ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation (delivered dose, the dose leaving the mouthpiece) contains glycopyrronium bromide 9 micrograms equivalent to 7.2 micrograms of glycopyrronium, and 5 micrograms of formoterol fumarate dihydrate.

This corresponds to a metered dose (i.e. the dose leaving the valve) of glycopyrronium bromide 10.4 micrograms equivalent to 8.3 micrograms of glycopyrronium, and 5.8 microgram of formoterol fumarate dihydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension (pressurised inhalation)

White suspension.

4. CLINICAL PARTICULARS

4.1 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 5.1).

4.2 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 5.2).

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 4.4 and 5.2).

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 4.4 and 5.2).

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 package 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 5.2).

4.3 Contraindications

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

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

Asthma

Bevespi Aerosphere should not be used to treat asthma.

Paradoxical bronchospasm

As with other inhalation therapy, administration of this medicinal product may result in paradoxical bronchospasm, which can be life-threatening. If paradoxical bronchospasm does occur, treatment with the medicinal product should be stopped and other treatments considered.

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 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 4.5).

Hypokalaemia

β_2-adrenergic agonists may produce significant hypokalaemia, which may increase the susceptibility to cardiac arrhythmias. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5).

Hyperglycaemia

Inhalation of high doses of β_2-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 4.8).

Patients with severe renal impairment

As glycopyrronium 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 5.2).

Patients with severe hepatic impairment

In patients with severe hepatic impairment, Bevespi 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 products and other forms of interaction

Pharmacokinetic interactions

No interaction studies have been performed with Bevespi Aerosphere; however, the potential for metabolic interactions is considered to be low based on *in-vitro* studies (see section 5.2).

Since glycopyrronium is eliminated mainly by the renal route, interactions could potentially occur with medicinal products affecting renal excretion mechanisms. *In-vitro* glycopyrronium is a substrate for the renal transporters OCT2 and MATE1/2K. The effect of cimetidine, a probe inhibitor of OCT2 and MATE1, on inhaled glycopyrronium disposition showed a limited increase in its total systemic exposure (AUC_{0-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 Bevespi Aerosphere with other anticholinergic and/or long-acting β_2-adrenergic agonist containing medicinal products has not been studied and is not recommended as it may potentiate known inhaled muscarinic antagonist or β_2-adrenergic agonist adverse reactions (see sections 4.4 and 4.9).

Although no formal *in-vivo* 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 β_2-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 β_2-adrenergic agonists, therefore, caution is advised in their concomitant use (see section 4.4).

β-adrenergic blockers
β-adrenergic blockers (including eye drops) can weaken or inhibit the effect of β_2-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 4.4).

4.6 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 passed the placental barrier. In animal studies, formoterol and glycopyrronium, individually, have caused adverse effects in reproduction studies at very high doses/systemic exposure levels (see section 5.3).

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

Breast-feeding

It is not known whether glycopyrronium or formoterol are excreted in human milk. Evidence of transfer of glycopyrronium 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 5.3).

Fertility

Studies in rats have shown adverse effects on fertility only at dose levels higher than the maximum human exposure to formoterol (see section 5.3). Glycopyrronium 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.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

The safety profile is characterised by anticholinergic and β_2-adrenergic class effects related to the individual components of the combination. The most commonly reported adverse reactions in 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 clinical trials and post-approval experience with Bevespi Aerosphere as well as 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	Urinary tract infection	Common

disorders	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

Reporting of suspected adverse reactions

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

4.9 Overdose

An overdose of Bevespi Aerosphere may lead to exaggerated anticholinergic and/or β_2-adrenergic signs and symptoms, the most frequent of which include blurred vision, dry mouth, nausea, muscle spasm, tremor, headache, palpitations and systolic hypertension.

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, ATC code: R03AL07.

Mechanism of action

Bevespi Aerosphere contains two bronchodilators: glycopyrronium, a long-acting muscarinic antagonist (also referred to as an anticholinergic), and formoterol, a long-acting β_2-adrenergic agonist with a rapid onset of action.

Glycopyrronium 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 β_2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists are more effective in relaxing central airways, and β_2-adrenergic agonists are more effective in relaxing peripheral airways; relaxation of both central and peripheral airways with combination treatment may contribute to its beneficial effects on lung function.

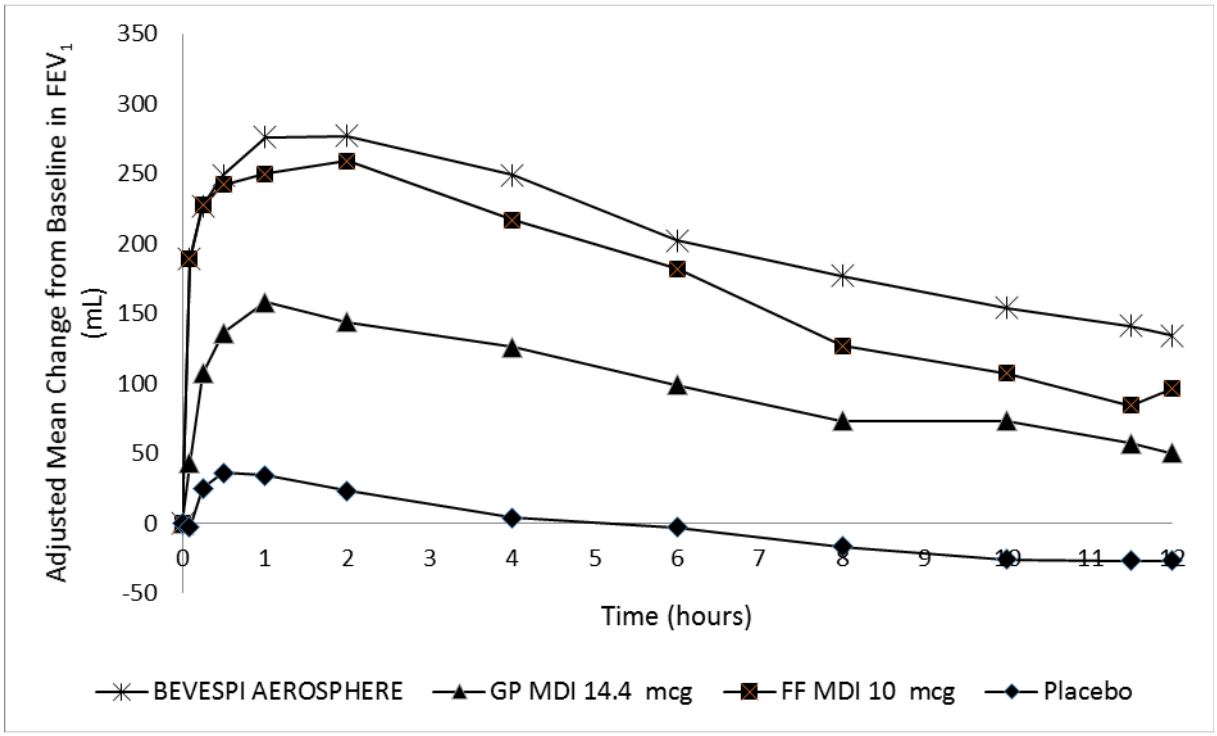
Pharmacodynamic effects

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 [FEV_1]), 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

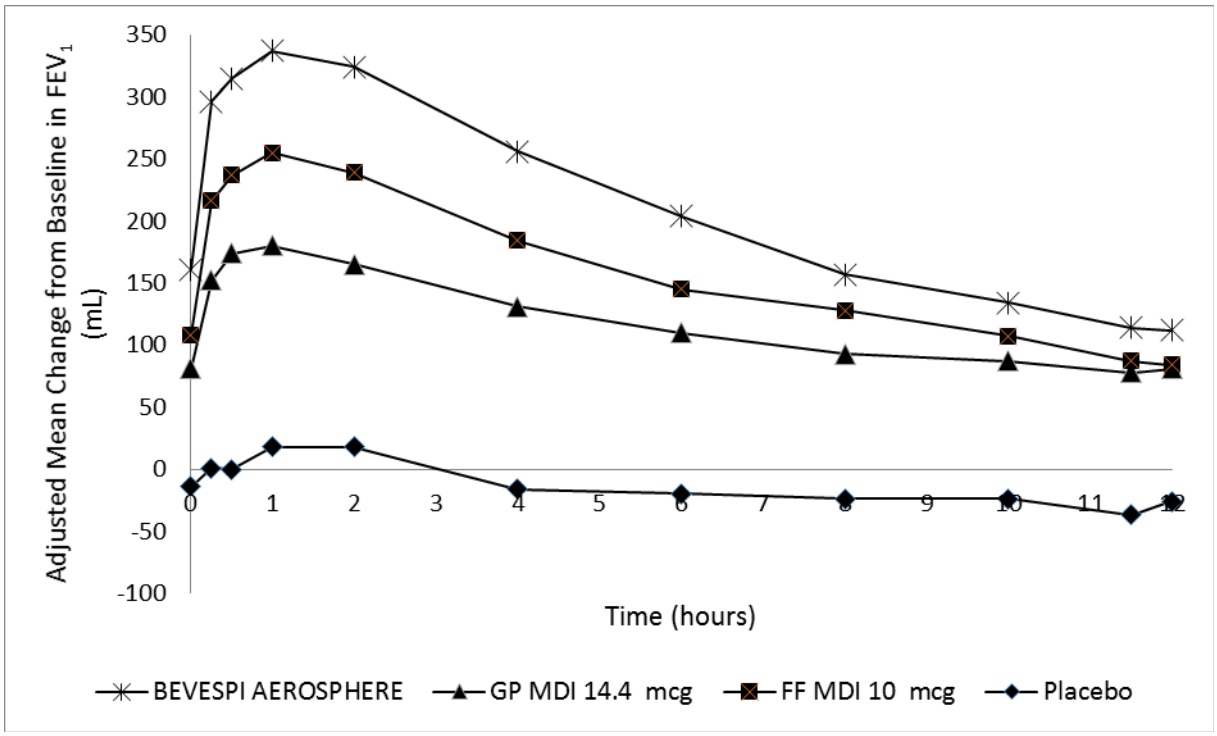
and 179 mL in PINNACLE 1, PINNACLE 2 and PINNACLE 4, respectively [p <0.001]). The mean bronchodilator effect derived from serial FEV1 measurements at Day 1 and Week 12 from PINNACLE 1 are shown in Figure 1. In PINNACLE 2, the results were similar to those observed in PINNACLE 1.

Figure 1 Mean Change from Baseline in FEV_1 over Time on Day 1 and at Week 12

DAY 1



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/formoterol with eight times the recommended dose of glycopyrronium 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 FEV_1 over 24 weeks relative to placebo, glycopyrronium 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 FEV_1 within 2 hours post-dose over 24 weeks relative to placebo, glycopyrronium and formoterol ($p<0.0001$) [see Table 2].

There were improvements in trough FEV_1 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 (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 (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 (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

Treatment comparisons with Bevespi Aersophere	**Treatment difference (95% confidence intervals, p-value)**				
	Trough FEV1 (ml)[a]	**Peak FEV1 (ml)**	**SAC-TDI / TDI Focal Score[b]**	**SGRQ total score**	**Daily rescue Ventolin (inhalations/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) vs placebo (N=235)	155 (129, 180) p<0.0001	293 (265, 321) p<0.0001	0.80 (0.47, 1.13) p<0.0001	-3.50 (-5.18, -1.82) p<0.0001	-0.98 (-1.47, -0.49) 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Bevespi Aerosphere in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following inhalation of the glycopyrronium 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 (as measured by AUC_{0-12}) by 16% while formoterol exposure was unchanged.

Absorption

Following inhaled administration of Bevespi Aerosphere in subjects with COPD, glycopyrronium C_{max} occurred at approximately 5 minutes, and formoterol C_{max} 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 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
The estimated glycopyrronium Vc/F (volume of the central compartment), and Vp1/F (volume of the peripheral compartment) are 741 L, and 2 990 L, respectively, via population pharmacokinetic analysis. Over the concentration range of 2-500 nmol/L, plasma protein binding of glycopyrronium ranged from 43% to 54%.

Formoterol
The estimated formoterol Vc/F (volume of the central compartment), and Vp1/F (volume of the peripheral compartment) are 1 030 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

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

In-vitro studies indicate the glycopyrronium 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 intravenous administration of a 0.2 mg dose of radiolabelled glycopyrronium, 85% of the dose was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile. The terminal elimination half-life of glycopyrronium 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 intravenous 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 (dose range: 14.4 to 115.2 mcg) and formoterol (dose range: 2.4 to 19.2 mcg) after oral inhalation.

Special populations

Elderly
Based on available data, no adjustment of the dose of Bevespi Aerosphere in geriatric patients is necessary.

Renal impairment
Studies evaluating the effect of renal impairment on the pharmacokinetics of glycopyrronium and formoterol have not been conducted. The effect of renal impairment on the exposure to glycopyrronium 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 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. 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 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 was performed based on data collected in a total of 311 subjects with COPD. The pharmacokinetics of glycopyrronium was best described by a two-compartment disposition model with first-order absorption and linear elimination. The typical clearance (CL/F) of glycopyrronium was 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 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.

5.3 Preclinical safety data

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

The toxicity observed in studies with the combination of glycopyrronium 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 β-adrenoceptor agonists. No significant effects attributable to glycopyrronium 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 β_2-adrenoreceptor agonists.

Animal reproduction studies with glycopyrronium 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.

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

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

6.4 Special precautions for storage

Do not store above 30ºC.

Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.

6.5 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.

Pack sizes:
Pack of 1 inhaler with 120 actuations.
Multipack containing 360 (3 inhalers of 120) actuations.

Not all pack sizes may be marketed.

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.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1339/001
EU/1/18/1339/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2018
Date of latest renewal: 15 September 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca Dunkerque Production
224 Avenue de la Dordogne
59640 Dunkerque
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – SINGLE INHALER

1. NAME OF THE MEDICINAL PRODUCT

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension
glycopyrronium/formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single actuation contains glycopyrronium bromide equivalent to 7.2 micrograms of glycopyrronium, and 5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, suspension.
120 actuations (1 inhaler)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Shake well before use.
Inhalation use
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1339/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bevespi aerosphere

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension
glycopyrronium/formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single actuation contains glycopyrronium bromide equivalent to 7.2 micrograms of glycopyrronium, and 5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, suspension.
Multipack: 360 (3 packs of 120) actuations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Shake well before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.
Do not expose to temperatures higher than 50°C.

Do not pierce the pressurised container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1339/002 360 actuations (3 packs of 120 actuations)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bevespi aerosphere

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITH NO BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension
glycopyrronium/formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single actuation contains glycopyrronium bromide equivalent to 7.2 micrograms of glycopyrronium, and 5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, suspension.
120 actuations (1 inhaler). Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Shake well before use.
Inhalation use
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1339/002 360 actuations (3 packs of 120 actuations)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

bevespi aerosphere

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FOIL POUCH

1. NAME OF THE MEDICINAL PRODUCT

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension
glycopyrronium/formoterol fumarate dihydrate

2. NAMES OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

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

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use
Read the package leaflet before use.
Shake well before use.

Do not swallow the desiccant.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER LABEL (ACTUATOR)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bevespi Aerosphere 7.2 mcg/5 mcg pressurised inhalation
glycopyrronium/formoterol fumarate dihydrate
Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations

6. OTHER

AstraZeneca

Date pouch opened:_____

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER LABEL (PRESSURISED CONTAINER)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bevespi Aerosphere 7.2 mcg/5 mcg pressurised inhalation
glycopyrronium/formoterol fumarate dihydrate
Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension
glycopyrronium/formoterol fumarate dihydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bevespi Aerosphere is and what it is used for

Bevespi Aerosphere contains two active substances called glycopyrronium and formoterol fumarate dihydrate. These belong to a group of medicines called long-acting bronchodilators.

Bevespi Aerosphere is used to make breathing easier for adults who have a lung disease called chronic obstructive pulmonary disease (COPD). COPD is a long-term disease of the airways in the lungs, which is often caused by smoking. In COPD, the muscles around the airways tighten which makes breathing difficult.

The medicine prevents the tightening of the muscles around the airways, making it easier for air to get in and out of the lungs.

Bevespi Aerosphere delivers the active substances directly to the airways in your lungs as you breathe in. It will help to reduce the effects of COPD on your everyday life.

2. What you need to know before you use Bevespi Aerosphere

Do not use Bevespi Aerosphere if

- you are allergic to glycopyrronium, formoterol fumarate dihydrate or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or pharmacist before using Bevespi Aerosphere.

Warnings and precautions

Bevespi Aerosphere is used regularly for long-term treatment of COPD. Do not use this medicine to treat a sudden attack of breathlessness or wheezing.

Immediate breathing difficulties

If you get tightness of the chest, coughing, wheezing or breathlessness immediately after using Bevespi Aerosphere:

Stop using this medicine and seek medical help immediately, as you may have a serious condition called paradoxical bronchospasm.

Talk to your doctor or pharmacist before using Bevespi Aerosphere if

- you have asthma. Do not use this medicine for asthma
- you have heart problems
- you have diabetes
- you have low levels of potassium in the blood
- you have thyroid gland problems (called 'thyrotoxicosis')
- you have an eye problem called narrow-angle glaucoma (also called angle-closure glaucoma)
- you have prostate problems, or difficulty passing urine
- you have kidney or liver problems

Always tell your doctor about other health problems.

Children and adolescents

Bevespi Aerosphere is not for use in children or adolescents below 18 years of age.

Other medicines and Bevespi Aerosphere

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Some medicines may affect how this medicine works, or make it more likely that you will have side effects. These include:

- any medicines that work in the same way as Bevespi Aerosphere, such as medicines containing active substances such as tiotropium, ipratropium, aclidinium, umeclidinium, salmeterol, vilanterol, olodaterol, or indacaterol. Ask your doctor or pharmacist if you are not sure. It is not recommended to use Bevespi Aerosphere together with these medicines;
- medicines that lower potassium in your blood. These include:
  - corticosteroids that you take by mouth (such as prednisolone),
  - diuretics (such as furosemide or hydrochlorothiazide) used for high blood pressure,
  - some medicines used to treat breathing conditions called methylxanthines (such as theophylline);
- medicines called beta-blockers that may be used to treat high blood pressure or other heart problems (such as atenolol or propranolol) or to treat glaucoma (such as timolol)
- medicines which can prolong 'QT interval' (a change in the electrical activity of the heart). These include medicines for the treatment of:
  - depression (such as monoamine oxidase inhibitors or tricyclic antidepressants),
  - bacterial infections (such as erythromycin, clarithromycin, telithromycin),
  - allergic reactions (anti-histamines).

If any of the above applies to you, or if you are not sure, talk to your doctor or pharmacist before using Bevespi Aerosphere.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking Bevespi Aerosphere.

Do not use Bevespi Aerosphere if you are pregnant unless your doctor tells you that you can.

Do not use Bevespi Aerosphere if you are breast-feeding unless your doctor tells you that you can.

Driving and using machines

It is unlikely that this medicine will affect your ability to drive and use machines. However, dizziness and nausea are common side effects which may occur. If this occurs, do not drive or use machines.

3. How to use Bevespi Aerosphere

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to use
The recommended dose is two puffs twice a day.
It is important to use Bevespi Aerosphere every day, even if you have no COPD symptoms at the time.

How to use
Bevespi Aerosphere is for inhalation use.
Please read the instructions for use at the end of this leaflet. If you are not sure of how to use Bevespi Aerosphere, contact your doctor or pharmacist.

Using Bevespi Aerosphere with a spacer
If you find it difficult breathing in and pressing the inhaler at the same time talk to your doctor or pharmacist. You may be able to use a 'spacer' with your inhaler.

If you use more Bevespi Aerosphere than you should

If you have used more Bevespi Aerosphere than you should, talk to a doctor or pharmacist immediately. You may need medical attention. You may notice that your heart is beating faster than usual, you feel shaky, you have visual disturbances, have a dry mouth, or have a headache or feel nauseous (sick).

If you forget to use Bevespi Aerosphere

Do not take a double dose to make up for a forgotten dose. Take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose. Do not take more than two puffs twice a day.

If you stop using Bevespi Aerosphere

This medicine is for long-term use. It will only be effective as long as you are using it.
Do not stop unless your doctor tells you to, even if you feel better, as your symptoms may get worse.
If you want to stop treatment, first talk to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop using Bevespi Aerosphere and seek immediate medical care if you notice any of the following symptoms:

Uncommon (may affect up to 1 in 100 people)
- swelling of your face, particularly around your mouth (swelling of your tongue or throat may make it difficult to swallow);
- rash or hives together with difficulty breathing;
- suddenly feeling faint.

These symptoms may be signs of an allergic reaction which may become serious.

Other possible side effects

Common (may affect up to 1 in 10 people)
- headache
- dry mouth
- feeling sick (nausea)
- painful and frequent urination (may be signs of urinary tract infection)
- muscle cramps
- chest pain
- anxiety
- feeling dizzy

Uncommon (may affect up to 1 in 100 people)
- shaking or tremor
- high blood sugar levels
- agitation
- feeling restless
- difficulty sleeping
- fast or irregular heart beat
- difficulty passing urine (urinary retention)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bevespi Aerosphere

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, pouch and pressurised container after 'EXP'. The expiry date refers to the last day of that month.

The inhaler can be used for up to 3 months after first opening the pouch. Write the date the pouch is opened on the inhaler label in the space provided.

Do not store above 30ºC.

Warning: Do not break, puncture or burn the pressurised container, even when apparently empty. Do not expose to temperatures higher than 50ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bevespi Aerosphere contains
The active substances are glycopyrronium and formoterol fumarate dihydrate.

Each single puff delivers a dose of 9 micrograms glycopyrronium bromide (equivalent to 7.2 micrograms of glycopyrronium), and 5 micrograms of formoterol fumarate dihydrate.

This corresponds to a metered dose (i.e. the dose leaving the valve) of glycopyrronium bromide 10.4 micrograms equivalent to 8.3 micrograms of glycopyrronium, and 5.8 microgram of formoterol fumarate dihydrate.

The other ingredients are norflurane, 1,2- distearoyl-sn-glycero-3-phosphocholine and calcium chloride.

What Bevespi Aerosphere looks like and contents of the pack

Bevespi Aerosphere is a pressurised inhalation, suspension.
Bevespi Aerosphere comes as a pressurised container with a dose indicator, supplied with a white plastic actuator body and mouthpiece (see Figure 1 of the Instructions for Use at the end of this leaflet). The mouthpiece is covered with an orange protective cap. Bevespi Aerosphere is supplied in a foil pouch that contains a drying packet (desiccant) and packed into a carton.

The active ingredients are present in a pressurised suspension inside the pressurised container.

Bevespi Aerosphere is available in packs containing 1 inhaler with 120 puffs and in multipacks comprising 3 inhalers, each containing 120 puffs.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca Dunkerque Production
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59640 Dunkerque
France

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This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Instructions for use

Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension
glycopyrronium/formoterol fumarate dihydrate

Read this instructions for use and the package leaflet before you start using Bevespi Aerosphere and each time you get a new inhaler. There may be new information. This information should be used alongside a discussion with your doctor about your medical condition and treatment.

Important Information:

- **For inhalation use only**.
- Use Bevespi Aerosphere exactly as your doctor tells you to.
- Talk to your doctor or pharmacist if you have any questions about the use of your inhaler.

The parts of your Bevespi Aerosphere inhaler (See Figure 1):

- Bevespi Aerosphere comes as a pressurised container with a dose indicator that fits into an actuator.
    - **Do not** use the Bevespi Aerosphere actuator with any other medicine.
    - **Do not** use the Bevespi Aerosphere pressurised container with an actuator from any other inhaler.

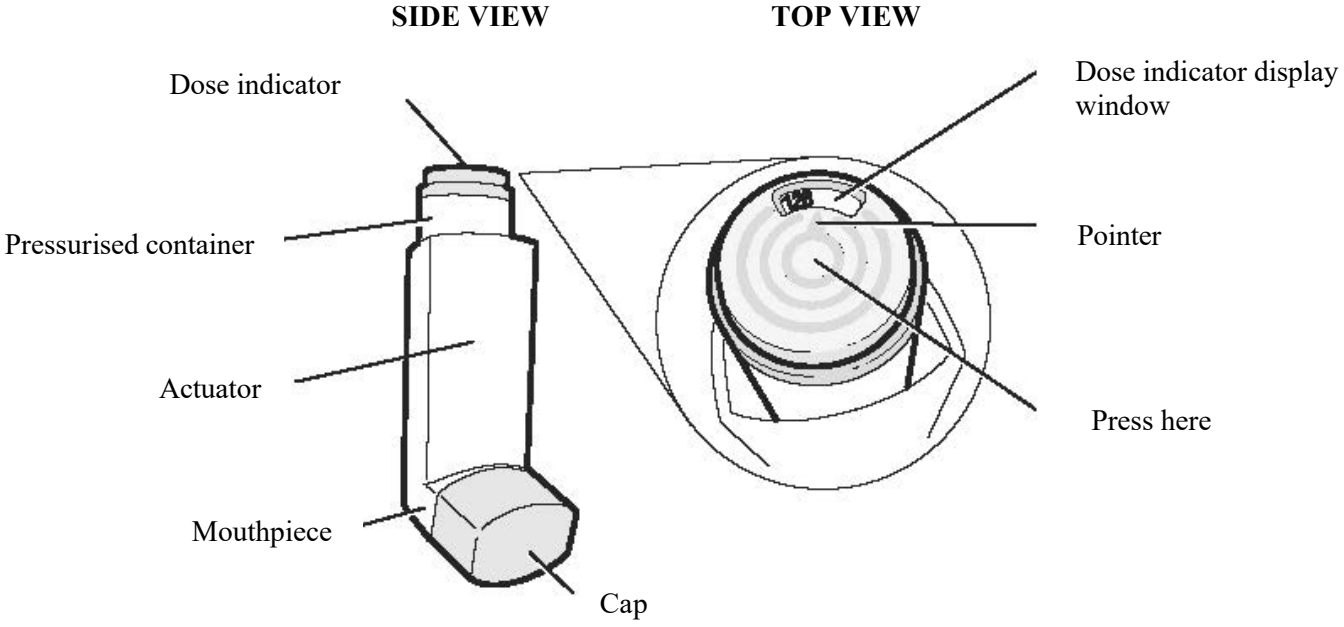

Figure 1

- Bevespi Aerosphere comes with a dose indicator on the top of the pressurised container (**See Figure 1**). The dose indicator display window shows how many puffs of medicine you have left. A puff of medicine is released each time you press the centre of the dose indicator.

Before you use Bevespi Aerosphere for the first time

Before you use Bevespi Aerosphere for the first time, make sure that the pointer on the dose indicator is pointing to the right of the "120" inhalation mark in the dose indicator display window (**See Figure 1**).

- The pointer points to 120 after 10 puffs are delivered from Bevespi Aerosphere. This means that there are 120 puffs of medicine left in the pressurised container (**See Figure 2a**).
- The pointer points between 100 and 120 after you use 10 more puffs. This means that there are 110 puffs of medicine left in the pressurised container (**See Figure 2b**).
- The pointer points to 100 after you take 10 more puffs. This means that there are 100 puffs of medicine left in the pressurised container (**See Figure 2c)**.

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

- The dose indicator display window will move after every 10 puffs. The number in the dose indicator display window will change after every 20 puffs.

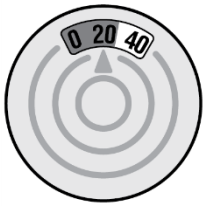

Figure 2d

- The colour in the dose indicator display window will change to red, as shown in the shaded area, when there are only 20 puffs of medicine left in your inhaler (**See Figure 2d).**
- When the arrow reaches '0', you must stop using your inhaler. Your inhaler may not feel empty and it may seem as though it still works. However, you will not get the right amount of medicine if you keep using it.

Preparing your Bevespi Aerosphere inhaler for use:

- Your Bevespi Aerosphere inhaler comes in a foil pouch that contains a drying packet (desiccant).
  - Take the Bevespi Aerosphere inhaler out of the foil pouch.
  - Throw away the pouch and the drying packet. Do not use the inhaler if the drying agent has leaked out of its packet.

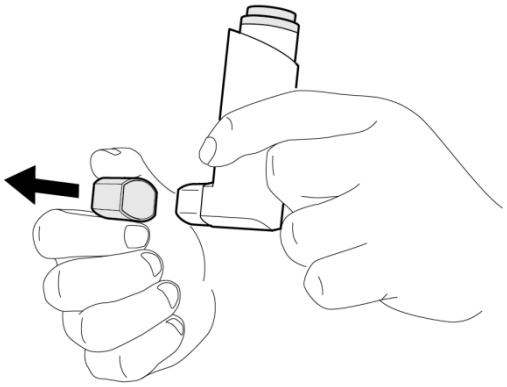

Figure 3

Priming your Bevespi Aerosphere inhaler:

Before you use Bevespi Aerosphere for the first time, you must prime the inhaler.

- Remove the cap from the mouthpiece (**See Figure 3**). Check inside the mouthpiece before you use the inhaler to make sure it is clear.
- Hold the inhaler upright, away from your face and shake it well (**See Figure 4**).

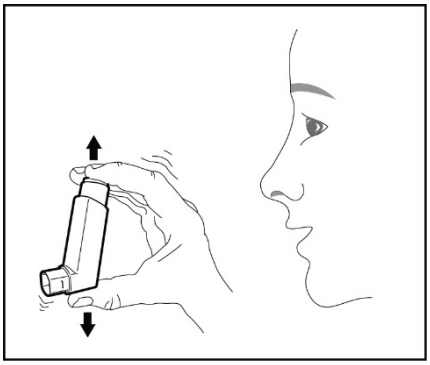

Figure 4

- Press down firmly on the centre of the dose indicator until the pressurised container stops moving in the actuator. This will release a puff of medicine from the mouthpiece (**See Figure 5**). You may hear a soft click from the dose indicator as it counts down during use.

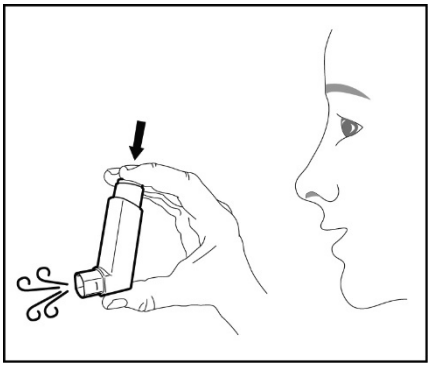

Figure 5

- **Repeat the priming steps 3 more times (See Figure 4 and Figure 5).** Shake the inhaler well before each priming puff.
- After priming 4 times, the dose indicator should be pointing to the right of "**120**" and your inhaler is now ready to use.

Using your Bevespi Aerosphere inhaler:

Step 1: Remove the cap from the mouthpiece (**See Figure 6**).

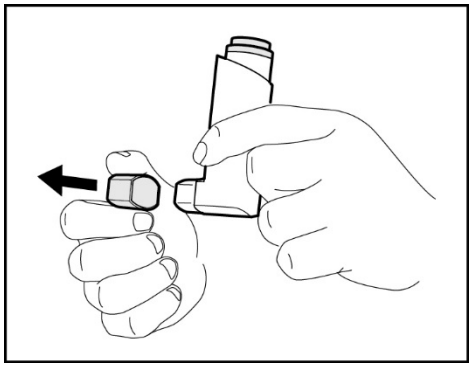

Figure 6

Step 2: Shake the inhaler well before each use (**See Figure 7**).

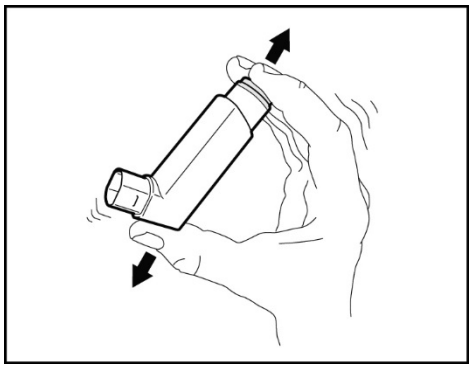

Figure 7

Step 3: Hold the inhaler with the mouthpiece pointing towards you and breathe out as fully as you comfortably can through your mouth (**See Figure 8**).

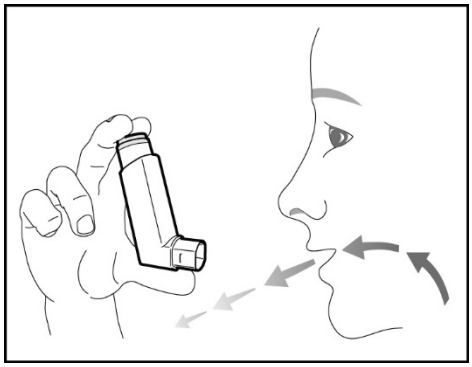

Figure 8

Step 4: Close your lips around the mouthpiece and tilt your head back, keeping your tongue below the mouthpiece (**See Figure 9**).

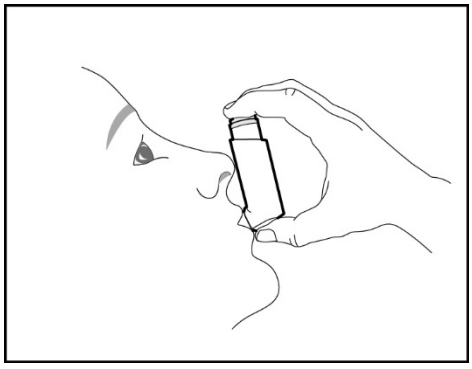

Figure 9

Step 5: While breathing in deeply and slowly, press down on the centre of the dose indicator until the pressurised container stops moving in the actuator and a puff of medicine has been released (**See Figure 10**). Then stop pressing the dose indicator.

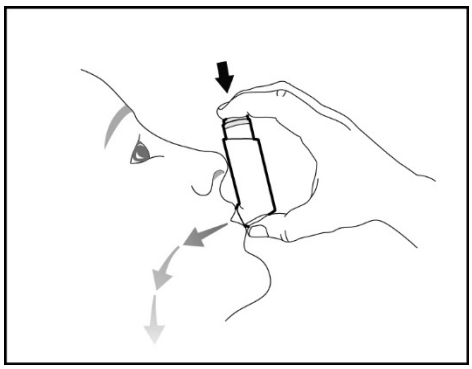

Figure 10

Step 6: When you have finished breathing in, remove the mouthpiece from your mouth. Hold your breath as long as you comfortably can, up to 10 seconds (**See Figure 11**).

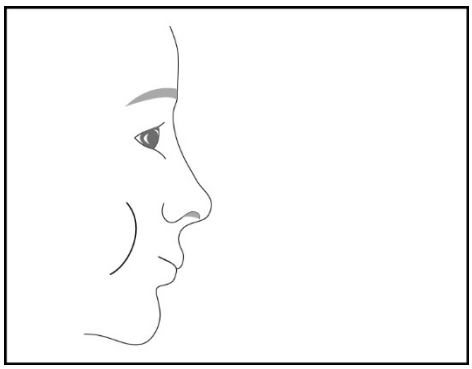

Figure 11

Step 7: Breathe out gently (**See Figure 12**). **Repeat steps 2 to 7** to take your second puff of Bevespi Aerosphere.

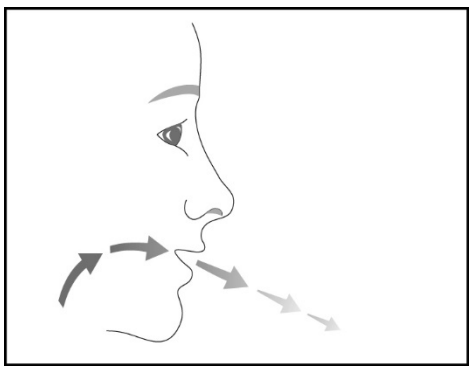

Figure 12

Step 8: Replace the cap over the mouthpiece right away after use (**See Figure 13**).

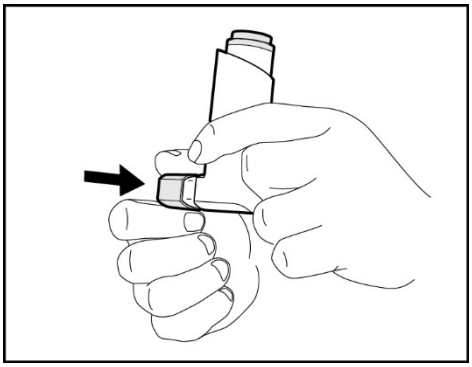

Figure 13

How to clean your Bevespi Aerosphere inhaler:

Clean the inhaler once each week for the first 3 weeks. It is very important to keep your inhaler clean so that medicine does not build-up and block the spray through the mouthpiece (**See Figure 14**).

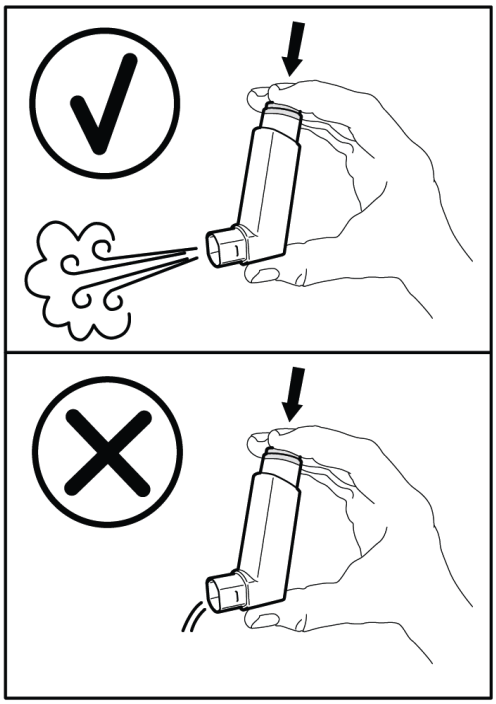

Figure 14

Step 1: Take the pressurised container out of the actuator (**See Figure 15**). **Do not** clean the pressurised container or let it get wet.

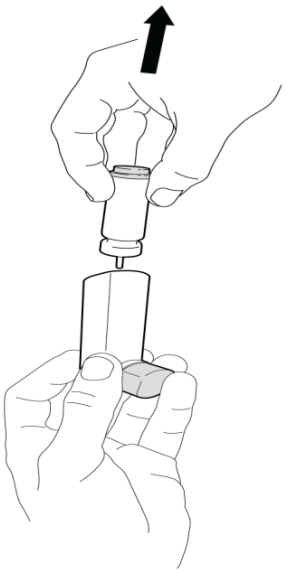

Figure 15

Step 2: Take the cap off the mouthpiece.

Step 3: Hold the actuator under the tap and run warm water through it for about 30 seconds. Turn the actuator upside down and rinse the actuator again through the mouthpiece for about 30 seconds (**See Figure 16**).

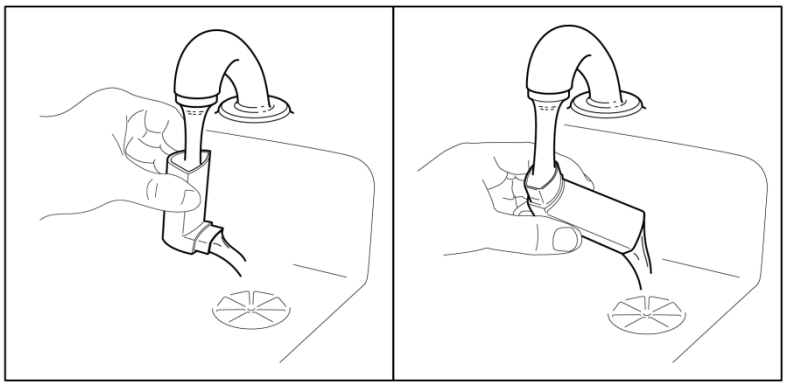

Figure 16

Step 4: Shake off as much water from the actuator as you can.

Step 5: Look into the actuator and the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any built-up medicine, repeat Steps 3 to 5 in the section.

Step 6: Let the actuator air-dry overnight (**See Figure 17**). **Do not** put the pressurised container back into the actuator if it is still wet.

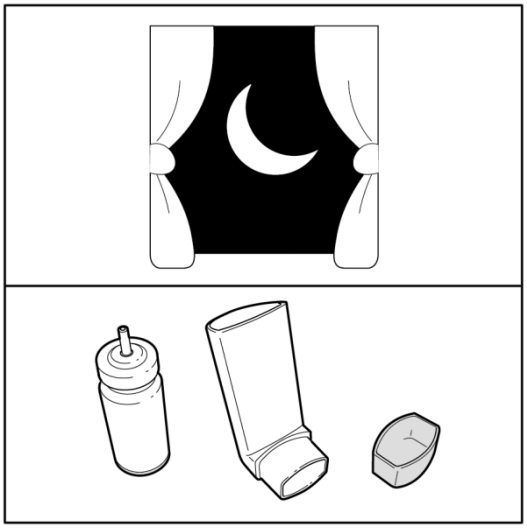

Figure 17

Step 7: When the actuator is dry, gently press the pressurised container down in the actuator (**See Figure 18**). Do not press down too hard on the pressurised container. This could cause a puff of medicine to be released.

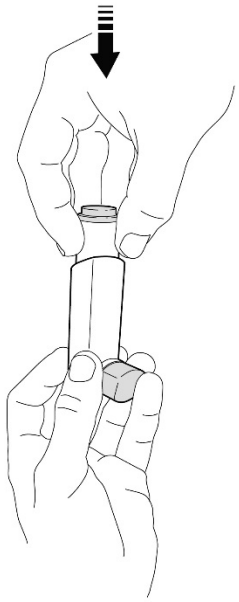

Figure 18

Step 8: Re-prime your **Bevespi Aerosphere** inhaler after each cleaning. To re-prime the inhaler, shake the inhaler well and press down on the centre of the dose indicator twice to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.

If you do not use your Bevespi Aerosphere for more than 7 days or if exposed to low temperatures or is dropped:

If you do not use your Bevespi Aerosphere for more than 7 days, or if the inhaler is exposed to low temperatures or has been dropped, you will need to re-prime it before use.

To re-prime the inhaler, shake the inhaler well and press down on the centre of the dose indicator twice to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.