235)	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Bevespi Aerosphere (N=551) vs glycopyrronium (N=474)	55 (35, 76) p<0.0001	141 (119, 163) p<0.0001	0.33 (0.07, 0.59) p=0.0125	-1.62 (-2.94, -0.30) p=0.0165	-0.77 (-1.16, -0.38) p<0.0001
Bevespi Aerosphere (N=551) vs formoterol fumarate (N=480)	72 (52, 92) p<0.0001	97 (75, 119) p<0.0001	0.15 (-0.11, 0.41) p=0.2530	-0.27 (-1.59, 1.05) p=0.6908	-0.41 (-0.80, -0.03) p=0.0345[#]

[N]number in Intent to Treat population

[a]primary endpoint in all studies

[b]PINNACLE 1 and PINNACLE 2 used SAC-TDI. PINNACLE 4 used TDI. SAC-TDI was a primary endpoint in PINNACLE 1 and PINNACLE 2 only

[c]From the Rescue Ventolin User Population in PINNACLE 4

[#]A hierarchical statistical testing procedure was used in this study and this comparison was below a comparison that did not achieve statistical significance. Therefore, statistical significance on this comparison cannot be inferred.

COPD exacerbations:
The individual studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the studies if a severe exacerbation or more than 2 moderate exacerbations occurred.

4.2 Pharmacokinetic properties

Following inhalation of the glycopyrronium bromide and formoterol combination, the pharmacokinetics of each component was similar to those observed when each active substance was administered separately. For pharmacokinetic purposes each component can therefore be considered separately.

Effect of a spacer

The use of Bevespi Aerosphere with the Aerochamber Plus Flow-Vu spacer in COPD patients increased the total systemic exposure to glycopyrronium bromide (as measured by AUC0-12) by 16% while formoterol exposure was unchanged.

Absorption

Following inhaled administration of Bevespi Aerosphere in subjects with COPD, glycopyrronium bromide Cmax occurred at approximately 5 minutes, and formoterol Cmax occurred within 20 to 60 minutes. Steady state is achieved within 2-3 days of repeated dosing of Bevespi Aerosphere, and the extent of exposure is approximately 2.3 times and 1.5 times higher than after the first dose, for glycopyrronium bromide and formoterol, respectively.

A lung deposition study with Bevespi Aerosphere conducted in healthy volunteers demonstrated that on average 38% of the nominal dose is deposited into the lung. Both central and peripheral deposition were observed.

Distribution

Glycopyrronium bromide

The estimated glycopyrronium bromide Vc/F (volume of the central compartment), and Vp1/F (volume of the peripheral compartment) are 741 L, and 2990 L, respectively, 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 Vc/F (volume of the central compartment), and Vp1/F (volume of the peripheral compartment) are 1030 L, and 647 L, respectively, via population pharmacokinetic analysis. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.

Biotransformation

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 .

In-vitro studies indicate the glycopyrronium bromide does not inhibit any subtype of cytochrome P450 and that there is no induction of CYP1A2, 2B6, or 3A4.

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.

In-vitro studies indicate that formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations.

Elimination

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 terminal elimination half-life of glycopyrronium bromide following oral inhalation derived via population pharmacokinetics analysis was 15 hours.

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 radiolabelled formoterol was excreted in the urine while 24% was eliminated in the faeces. The terminal elimination half-life of formoterol following oral inhalation derived via population pharmacokinetics analysis was 13 hours.

Linearity/non-linearity

Linear pharmacokinetics were observed for glycopyrronium bromide (dose range: 14.4 to 115.2 mcg) and formoterol (dose range: 2.4 to 19.2 mcg) after oral inhalation.

Special patient populations

Elderly patients

Based on available data, no adjustment of the dosage of Bevespi Aerosphere in geriatric patients is

necessary.

Renal impairment
Studies evaluating the effect of renal impairment on the pharmacokinetics of glycopyrronium bromide and formoterol have not been conducted. The effect of renal impairment on the exposure to glycopyrronium bromide and formoterol for up to 12 weeks was evaluated in a population pharmacokinetic analysis. Estimated glomerular filtration rate (eGFR) varied from 30-196 mL/min, representing a range of moderate to no renal impairment. The systemic exposure (AUC_{0-12}) in subjects with COPD with moderate-severe renal impairment (eGFR of 30-45 mL/min) is approximately 30% higher for glycopyrronium bromide compared to subjects with COPD with normal renal function (eGFR of >90 mL/min). 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 . Renal function was found not to affect exposure to formoterol.

Hepatic impairment
No pharmacokinetic studies have been performed with Bevespi Aerosphere in patients with hepatic impairment. However, because formoterol is 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 lead to unsafe systemic exposure.

Other special populations
A population pharmacokinetic analysis of glycopyrronium bromide was performed based on data collected in a total of 311 subjects with COPD. The pharmacokinetics of glycopyrronium bromide was best described by a two-compartment disposition model with first-order absorption and linear elimination. The typical clearance (CL/F) of glycopyrronium bromide was 124 L/h.

A population pharmacokinetic analysis of formoterol was performed based on data collected in a total of 437 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 99 L/h.

Dose adjustments are not necessary based on the effect of age, sex and weight on the pharmacokinetic parameters of glycopyrronium bromide and formoterol.

There were no major differences in total systemic exposure (AUC) for both compounds between healthy Japanese and Western subjects. Insufficient pharmacokinetic data are available to compare exposure for other ethnicities or races.

4.3 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 studies with the combination of glycopyrronium bromide and formoterol in dogs were associated with the pharmacological actions of formoterol, including effects mainly on the cardiovascular system, consisting of hyperaemia, tachycardia, arrhythmias and myocardial lesions.

These are known pharmacological manifestations seen after administration of high doses of beta-

adrenoceptor agonists. No significant effects attributable to glycopyrronium bromide were seen.

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. However, these animal experimental results have little relevance to man. 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 fetal weights, and low body weight gain of rat offspring before weaning was observed at considerably higher systemic exposures than those reached during clinical use. No evidence of carcinogenicity was seen in 2-year studies in rats and mice.

5. PHARMACEUTICAL PARTICULARS

5.1 List ofexcipients

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

5.2 Incompatibilities

Not applicable.

5.3 Shelf life

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

5.4 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.

5.5 Nature and contents of container

The inhaler is a pressurised metered dose inhaler, comprising an aluminium pressurised container with an attached dose indicator, supplied with a white plastic actuator body and mouthpiece with an orange dust cap. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed into a carton.

Carton containing 1 inhaler with 120 actuations.

5.6 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 apparentlyempty.

HARUS DENGAN RESEP DOKTER

Registration No. :

Manufactured by
AstraZeneca Dunkerque Production

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Imported by
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Cikarang, Bekasi – Indonesia

Date of revision of text
As approval date
ANGEL Locator: Doc ID-004900223

Proposed packaging material		
Code	BEVESPI AEROSPHERE SPI-PIL-01.01	
Submission	☒NDA ☐Renewal ☐Variation change detail no.: RO-Primary Event-0002578-0019	
Code of previous version	N/A	
Changes	MAA for Bevespi 9 ug + 5.0 ug - Stage 2 of 2	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: EMA SmPC 18 December 2018 ☒GRL approval: Vikram Soundale
Name & Date	ADR, 17 April 2023	

Informasi Untuk Pasien

Bevespi Aerosphere 9 mikrogram / 5 mikrogram suspensi inhalasi bertekanan
glikopironium bromida / formoterol fumarat dihidrat

Baca seluruh leafet 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 hanya untuk Anda. Dilarang memberikan obat ini untuk orang lain karena dapat membahayakan mereka meskipun tanda dan gejala penyakitnya sama dengan Anda.
- Jika Anda mengalami efek samping, beri tahu dokter, apoteker, atau perawat Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Lihat bagian 4.

Informasi yang terkandung pada leaflet ini

1. Bevespi Aerosphere dan kegunaannya

Bevespi Aerosphere mengandung dua bahan aktif yang disebut glikopironium bromida dan formoterol fumarat dihidrat. Obat ini termasuk dalam kelompok obat yang disebut bronkodilator kerja panjang.

Bevespi Aerosphere digunakan untuk melegakan pernapasan bagi orang dewasa yang memiliki penyakit paru-paru yang disebut penyakit paru obstruktif kronik (PPOK). PPOK adalah penyakit jangka panjang pada saluran udara di paru-paru, yang sering disebabkan karena merokok. Pada PPOK, otot-otot di sekitar saluran udara menyempit hingga menyebabkan kesulitan bernapas.

Obat tersebut mencegah otot-otot di sekitar saluran udara menyempit, sehingga memudahkan udara masuk dan keluar dari paru-paru.

Bahan aktif dari Bevespi Aerosphere akan langsung menuju ke saluran udara di paru-paru saat Anda menarik napas. Alat ini akan membantu mengurangi efek PPOK.

2. Hal yang harus diketahui sebelum menggunakan Bevespi Aerosphere

Jangan gunakan Bevespi Aerosphere jika

- Anda alergi terhadap glikopironium bromida , formoterol fumarat dihidrat, atau salah satu bahan lainnya dari obat ini (tercantum di bagian 6). Jika Anda tidak yakin, konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan Bevespi Aerosphere.

Peringatan dan pencegahan

Bevespi Aerosphere digunakan secara teratur untuk pengobatan jangka panjang PPOK. Jangan menggunakan obat ini untuk mengobati serangan sesak napas atau mengi yang mendadak.

Kesulitan bernapas tiba-tiba
Jika Anda merasa otot dada Anda mengencang, batuk, mengi, atau sesak napas segera setelah menggunakan Bevespi Aerosphere:
Hentikan penggunaan obat ini dan segera cari bantuan medis, karena Anda mungkin mengalami kondisi serius yang disebut bronkospasme paradoksikal
Beri tahu dokter Anda atau apoteker sebelum menggunakan Bevespi Aerosphere jika

- Anda memiliki asma. Jangan gunakan obat ini untuk asma
- Anda memiliki gangguan jantung
- Anda memiliki diabetes
- Kadar kalium dalam darah Anda rendah
- Anda memiliki gangguan kelenjar tiroid (disebut 'tirotoksikosis')
- Anda memiliki gangguan mata glaukoma sudut sempit (juga disebut glaukoma sudut tertutup)
- Anda memiliki gangguan prostat, atau kesulitan buang air kecil
- Anda memiliki gangguan ginjal atau lever

Komunikasikan dengan dokter tentang gangguan kesehatan Anda yang lain.

Anak-anak dan remaja

Bevespi Aerosphere tidak boleh digunakan untuk anak-anak atau remaja dibawah umur 18 tahun.

Obat-obatan lain dan Bevespi Aerosphere

Beri tahu dokter atau apoteker Anda jika Anda sedang menggunakan, baru saja menggunakan atau akan menggunakan obat-obatan lain.
Beberapa obatan-obatan dapat memengaruhi kerja obat ini, atau cenderung menimbulkan efek samping. Antara lain:

- obat-obatan yang bekerja dengan cara yang sama seperti Bevespi Aerosphere, seperti obat-obatan yang mengandung bahan aktif seperti tiotropium, ipratropium, aklidinium, umeklidinium, salmeterol, vilanterol, olodaterol, atau indakaterol. Tanyakan pada dokter atau apoteker jika Anda tidak yakin. Tidak direkomendasikan menggunakan Bevespi Aerosphere bersama dengan obat-obatan ini;
- obat-obatan yang menurunkan kadar kalium dalam darah. Antara lain:
  - kortikosteroid oral (misalnya prednisolon),
  - diuretik (misalnya furosemida atau hidroklorotiazid) yang digunakan untuk tekanan darah tinggi,
  - beberapa obat, yang digunakan untuk mengobati kondisi pernapasan, yang disebut metilxantin (seperti teofilin);
- obat-obatan yang disebut beta-blocker yang dapat digunakan untuk mengobati tekanan darah tinggi atau gangguan jantung lainnya (seperti atenolol atau propranolol) atau untuk mengobati glaukoma (seperti timolol)

- obat-obatan yang dapat memperpanjang 'interval QT' (perubahan aktivitas listrik jantung). Termasuk obat-obatan untuk pengobatan:
    - 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 Bevespi Aerosphere.

Kehamilan dan menyusui

Jika Anda sedang hamil atau menyusui, memiliki kemungkinan hamil, atau berencana memiliki bayi, mintalah saran dokter atau apoteker sebelum menggunakan Bevespi Aerosphere.

Jangan menggunakan Bevespi Aerosphere jika Anda sedang hamil, kecuali atas izin dokter Anda.

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

Mengendarai kendaraan bermotor dan menjalankan mesin

Kecil kemungkinan obat ini dapat memengaruhi kesadaran Anda dalam mengendarai kendaraan bermotor dan menjalankan mesin. Namun, pusing dan mual adalah efek samping umum yang mungkin terjadi. Jangan mengemudi, menggunakan alat ataupun mesin, apabila Anda merasa pusing dan mual setelah menggunakan obat ini.

3. Cara menggunakan Bevespi Aerosphere

Selalu gunakan obat ini persis seperti yang diinstruksikan dokter Anda. Tanyakan kembali ke dokter atau apoteker jika Anda tidak yakin.

Dosis penggunaan
Dosis yang dianjurkan adalah dua hisapan (*puff*) dua kali sehari. Dua hisapan di pagi hari dan dua hisapan di malam hari.
Penting untuk menggunakan Bevespi Aerosphere setiap hari meskipun Anda tidak bergejala PPOK saat itu.

Cara penggunaan
Bevespi Aerosphere untuk penggunaan inhalasi.
Harap baca petunjuk penggunaan di akhir leaflet ini. Jika Anda tidak yakin tentang cara menggunakan Bevespi Aerosphere, hubungi dokter atau apoteker Anda.

Menggunakan Bevespi Aerosphere dengan *spacer*
Jika Anda kesulitan untuk menghirup napas sambil menekan inhaler, konsultasikan dengan dokter atau apoteker Anda. Anda dapat memasang alat bantu yang disebut '*spacer*' pada inhaler Anda.

Jika Anda menggunakan Bevespi Aerosphere lebih banyak dari yang seharusnya

Jika Anda telah menggunakan Bevespi Aerosphere lebih dari yang seharusnya, segera konsultasikan dengan dokter atau apoteker. Mungkin Anda memerlukan pertolongan medis. Mungkin Anda menyadari jantung Anda berdetak lebih cepat dari biasanya, Anda merasa gemetar, Anda memiliki gangguan penglihatan, mulut kering, sakit kepala, atau mual (tidak enak badan).

Jika Anda lupa menggunakan Bevespi Aerosphere

Jangan menggandakan dosis untuk mengganti dosis yang terlewat. Gunakan segera setelah mengingatnya. Namun, jika sudah mendekati waktu untuk dosis berikutnya, abaikan dosis yang terlewat. Jangan

menggunakan lebih dari dua *puff* dua kali sehari.

Jika Anda berhenti menggunakan Bevespi Aerosphere

Obat ini untuk penggunaan jangka panjang. Ini hanya akan efektif selama Anda menggunakannya. Jangan berhenti 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

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping meskipun tidak semua orang mengalaminya.

Efek samping serius
Hentikan penggunaan Bevespi Aerosphere dan segera cari pengobatan medis jika Anda menyadari salah satu gejala berikut:

Jarang: bisa dialami oleh 1 dari 100 orang:

- bengkak pada wajah, terutama di sekitar mulut (pembengkakan lidah atau tenggorokan dapat membuat Anda sulit menelan);
- ruam atau gatal-gatal disertai kesulitan bernapas
- tiba-tiba merasa lemas.

Gejala-gejala ini mungkin merupakan tanda-tanda reaksi alergi yang bisa menjadi serius.

Efek samping lain yang mungkin terjadi

Umum: bisa dialami 1 dari 10 orang
- sakit kepala
- mulut kering
- tidak enak badan (mual)
- sering buang air kecil dan terasa nyeri (mungkin tanda infeksi saluran kencing)
- kram otot
- nyeri dada
- gelisah
- pusing

Jarang: bisa dialami 1 dari 100 orang
- gemetar atau tremor
- kadar gula darah tinggi
- agitasi
- merasa gelisah
- susah tidur
- detak jantung cepat atau tidak beraturan
- kesulitan buang air kecil (retensi urine)

Pelaporan efek samping

Jika Anda mengalami efek samping apapun, komunikasikan pada dokter atau apoteker Anda. Termasuk efek samping yang mungkin terjadi yang tidak tercantum dalam leaflet ini. Anda juga dapat melaporkan efek samping secara langsung melalui sistem pelaporan nasional yang tercantum pada :
Pusat Farmakovigilans/MESO Nasional Badan Pengawasan Obat dan Makanan RI
Jl. Percetakan Negara No. 23

Telpon: (021) 4244691 / Ext. 1079
Email: pv-center@pom.go.id
Dengan melaporkan efek samping, Anda membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan Bevespi Aeroshere

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan setelah 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. Tulis tanggal kantong dibuka pada label inhaler di tempat yang tersedia.

Jangan disimpan di atas suhu 30ºC.

Peringatan: Jangan merusak, menusuk, atau membakar tabung *canister*, meskipun tampaknya kosong. Jangan terpapar suhu melebihi 50ºC.

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

6. Isi kemasan dan informasi lain

Kandungan Bevespi Aerosphere
Bahan aktif terdiri dari glikopironium bromida dan formoterol fumarat dihidrat.

Tiap satu kali hisapan (*puff*) memberikan dosis 9 mikrogram glikopironium bromida dan 5 mikrogram formoterol fumarat dihidrat.

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

Tampilan Bevespi Aerosphere dan isi kemasan

Bevespi Aerosphere adalah suspensi inhalasi bertekanan.
Bevespi Aerosphere hadir dengan bentuk tabung *canister* dengan indikator dosis, dilengkapi dengan badan aktuator plastik putih dan corong mulut (*mouthpiece*) (lihat Gambar 1 dari Petunjuk Penggunaan di akhir selebaran ini). *Mouthpiece* dilengkapi tutup pelindung berwarna jingga. Bevespi Aerosphere disediakan dalam kantong foil yang berisi bahan pengering (desikan) dan dikemas dalam karton.

Bahan aktifnya dalam bentuk suspensi bertekanan di dalam tabung *canister*.

Bevespi Aerosphere tersedia dalam kemasan yang berisi 1 inhaler dengan 120 dosis.

Petunjuk penggunaan

Bevespi Aerosphere 9 mikrogram / 5 mikrogram suspensi inhalasi bertekanan
glikopironium bromida / formoterol fumarat dihidrat

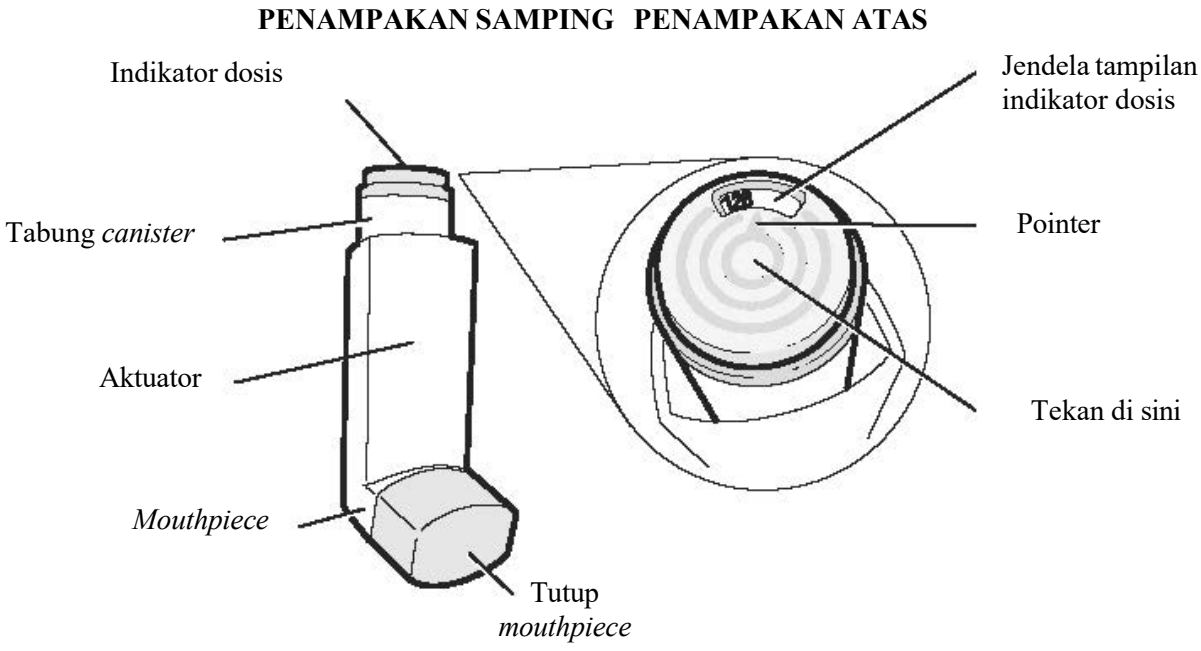
Baca petunjuk penggunaan dan leaflet kemasan ini sebelum mulai menggunakan Bevespi Aerosphere dan setiap kali Anda mendapat inhaler baru. Memungkinkan adanya informasi baru. Informasi ini harus digunakan bersamaan dengan konsultasi dengan dokter tentang kondisi medis dan pengobatan Anda.

Informasi penting:

- **Untuk penggunaan inhalasi saja**.
- Gunakan Bevespi Aerosphere seperti yang diinstruksikan dokter Anda.
- Konsultasikan dengan dokter atau apoteker jika memiliki pertanyaan terkait penggunaan inhaler Anda.

Bagian-bagian inhaler Bevespi Aerosphere (Lihat Gambar 1):

- Bevespi Aerosphere hadir dalam bentuk tabung *canister* dengan indikator dosis yang sesuai dengan aktuator.
  - **Jangan** menggunakan aktuator Bevespi Aerosphere dengan obat lain apapun.
  - **Jangan** menggunakan tabung *canister* Bevespi Aerosphere dengan aktuator dari inhaler lain.



Gambar 1

- Bevespi Aerosphere dilengkapi dengan indikator dosis di bagian atas tabung bertekanan (**Lihat Gambar 1**). Jendela tampilan indikator dosis menunjukkan berapa banyak puff/embusan obat yang tersisa. Obat terembus keluar setiap kali Anda menekan bagian tengah indikator dosis.

Sebelum Anda menggunakan Bevespi Aerosphere untuk pertama kalinya

Sebelum Anda menggunakan Bevespi Aerosphere untuk pertama kalinya, pastikan penunjuk pada indikator dosis mengarah ke sebelah kanan tanda "120" di jendela tampilan indikator dosis (**Lihat Gambar 1**).

- Tanda panah menunjuk ke 120 setelah 10 dosis keluar dari Bevespi Aerosphere. Ini berarti ada 120 dosis obat yang tersisa dalam tabung (**Lihat Gambar 2a**).
- Tanda panah menunjuk antara 100 dan 120 setelah Anda menggunakan 10 dosis lagi. Ini berarti ada 110 dosis obat yang tersisa dalam tabung (**Lihat Gambar 2b**).
- Tanda panah menunjuk ke 100 setelah Anda menggunakan 10 dosis lagi. Ini berarti ada 100 dosis obat yang tersisa dalam tabung (**Lihat Gambar 2c)**.

Gambar 2a
120 dosis

Gambar 2b
110 dosis

Gambar 2c
100 dosis

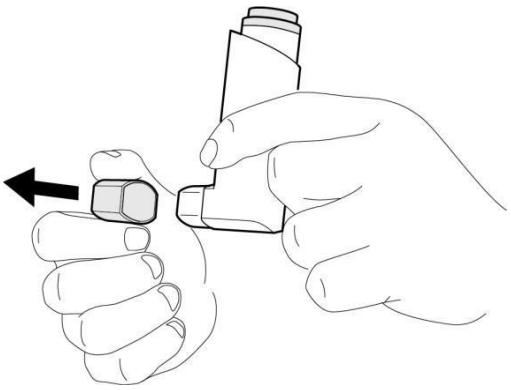
- Jendela tampilan indikator dosis akan bergerak tiap 10 dosis telah digunakan. Angka di jendela tampilan indikator dosis akan berubah tiap 20 dosis digunakan.

Gambar 2d

- Warna pada jendela tampilan indikator dosis akan berubah menjadi merah, seperti yang ditunjukkan pada area yang diarsir, ketika hanya ada 20 dosis obat yang tersisa di inhaler Anda (**Lihat Gambar 2d).**
- Ketika panah mencapai '0', Anda harus berhenti menggunakan inhaler Anda. Inhaler Anda mungkin tidak terasa kosong dan seperti masih berfungsi. Namun, Anda tidak akan mendapatkan jumlah dosis obat yang tepat jika terus menggunakannya.

Mempersiapkan inhaler Bevespi Aerosphere sebelum digunakan:

- Inhaler Bevespi Aerosphere disediakan dalam kantong foil yang berisi bahan pengering (desikan).
  - Keluarkan inhaler Bevespi Aerosphere dari kantong foil.
  - Buang kantong dan bahan pengering. Jangan menggunakan inhaler jika bahan pengering bocor dari kemasannya.

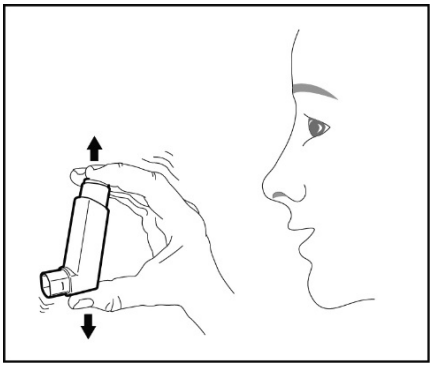


Gambar 3

Menyiapkan inhaler Bevespi Aerosphere (*priming*):

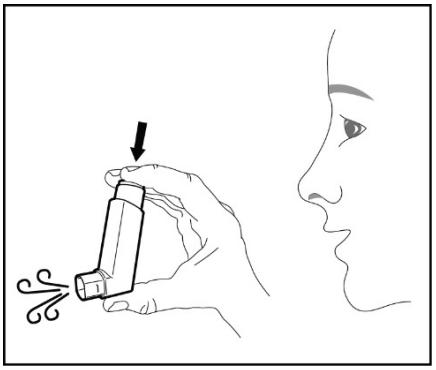
Sebelum menggunakan Bevespi Aerosphere untuk pertama kalinya, Anda harus melakukan proses penyiapan (*priming*) terlebih dahulu.

1. Lepas tutup *mouthpiece* (**Lihat Gambar 3**). Periksa bagian dalam *mouthpiece* sebelum menggunakan inhaler untuk memastikannya bersih.
2. Pegang inhaler dalam posisi tegak, jauh dari wajah Anda, lalu kocok dengan seksama (**Lihat Gambar 4**).



Gambar 4

3. Tekan dengan kuat pada bagian tengah indikator dosis sampai tabung *canister* berhenti bergerak di aktuator. Puff/embusan obat akan keluar dari *mouthpiece* (**Lihat Gambar 5**). Anda bisa mendengar bunyi klik pelan dari indikator dosis saat menghitung mundur selama penggunaan.

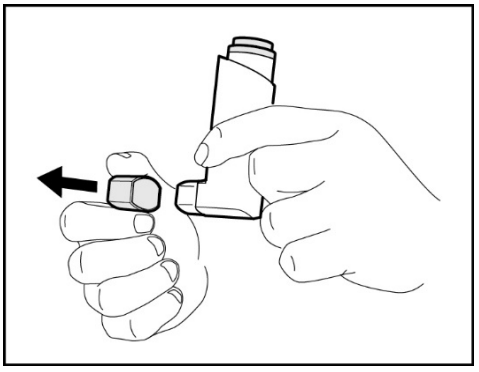


Gambar 5

4. **Ulangi langkah penyiapan (*priming*) nomor 1 hingga 3 sebayak 3 kali (Lihat Gambar 4 dan Gambar 5).** Kocok inhaler dengan seksama tiap sebelum *puff* penyiapan.
5. Setelah 4 kali penyiapan, indikator dosis harus menunjuk ke kanan ke tanda "**120**" dan sekarang inhaler Anda siap digunakan.

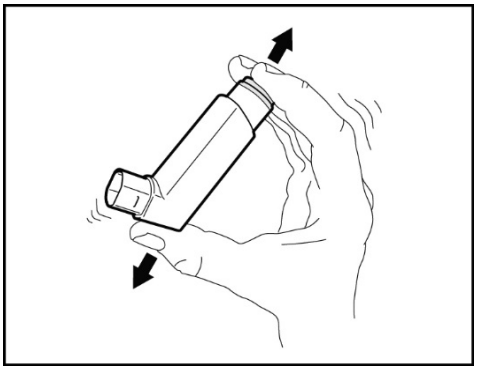
Langkah menggunakan inhaler Bevespi Aerosphere:

Langkah 1: Lepas tutup *mouthpiece* (**Lihat Gambar 6**).



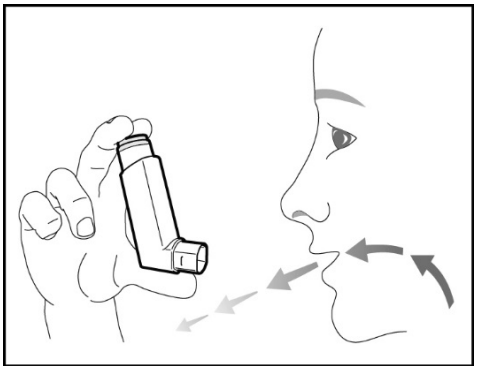
Gambar 6

Langkah 2: Kocok inhaler dengan seksama sebelum digunakan (**Lihat Gambar 7**).



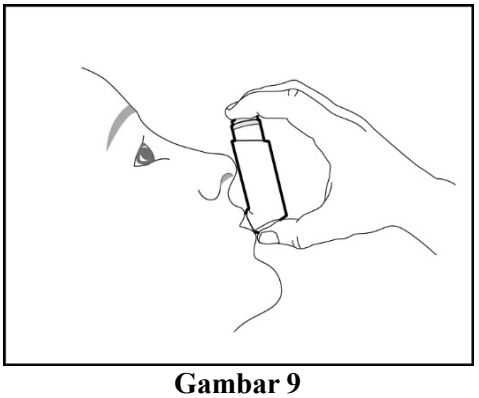
Gambar 7

Langkah 3: Pegang inhaler dengan *mouthpiece* mengarah ke mulut Anda lalu hembuskan napas senyaman mungkin melalui mulut Anda (**Lihat Gambar 8**).



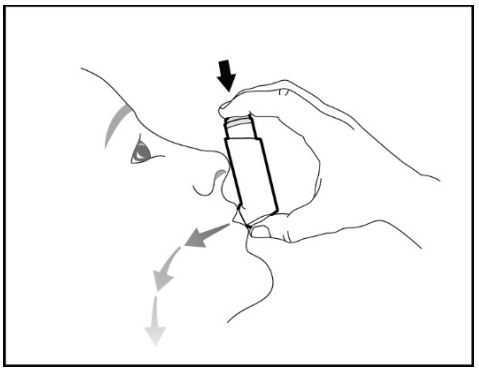
Gambar 8

Langkah 4: Katupkan bibir Anda pada *mouthpiece* lalu tengadahkan kepala, pertahankan lidah Anda di bawah *mouthpiece* (**Lihat Gambar 9**).



Gambar 9

Langkah 5: Sambil menarik napas dalam-dalam dan perlahan, tekan bagian tengah indikator dosis sampai tabung *canister* berhenti bergerak di aktuator dan *puff* obat keluar (**Lihat Gambar 10**). Kemudian hentikan menekan indikator dosis.

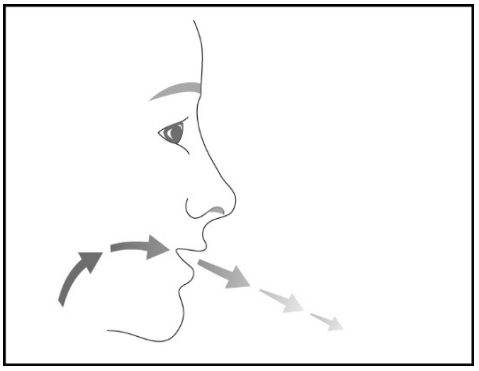


Gambar 10

Langkah 6: Setelah menarik napas, keluarkan *mouthpiece* dari mulut Anda. Tahan napas selama yang Anda bisa dengan nyaman, hingga 10 detik (**Lihat Gambar 11**).

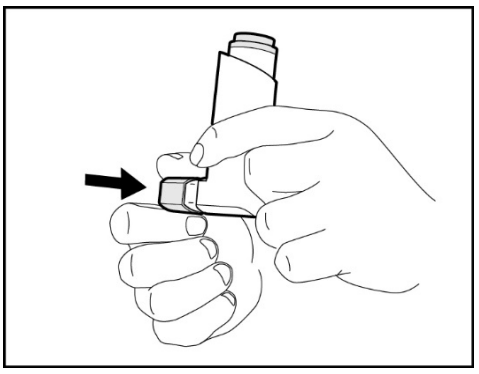
Gambar 11

Langkah 7: Hembuskan napas perlahan (**Lihat Gambar 12**). **Ulangi langkah 2 sampai 7** untuk menggunakan *puff* kedua Bevespi Aerosphere.



Gambar 12

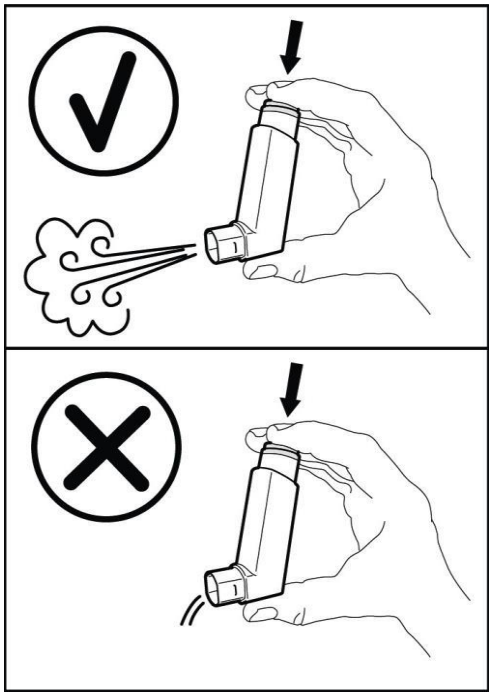
Langkah 8: Pasang tutup *mouthpiece* dengan benar segera setelah digunakan (**Lihat Gambar 13**).



Gambar 13

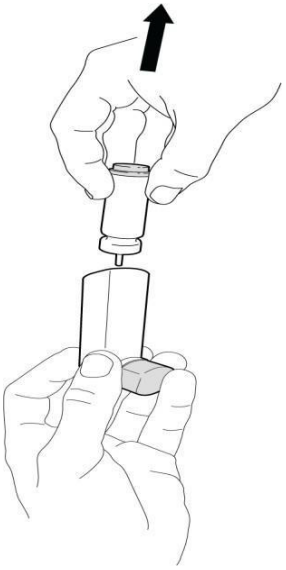
Cara membersihkan inhaler Bevespi Aerosphere:

Bersihkan inhaler seminggu sekali selama 3 minggu pertama. Sangat penting untuk menjaga kebersihan inhaler agar obat tidak menumpuk dan menghalanginya keluar dari *mouthpiece* (**Lihat Gambar 14**).



Gambar 14

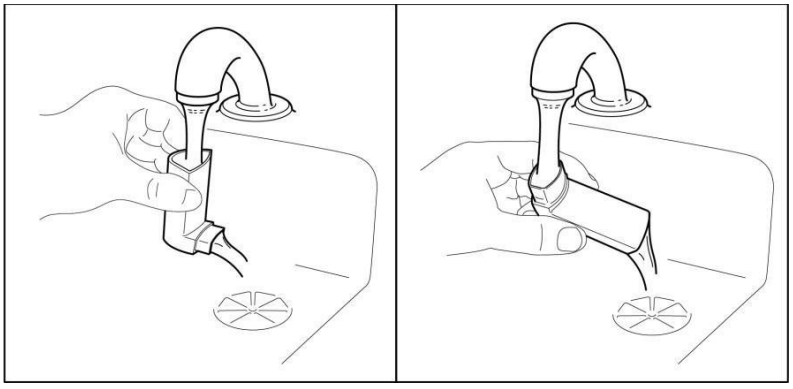
Langkah 1: Keluarkan tabung *canister* dari aktuator (**Lihat Gambar 15**). **Jangan** membersihkan tabung *canister* atau membiarkannya basah.



Gambar 15

Langkah 2: Cabut tutup *mouthpiece*.

Langkah 3: Pegang aktuator, posisikan di bawah keran, lalu aliri dengan air hangat selama sekitar 30 detik. Balikkan aktuator dan bilas aktuator lagi melalui *mouthpiece* selama sekitar 30 detik (**Lihat Gambar 16**).

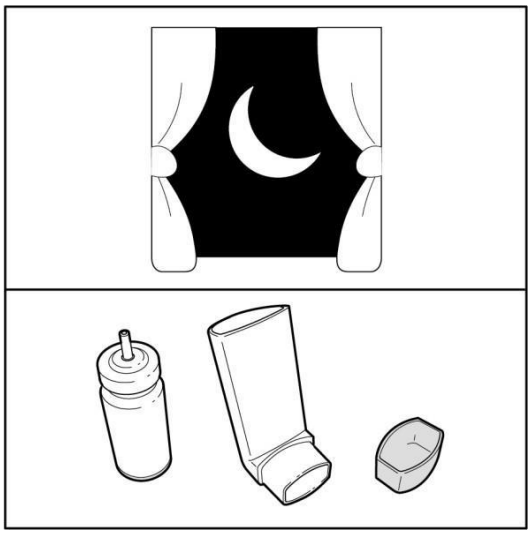


Gambar 16

Langkah 4: Kibaskan agar air jatuh sebanyak mungkin dari aktuator.

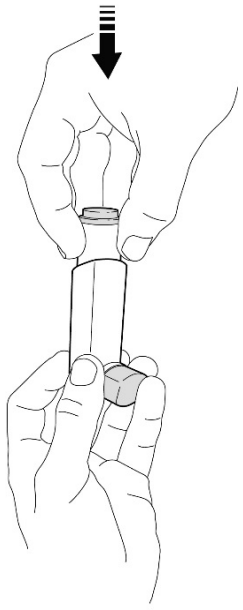
Langkah 5: Lihat ke dalam aktuator dan *mouthpiece*, pastikan obat yang menumpuk benar-benar hilang. Jika ada obat yang menumpuk, ulangi Langkah 3 sampai 5 di bagian ini.

Langkah 6: Biarkan aktuator mengering semalaman (**Lihat Gambar 17**). **Jangan** memasukkan kembali tabung bertekanan ke dalam aktuator jika masih basah.



Gambar 17

Langkah 7: Setelah aktuator kering, tekan perlahan tabung di aktuator (**Lihat Gambar 18**). Jangan menekan terlalu keras pada tabung. Hal ini dapat menyebabkan *puff* obat keluar.



Gambar 18

Langkah 8: Siapkan lagi inhaler **Bevespi Aerosphere** Anda tiap setelah dibersihkan. Untuk menyiapkan ulang inhaler, kocok inhaler dengan seksama dan tekan bagian tengah indikator dosis dua kali untuk melepaskan total 2 *puff* ke udara jauh dari wajah Anda. Inhaler Anda sekarang siap digunakan.

Jika Anda tidak menggunakan Bevespi Aerosphere selama lebih dari 7 hari atau jika inhaler Anda terpapar suhu rendah atau setelah terjatuh:

Jika Anda tidak menggunakan Bevespi Aerosphere selama lebih dari 7 hari, atau jika inhaler Anda terpapar suhu rendah, atau setelah jatuh, Anda perlu melakukan penyiapan ulang sebelum digunakan.

Untuk menyiapkan ulang inhaler, kocok inhaler dengan seksama dan tekan bagian tengah indikator dosis dua kali untuk melepaskan total 2 *puff* ke udara jauh dari wajah Anda. Inhaler Anda sekarang siap digunakan.

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