ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Riltrava Aerosphere 5 micrograms/7.2 micrograms/160 micrograms pressurised inhalation, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation (delivered dose, ex-actuator) contains 5 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 9 micrograms, equivalent to 7.2 micrograms of glycopyrronium, and budesonide 160 micrograms.

This corresponds to a metered dose of 5.3 micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 9.6 micrograms, equivalent to 7.7 micrograms of glycopyrronium, and budesonide 170 micrograms.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

White suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

If a dose is missed, it should be taken as soon as possible and the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

Special populations

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

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

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

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

Method of administration

For inhalation use.

Instructions for use
To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler correctly by a physician or other healthcare professional, who should also regularly check the adequacy of the patient's inhalation technique. The patient should be advised to read the Package Leaflet carefully and follow the instructions for use as given in the leaflet.
Note: It is important to instruct the patients to:

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

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

Patients who find it difficult to coordinate actuation with inhalation may use Riltrava Aerosphere with a spacer to ensure proper administration of the medicinal product. Riltrava Aerosphere can be used with spacer devices including the Aerochamber Plus Flow-Vu (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

This medicinal product is not indicated for the treatment of acute episodes of bronchospasm, i.e. as a rescue therapy.

Paradoxical bronchospasm

Administration of formoterol/glycopyrronium/budesonide may produce paradoxical bronchospasm with an immediate wheezing and shortness of breath after dosing and may be life-threatening. Treatment with this medicinal product should be discontinued immediately if paradoxical bronchospasm occurs. The patient should be assessed, and alternative therapy instituted if necessary.

Deterioration of disease

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

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including glycopyrronium and formoterol. This medicinal product should be used with caution in patients with clinically significant uncontrolled and severe cardiovascular disease such as unstable ischemic heart disease, acute myocardial infarction, cardiomyopathy, cardiac arrhythmias, and severe heart failure.

Caution should also be exercised when treating patients with known or suspected prolongation of the QTc interval (QTc > 450 milliseconds for males, or > 470 milliseconds for females), either congenital or induced by medicinal products.

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma. Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis.

Visual disturbances

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

Transfer from oral therapy

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

Pneumonia in patients with COPD

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

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

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Hypokalaemia

Potentially serious hypokalaemia may result from β_2-agonist therapy. This has the potential to produce adverse cardiovascular effects. Particular caution is advised in severe COPD as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see section 4.5).

Hyperglycaemia

Inhalation of high doses of β_2-adrenergic agonists may produce increases in plasma glucose. Therefore, blood glucose should be monitored during treatment following established guidelines in patients with diabetes.

Co-existing conditions

This medicinal product should be used with caution in patients with thyrotoxicosis.

Anticholinergic activity

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

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

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 this medicinal product if the expected benefit outweighs the potential risk (see section 5.2).

Hepatic impairment

In patients with severe hepatic impairment, this medicinal product 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

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

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

The metabolism of budesonide is primarily mediated by CYP3A4 (see section 5.2). Co-treatment with strong CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects, and should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid adverse reactions, in which case patients should be monitored for systemic corticosteroid adverse reactions. This is of limited clinical importance for short-term (1-2 weeks) treatment.

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

Since glycopyrronium is eliminated mainly by the renal route, drug interaction could potentially occur with medicinal products affecting renal excretion mechanisms. *In vitro*, glycopyrronium is a substrate for the renal transporters OCT2 and MATE1/2K. The effect of cimetidine, a probe inhibitor of OCT2 and MATE1, on inhaled glycopyrronium disposition showed a limited increase in its total systemic exposure (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 this medicinal product 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 β2-adrenergic agonist adverse reactions (see section 4.4 and section 4.9).

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

No animal reproductive toxicology studies have been conducted with this medicinal product. Budesonide has been shown to induce embryofoetal toxicity in rats and rabbits, a class effect of glucocorticoids. At very high doses/systemic exposure levels, formoterol caused implantation losses as well as decreases in birth weight and early postnatal survival, whereas glycopyrronium had no significant effects on reproduction (see section 5.3).

Administration of this medicinal product to pregnant women should only be considered if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

A clinical pharmacology study has shown that inhaled budesonide is excreted in breast milk. However, budesonide was not detected in nursing infant blood samples. Based on pharmacokinetic parameters, the plasma concentration in the child is estimated to be less than 0.17% of the mother's plasma concentration. Consequently, no effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of this medicinal product. 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 this medicinal product to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile is characterised by corticosteroid, anticholinergic and β_2-adrenergic class effects related to the individual components of the combination. The most commonly reported adverse

reactions in patients receiving this medicinal product were pneumonia (4.6%), headache (2.7%) and urinary tract infection (2.7%).

Tabulated list of adverse reactions

The tabulated list of adverse reactions is based on the experience with this medicinal product in clinical trials and experience with the individual components.

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

Table 1: Adverse reactions by frequency and system organ class (SOC)

System Organ Class	**Preferred term**	**Frequency**
Infections and infestations	Oral candidiasis Pneumonia	Common
Immune system disorders	Hypersensitivity	Uncommon
	Angioedema	Not known
Endocrine disorders	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland	Very rare
Metabolism and nutrition disorders	Hyperglycaemia	Common
Psychiatric disorders	Anxiety Insomnia	Common
	Depression Agitation Restlessness Nervousness	Uncommon
	Abnormal behaviour	Very rare
Nervous system disorders	Headache	Common
	Dizziness Tremor	Uncommon
Eye disorders	Vision blurred (see section 4.4) Cataract Glaucoma	Not known
Cardiac disorders	Palpitations	Common
	Angina pectoris Tachycardia Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles)	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough	Common
	Throat irritation Bronchospasm	Uncommon
Gastrointestinal disorders	Nausea	Common
	Dry mouth	Uncommon
Skin and subcutaneous tissue disorders	Bruising	Uncommon
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
Renal and urinary disorders	Urinary tract infection	Common
	Urinary retention	Uncommon

System Organ Class	Preferred term	Frequency
General disorders and administration site conditions	Chest pain	Uncommon

Description of selected adverse reactions

Pneumonia

KRONOS was a 24-week study in a total of 1,896 patients with moderate to very severe COPD (mean post-bronchodilator screening FEV_1 50% of predicted, standard deviation [SD] 14%), 26% of whom had experienced a COPD exacerbation in the year prior to study entry. The incidence of confirmed pneumonia events reported up to 24 weeks was 1.9% (12 patients) for Riltrava Aerosphere (n=639), 1.6% (10 patients) for formoterol fumarate dihydrate/glycopyrronium (FOR/GLY) MDI 5/7.2 micrograms (n=625), 1.9% (6 patients) for formoterol fumarate dihydrate/budesonide (FOR/BUD) MDI 5/160 micrograms (n=314) and 1.3% (4 patients) for open-labelled formoterol fumarate dihydrate/budesonide Turbuhaler (FOR/BUD) TBH 6/200 micrograms (n=318). In KRONOS, there were no fatal cases of pneumonia with Riltrava Aerosphere.

ETHOS was a 52-week study in a total of 8,529 patients (in the safety population) with moderate to very severe COPD and a history of moderate or severe exacerbations within the prior 12 months (mean post-bronchodilator screening FEV_1 43% of predicted, SD 10%). The incidence of confirmed pneumonia was 4.2% (90 patients) for Riltrava Aerosphere (n=2144), 3.5% (75 patients) for formoterol fumarate dihydrate/glycopyrronium/budesonide (FOR/GLY/BUD) MDI 5/7.2/80 micrograms (n=2124), 2.3% (48 subjects) for FOR/GLY MDI 5/7.2 micrograms (n=2125) and 4.5% (96 subjects) FOR/BUD MDI 5/160 micrograms (n=2136). In ETHOS, there were five fatal cases of pneumonia during the treatment phase of the study (two with FOR/GLY/BUD MDI 5/7.2/80, three with FOR/GLY MDI and none with Riltrava Aerosphere).

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Riltrava Aerosphere contains budesonide, a glucocorticosteroid, and two bronchodilators: glycopyrronium, a long-acting muscarinic antagonist (anticholinergic) and formoterol, a long-acting β_2-adrenergic agonist.

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

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

Formoterol is a selective β_2-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy

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

ETHOS was a 52-week trial (N=8,588 randomised; 60% male, mean age of 65) that compared two inhalations twice daily of Riltrava Aerosphere, formoterol fumarate dihydrate/glycopyrronium (FOR/GLY) MDI 5/7.2 micrograms, and formoterol fumarate dihydrate/budesonide (FOR/BUD) MDI 5/160 micrograms. Patients had moderate to very severe COPD (post-bronchodilator FEV_1 ≥25% to <65% predicted) and were required to have a history of one or more moderate or severe COPD exacerbations in the year prior to screening. The proportion of patients with moderate, severe and very severe COPD was 29%, 61% and 11% respectively. The mean baseline FEV_1 across all groups was 1,021-1,066 mL, and during screening the mean post-bronchodilator percent predicted FEV_1 was 43% and mean CAT score was 19.6. The primary endpoint of the ETHOS trial was the rate of on-treatment moderate or severe COPD exacerbations for Riltrava Aerosphere compared with FOR/GLY MDI and FOR/BUD MDI.

KRONOS was a 24-week trial (N=1,902 randomised; 71% male, mean age of 65) that compared two inhalations twice daily of Riltrava Aerosphere, FOR/GLY MDI 5/7.2 micrograms, FOR/BUD MDI 5/160 micrograms and open-label active comparator formoterol fumarate dihydrate/budesonide Turbuhaler (FOR/BUD TBH) 6/200 micrograms. Patients had moderate to very severe COPD (post-bronchodilator FEV_1 ≥25% to <80% predicted). The proportion of patients with moderate, severe and very severe COPD was 49%, 43% and 8% respectively. The mean baseline FEV_1 across all groups was 1,050-1,193 mL, and during screening the mean post-bronchodilator percent predicted FEV_1 was 50%, over 26% of patients reported a history of one or more moderate or severe COPD exacerbation in the past year and the mean CAT score was 18.3. There was a 28-week extension, for up to 52 weeks of treatment, in a subset of subjects. The primary endpoints of the KRONOS trial were the on-treatment FEV_1 area under the curve from 0-4 hours (FEV_1 AUC_{0-4}) over 24 weeks for Riltrava Aerosphere compared to FOR/BUD MDI and the on-treatment change from baseline in morning pre-dose trough FEV_1 over 24 weeks for Riltrava Aerosphere compared to FOR/GLY MDI.

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

Effect on exacerbations

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

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

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

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

Effects on lung function

In ETHOS and KRONOS, Riltrava Aerosphere improved on-treatment lung function (FEV_1) compared with FOR/GLY MDI and FOR/BUD MDI (see Table 2 for ETHOS and Table 3 for KRONOS). There was a sustained effect over the 24-week treatment period in both studies, and over 52 weeks in ETHOS.

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

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

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

Table 3: Lung function analyses – KRONOS

	Riltrava Aero-sphere (N=639)	FOR/ GLY MDI (N=625)	FOR/ BUD MDI (N=314)	FOR/ BUD TBH (N=318)	Treatment difference 95% CI		
					Riltrava Aerosphere vs. FOR/GLY MDI	Riltrava Aerosphere vs. FOR/BUD MDI	Riltrava Aerosphere vs. FOR/BUD TBH
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	147 (6.5)	125 (6.6)	73 (9.2)	88 (9.1)	22 mL (4, 39) p=0.0139	74 mL (52, 95) p<0.0001	59 mL (38, 80) p<0.0001#
FEV_1 AUC_{0-4} over 24 weeks; LS mean change from baseline (SE)	305 (8.4)	288 (8.5)	201 (11.7)	214 (11.5)	16 mL (-6, 38) p=0.1448#	104 mL (77, 131) p<0.0001	91 mL (64, 117) p<0.0001

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

Symptom relief

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

Health-related quality of life

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

Use of rescue medication

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Riltrava 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 formoterol, glycopyrronium and budesonide combination, the pharmacokinetics of each component was similar to those observed when each active substance was administered separately.

Effect of a spacer
The use of this medicinal product with the Aerochamber Plus Flow-Vu spacer in healthy volunteers increased the total systemic exposure (as measured by AUC0-t) to budesonide and glycopyrronium by 33% and 55%, respectively, while exposure to formoterol was unchanged. In patients with good inhalation technique, systemic exposure was not increased with the use of a spacer.

Absorption

Budesonide
Following inhaled administration of this medicinal product in subjects with COPD, budesonide C_{max} occurred within 20 to 40 minutes. Steady state is achieved after approximately 1 day of repeated dosing of this medicinal product and the extent of exposure is approximately 1.3 times higher than after the first dose.

Glycopyrronium
Following inhaled administration of this medicinal product in subjects with COPD, glycopyrronium C_{max} occurred at 6 minutes. Steady state is achieved after approximately 3 days of repeated dosing of this medicinal product and the extent of exposure is approximately 1.8 times higher than after the first dose.

Formoterol
Following inhaled administration of this medicinal product in subjects with COPD, formoterol C_{max} occurred within 40 to 60 minutes. Steady state is achieved after approximately 2 days of repeated dosing with this medicinal product and the extent of exposure is approximately 1.4 times higher than after the first dose.

Distribution

Budesonide
The estimated budesonide apparent volume of distribution at steady-state is 1200 L, via population pharmacokinetic analysis. Plasma protein binding is approximately 90% for budesonide.

Glycopyrronium
The estimated glycopyrronium apparent volume of distribution at steady-state is 5500 L, via population pharmacokinetic analysis. Over the concentration range of 2-500 nmol/L, plasma protein binding of glycopyrronium ranged from 43% to 54%.

Formoterol
The estimated formoterol apparent volume of distribution at steady-state is 2400 L, via population pharmacokinetic analysis. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.

Biotransformation

Budesonide
Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 β-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide.

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

Formoterol
The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Elimination

Budesonide
Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. The effective terminal elimination half-life of budesonide derived via population pharmacokinetic analysis was 5 hours.

Glycopyrronium
After IV administration of a 0.2 mg dose of radiolabelled glycopyrronium, 85% of the dose was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile. The effective terminal elimination half-life of glycopyrronium derived via population pharmacokinetic analysis was 15 hours.

Formoterol
The excretion of formoterol was studied in six healthy subjects following simultaneous administration of radiolabelled formoterol via the oral and IV routes. In that study, 62% of the drug related radioactivity was excreted in the urine while 24% was eliminated in the faeces. The effective terminal elimination half-life of formoterol derived via population pharmacokinetic analysis was 10 hours.

Special populations

Age, gender, race/ethnicity and weight

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

Hepatic impairment
No pharmacokinetic studies have been performed with this medicinal product in patients with hepatic impairment. However, because both budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment. Glycopyrronium is primarily cleared from the systemic circulation by renal excretion and hepatic impairment would therefore not be expected to affect systemic exposure.

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

The effect of renal impairment on the exposure to budesonide, glycopyrronium and formoterol for up to 24 weeks was evaluated in a population pharmacokinetic analysis. Estimated glomerular filtration rate (eGFR) varied from 31-192 mL/min representing a range of moderate to no renal impairment. Simulation of the systemic exposure (AUC_{0-12}) in subjects with COPD with moderate renal

impairment (eGFR of 45 mL/min) indicates an approximate 68% increase for glycopyrronium compared to subjects with COPD with normal renal function (eGFR of >90 mL/min). Renal function was found not to affect exposure to budesonide or formoterol. Subjects with COPD with both low body weight and moderate-severe impaired renal function may have an approximate doubling of systemic exposure to glycopyrronium.

5.3 Preclinical safety data

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

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

In animal reproduction studies, glucocorticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results are not relevant in humans at the recommended doses (see section 4.6). Budesonide demonstrated no tumourigenic potential in mice. In rats, an increased incidence of hepatocellular tumours was observed, considered to be a class-effect in rats from long-term exposure to corticosteroids.

Animal reproduction studies with formoterol have shown a slightly reduced fertility in male rats at high systemic exposure and implantation losses, as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. A slight increase in the incidence of uterine leiomyomas has been observed in rats and mice treated with formoterol; an effect which is considered to be a class-effect in rodents after long-term exposure to high doses of β_2-adrenoreceptor agonists.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

To be used within 3 months of opening the pouch.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

Pack sizes of 1 container of 120 actuations.
Multipacks of 360 (3 containers of 120) actuations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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/1/21/1604/001 120 actuations
EU/1/21/1604/002 360 actuations (3 packs of 120)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 January 2022

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

Riltrava Aerosphere 5/7.2/160 micrograms pressurised inhalation, suspension
formoterol fumarate dihydrate/glycopyrronium/budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single actuation contains 5 micrograms of formoterol fumarate dihydrate, 9 micrograms glycopyrronium bromide equivalent to 7.2 micrograms of glycopyrronium, and 160 micrograms of budesonide.

3. LIST OF EXCIPIENTS

Norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.
Contains fluorinated greenhouse gases.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, suspension.
120 actuations (1 inhaler)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet 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 30°C.
Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.
Store in a dry place.

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/1/21/1604/001 120 actuations

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

riltrava 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

Riltrava Aerosphere 5/7.2/160 micrograms pressurised inhalation, suspension
formoterol fumarate dihydrate/glycopyrronium/budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single actuation contains 5 micrograms of formoterol fumarate dihydrate, 9 micrograms glycopyrronium bromide equivalent to 7.2 micrograms of glycopyrronium, and 160 micrograms of budesonide.

3. LIST OF EXCIPIENTS

Norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.
Contains fluorinated greenhouse gases.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet 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 30°C.
Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.
Store in a dry place.

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/1/21/1604/002 360 actuations (3 packs of 120)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

riltrava 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

INNER CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Riltrava Aerosphere 5/7.2/160 micrograms pressurised inhalation, suspension
formoterol fumarate dihydrate/glycopyrronium/budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single actuation contains 5 micrograms of formoterol fumarate dihydrate, 9 micrograms glycopyrronium bromide equivalent to 7.2 micrograms of glycopyrronium, and 160 micrograms of budesonide.

3. LIST OF EXCIPIENTS

Norflurane, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride.
Contains fluorinated greenhouse gases.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet 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 30°C.
Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.
Store in a dry place.

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/1/21/1604/002 360 actuations (3 packs of 120)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

riltrava 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

Riltrava Aerosphere 5/7.2/160 micrograms pressurised inhalation, suspension
formoterol fumarate dihydrate/glycopyrronium/budesonide

2. NAME 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

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

Riltrava Aerosphere 5/7.2/160 mcg pressurised inhalation
formoterol fumarate dihydrate/glycopyrronium/budesonide
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

Opened on:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRESSURISED CONTAINER LABEL

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

Riltrava Aerosphere 5/7.2/160 mcg pressurised inhalation
formoterol fumarate dihydrate/glycopyrronium/budesonide
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 patient

Riltrava Aerosphere 5 micrograms/7.2 micrograms/160 micrograms, pressurised inhalation, suspension
formoterol fumarate dihydrate/glycopyrronium/budesonide

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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

Riltrava Aerosphere contains three active substances: formoterol fumarate dihydrate, glycopyrronium, and budesonide.
- Formoterol fumarate dihydrate and glycopyrronium belong to a group of medicines called ‘bronchodilators’. They work in different ways to prevent tightening of the muscles around the airways, making it easier for air to get in and out of the lungs.
- Budesonide belongs to a group of medicines called ‘corticosteroids’. These work by reducing inflammation in your lungs.

Riltrava Aerosphere is an inhaler that is used for adults with a lung disease called ‘chronic obstructive pulmonary disease’ (or ‘COPD’), a long-term disease of the airways in the lungs.

Riltrava Aerosphere is used to make breathing easier and improve symptoms of COPD such as shortness of breath, wheezing and cough. Riltrava Aerosphere can also prevent flare-ups (exacerbations) of COPD.

Riltrava Aerosphere delivers the active substances into your lungs as you breathe in. If you use this medicine regularly twice a day, it will help to reduce the effects of COPD on your everyday life.

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

Do not use Riltrava Aerosphere
- if you are allergic to formoterol fumarate dihydrate, glycopyrronium, budesonide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Riltrava Aerosphere is used as a long-term maintenance treatment for COPD. **Do not use it 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 Riltrava Aerosphere, **stop using it and tell your doctor straight away** (see 'Serious side effects' at the top of Section 4 for more information).

If your breathlessness, tightness of the chest, wheezing or coughing is getting worse while using Riltrava Aerosphere, you should continue to use Riltrava Aerosphere but contact your doctor as soon as possible, as you may need additional treatment.

Talk to your doctor before using Riltrava Aerosphere if:
- you have high blood pressure or heart problems
- you have diabetes
- you have a lung infection
- you have problems with your thyroid gland
- you have low levels of potassium in your blood
- you have prostate problems or any problems passing urine
- you have an eye problem called 'angle-closure glaucoma'
- you have kidney or liver problems.

Talk to your doctor if you think any of these may apply to you.

Children and adolescents
Riltrava Aerosphere has not been studied in children and adolescents. Do not give this medicine to children or adolescents below the age of 18 years.

Other medicines and Riltrava Aerosphere
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, and herbal medicines. This is because Riltrava Aerosphere can affect the way some medicines work. Also some medicines can affect how Riltrava Aerosphere works, or make it more likely that you will have side effects.

Tell your doctor or pharmacist if you are taking any of the following:
- medicines called beta-blockers (such as atenolol or propranolol), that may be used for high blood pressure or heart problems, or to treat glaucoma (such as timolol)
- medicines which are used to treat fungal infections – such as ketoconazole or itraconazole
- medicines which are used to treat HIV infection – such as ritonavir or cobicistat
- medicines that lower the amount of potassium in your blood, such as:
    - corticosteroids that you take by mouth (such as prednisolone),
    - diuretics – medicines that increase urine production (such as furosemide or hydrochlorothiazide), which can be used for treating high blood pressure,
    - some medicines used to treat breathing problems (such as theophylline) – called 'methylxanthines',
- any medicines that work in the same way as Riltrava Aerosphere – such as tiotropium, ipratropium, aclidinium, umeclidinium or salmeterol, arformoterol, vilanterol, olodaterol or indacaterol. Do not use Riltrava Aerosphere if you already use these medicines.
- medicines which are used to treat heart rhythm problems – such as amiodarone
- medicines which can change some electrical activity of the heart (called the 'QT interval') – such as medicines for:
    - depression (such as monoamine oxidase inhibitors or tricyclic antidepressants),
    - bacterial infections (such as erythromycin, clarithromycin or 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 Riltrava 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 this medicine.

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

Do not use this medicine 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 or use machines. However, dizziness is an uncommon side effect which should be taken into account when driving or using machines.

3. How to use Riltrava Aerosphere

Always use 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 – two puffs in the morning and two puffs in the evening.

It is important to use Riltrava Aerosphere every day – even if you have no COPD symptoms at the time.

Remember: Always rinse your mouth with water after using Riltrava Aerosphere. This is to remove any medicine which is left in the mouth. Spit this water out – do not swallow.

How to use
Riltrava Aerosphere is for inhalation use.
Please read the 'Instructions for Use' at the end of this leaflet. If you are not sure how to use Riltrava Aerosphere, talk to your doctor or pharmacist.

Using Riltrava Aerosphere with a spacer
You may find it difficult breathing in and pressing the inhaler at the same time. If this happens, talk to your doctor or pharmacist. It may help to use a 'spacer' with your inhaler.

If you use more Riltrava Aerosphere than you should
If you have used more Riltrava Aerosphere than you should, talk to a doctor or pharmacist straight away. You may need medical attention. You may notice that your heart is beating faster than usual, you feel shaky, you have problems with your sight, you have a dry mouth or you have a headache or feel sick (nausea).

If you forget to use Riltrava 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 on the same day.

If you stop using Riltrava Aerosphere
This medicine is for long-term use. Use this medicine for as long as your doctor tells you to. 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, talk to your doctor first.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Serious side effects

Uncommon (may affect up to 1 in 100 people)

Immediate breathing difficulties:
- if you get breathing difficulties straight after using Riltrava Aerosphere, such as tightness of the chest, coughing, wheezing or feeling breathless, **stop using this medicine** and **tell your doctor straight away**.

Allergic reactions:
- 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. Stop using this medicine and call for medical help straight away if you notice the serious side effects above.

Other side effects
Tell your doctor or pharmacist if you notice any of the following side effects:

Common (may affect up to 1 in 10 people)
- thrush in the mouth (a fungal infection). Rinsing your mouth out with water immediately after using Riltrava Aerosphere may help prevent this.
- feeling anxious
- difficulty sleeping
- feeling sick (nausea)
- headache
- coughing or a hoarse voice
- muscle cramps
- awareness of your heart beating (palpitations)
- high blood sugar levels (as shown in tests)
- painful and frequent urination (may be signs of a urinary tract infection)
- pneumonia (infection of the lung).

Tell your doctor if you have any of the following while using Riltrava Aerosphere, they could be symptoms of a lung infection:
- fever or chills,
- increased mucus production, change in mucus colour,
- increased cough or increased breathing difficulties.

Uncommon (may affect up to 1 in 100 people)
- shaking, tremor or feeling dizzy
- dry mouth, or mild irritation in the throat
- bruising of the skin
- feeling restless, nervous or agitated
- depression
- fast heart beat or uneven heart beat
- chest pain or tightening in the chest (angina pectoris)

Very rare (may affect up to 1 in 10,000 people)
- changes in behaviour
- an effect on the adrenal gland

Not known (frequency cannot be estimated from the available data):
- blurred vision
- clouding of the lens of your eyes (signs of cataract)
- increased pressure in the eye (glaucoma)
- swelling of your face, particularly around your mouth (swelling of your tongue or throat may make it difficult to swallow)

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 Riltrava Aerosphere

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

Do not use Riltrava Aerosphere 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.

After opening the pouch, the inhaler must be used within 3 months.

Keep the inhaler inside the sealed pouch – only remove the inhaler from the sealed pouch immediately before first use. On the day the pouch is opened, write the date on the inhaler label in the space provided.

Do not store above 30°C. Store in a dry place.

For best results, the inhaler should be at room temperature before you use it.

Do not break, puncture or burn the pressurised container, even when apparently empty. Do not use or store near heat or open flames.

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 Riltrava Aerosphere contains
The active substances are formoterol fumarate dihydrate, glycopyrronium and budesonide.

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 5 micrograms of formoterol fumarate dihydrate, 9 micrograms glycopyrronium bromide equivalent to 7.2 micrograms glycopyrronium and 160 micrograms of budesonide.

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

This medicine contains fluorinated greenhouse gases. Each inhaler contains 10.6 g of norflurane (HFC-134a) corresponding to 0.015 tonne CO_2 equivalent (global warming potential GWP = 1,430).

What Riltrava Aerosphere looks like and contents of the pack
Riltrava Aerosphere is a pressurised inhalation, suspension.

Riltrava Aerosphere comes as a canister with a dose indicator, supplied with a yellow plastic actuator body and white mouthpiece. The mouthpiece is covered with a removable grey protective cap.

Riltrava Aerosphere is supplied in a foil pouch that contains a drying packing (desiccant) and packed into a carton.

Each inhaler contains 120 puffs. Additionally, there are multipacks containing 3 pressurised containers with 120 puffs, each.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca Dunkerque Production
224 Avenue de la Dordogne
Dunkerque
59640
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

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

Read prior to using inhaler

INSTRUCTIONS FOR USE

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

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

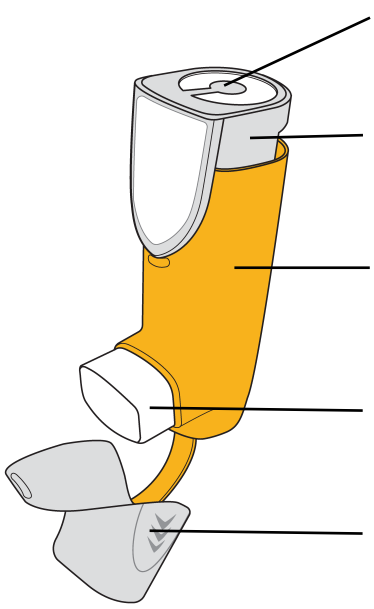
Important information

- **For oral inhalation use only**
- **Prepare your inhaler for its first time use by priming it**
- **Rinse your yellow actuator weekly**
- **Take 2 puffs of medicine in the morning and 2 puffs of medicine in the evening**

Storing your inhaler

- Do not store above 30°C. Store in a dry place
- **Do not store in a humid environment, such as a bathroom**
- Keep your inhaler and all medicines out of the sight and reach of children

Parts of your inhaler



Puff indicator
Attached to the top of the pressurised canister.

Pressurised Canister (inside)
Holds the medicine.

Actuator
Contains the pressurised canister.

Mouthpiece
Sprays the medicine.

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

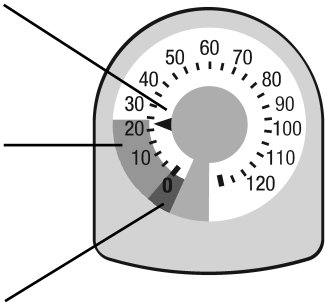
Reading the puff indicator

ⓘ **The puff indicator will count down by 1 each time you spray a puff of medicine.**

Pointer
Points to number of puffs remaining

Yellow zone
Order a new inhaler when the pointer is in the yellow zone

Red zone
Throw away your inhaler when the pointer is at 0 in the red zone



ⓘ **Do not try to take a puff when the pointer is at 0 because you will not receive a full dose.**

Ordering a new inhaler

- Order a new inhaler when the pointer on the puff indicator is in the yellow zone.

Throwing away your inhaler

Throw away your inhaler following local guidelines when:

- puff indicator shows 0

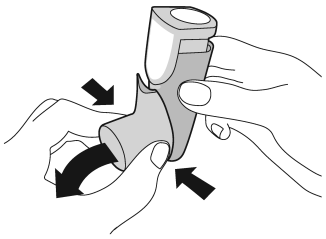
or

- **3 months** after your inhaler has been removed from the foil pouch

Do not reuse or use the actuator with medicine canisters from other inhalers.
Do not puncture or throw the canister into a fire or incinerator.

BEFORE FIRST USE – Prime your inhaler 4 times before first use

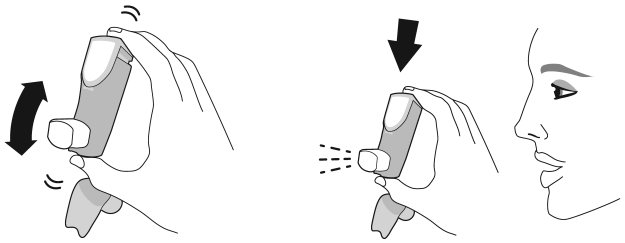
- Before you use your inhaler for the first time, prime it so that you will get the right amount of medicine when you use it.

Prime 1
Remove mouthpiece cover. 

Prime 2

Shake the inhaler well and spray **1 Test-puff** into the air facing away from you. Repeat for a total of **4 Test-puffs**, shaking before each Test-puff.

x4 total
Shake and Test-puffs



ⓘ Extra puffs are provided for priming. **Do not skip priming.**

ⓘ **Re-prime your inhaler:**

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

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

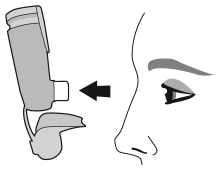
x2 total
Shake and Test-puffs

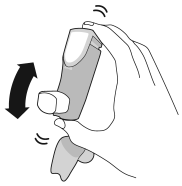
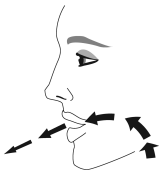
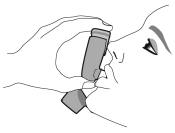
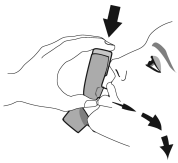
DAILY USE, morning & evening – Inhale your medicine

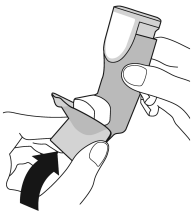
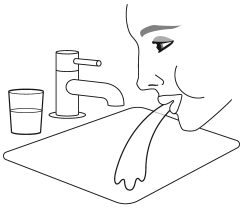
- **Daily Dose: 2 puffs in the morning and 2 puffs in the evening.**
- Rinse mouth with water after the 2 puffs to prevent fungal infection.

Step 1

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

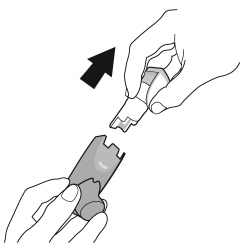
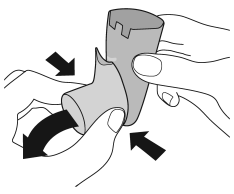


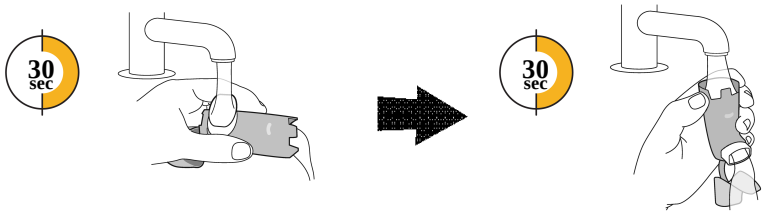
Step 2				
Shake the inhaler well before each puff. 	Breathe out fully. 	Place mouthpiece into mouth and close lips around the mouthpiece. Tilt your head back, keeping your tongue below the mouthpiece. 	Start to breathe in deeply and slowly while spraying **1 puff**. Continue breathing in until you cannot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

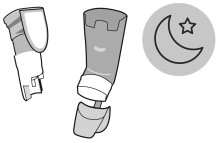
Step 3	Step 4	Step 5
Repeat Step 2 for a second puff	Put mouthpiece cover back on. 	Rinse mouth with water. Spit out water. **Do not swallow.** 

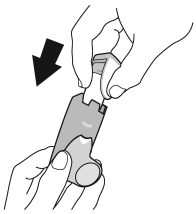
WEEKLY RINSE – Rinse your actuator once a week

- **Rinse yellow actuator weekly** so that medicine does not build up and block the spray through the mouthpiece.
- **Do not allow the canister to get wet.**
- **Re-prime after rinsing.**

Rinse 1	Rinse 2
Remove canister and set aside. **Do not allow the canister to get wet.** 	Remove mouthpiece cover. 

Rinse 3	Rinse 4
Run warm water through the mouthpiece for 30 seconds and then through the top of the actuator for 30 seconds. **Rinse for 60 seconds in total.** 	**Shake off as much water as you can.**  **Do not dry with a towel or tissue.**

Rinse 5	Rinse 6
Look into the actuator and mouthpiece for medicine build-up. If there is any build-up, repeat steps Rinse 3 through 5. 	Air-dry, preferably overnight. **Do not** put the canister back into the actuator if it is still wet. 

Rinse 7	Rinse 8
When dry, **replace the mouthpiece cover first** and then gently press the canister down into the actuator. 	Re-prime the inhaler by spraying **2 Test-puffs,** shaking before each Test-puff. **x2 total Shake and Test-puffs**