1. NAME OF THE MEDICINAL PRODUCT

Trixeo Aerosphere

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.

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

Trixeo 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.

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

Trixeo Aerosphere is not indicated in children and adolescents below 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.

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 well 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 Trixeo 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 Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product. Trixeo 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 sections 4.2 and 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 sections 4.2 and 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 β_2-adrenergic agonist adverse reactions (see sections 4.4 and 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 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

Trixeo 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%), oral candidiasis (3.0%), 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	Pneumonia Urinary tract infection Oral candidiasis	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	Glaucoma Cataract Vision blurred (see section 4.4)	Not known

Cardiac disorders	Palpitations	Common
	Angina pectoris Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles) Tachycardia	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough	Common
	Bronchospasm Throat irritation	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 retention	Uncommon
General disorders and administration site conditions	Chest pain	Uncommon

Description of selected adverse reactions

Pneumonia

KRONOS was a 24-week study in a total of 1,896 patients with moderate to very severe COPD (mean post-bronchodilator screening 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 Trixeo 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).

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 Trixeo 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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

Trixeo 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 Trixeo 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 Trixeo 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 Trixeo 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 Trixeo 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 Trixeo Aerosphere compared to FOR/BUD MDI and the on-treatment change from baseline in morning pre- dose trough FEV_1 over 24 weeks for Trixeo Aerosphere compared to FOR/GLY MDI.

At study entry, the most common COPD maintenance treatment 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, Trixeo 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, Trixeo Aerosphere 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 by 20% (95% CI: 3, 34; p=0.0221, not considered statistically significant when adjusting for all multiple comparisons) 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, Trixeo 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)

	Trixeo Aerosphere (N=747)	**FOR/GLY MDI (N=779)**	**FOR/BUD MDI (N=755)**	**Treatment difference 95% CI**	
				Trixeo Aerosphere vs. FOR/GLY MDI	**Trixeo 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

	Trixeo Aerosphere (N=639)	**FOR/ GLY MDI (N=625)**	**FOR/ BUD MDI (N=314)**	**FOR/ BUD TBH (N=318)**	**Treatment difference 95% CI**		
					Trixeo Aerosphere vs. FOR/GLY MDI	**Trixeo Aerosphere vs. FOR/BUD MDI**	**Trixeo 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. Trixeo 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. Trixeo 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, Trixeo 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 therapy

In ETHOS, Trixeo Aerosphere significantly reduced the on-treatment use of rescue therapy over 24 weeks compared with FOR/GLY MDI (treatment difference -0.51 puffs/day; 95% CI: -0.68, -0.34; p<0.0001) and FOR/BUD MDI (treatment difference -0.37 puffs/day; 95% CI: -

0.54, -0.20; p<0.0001). Reductions were sustained over 52 weeks. In KRONOS, differences compared with FOR/GLY MDI, FOR/BUD MDI and FOR/BUD TBH were not statistically significant.

5.2 Pharmacokinetic properties

Following inhalation of the formoterol, glycopyrronium 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 AUC_{0-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 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 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 intravenous 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

HFA-134a
1,2-distearoyl-sn-glycero-3-phosphocholine
Calcium chloride dihydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

To be used within 3 months of opening the pouch when stored under the conditions indicated below.

6.4 Special precautions for storage

Do not store above 30°C. Store in a dry place.
Do not break, puncture or burn the pressurised container, even when apparently empty.
Do not use or store near heat or open flames.

6.5 Nature and contents of container

Trixeo Aerosphere is a pressurised metered dose inhaler, comprising a coated aluminium canister, a yellow plastic actuator and 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 into a carton.

Pack size of 1 container of 120 actuations.

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. MANUFACTURER

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Dunkerque
France

8. LICENSE HOLDER AND IMPORTER

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