EU RMP	
Drug Substance	Formoterol, glycopyrronium, budesonide
Version Number	2
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for TRIXEO AEROSPHERE™, RILTRAVA AEROSPHERE™ (FORMOTEROL FUMARATE DIHYDRATE, GLYCOPYRRONIUM, BUDESONIDE)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's deputy QPPV, as delegated by the QPPV in the EU.

Administrative Information

Explanatory note: In this document, the acronyms BGF or BGF MDI (where BGF is an abbreviation for budesonide, glycopyrronium, and formoterol fumarate, and MDI is an abbreviation for metered dose inhaler) are used to refer to the fixed-dose triple combination product.

Rationale for submitting an updated RMP

This RMP is updated to add information on BGF MDI formulated with HFO, a new propellant with low global warming potential.

Summary of significant changes in this RMP:

Part I

Information on pharmaceutical forms and strengths added.

Part II SII

Inclusion of results from the completed non-clinical studies with HFO (alone or in combination with BGF).

Part II SIII

Clinical trial exposure tables have been updated to add data from 2 completed trials in COPD patients, one conducted with the BGF MDI formulation containing HFA propellant (PT010007) and one conducted with 2 different BGF MDI formulations, containing either the HFA or the HFO propellant (D5985C00003). Exposure data for healthy volunteers have been removed.

Part II SV

Post-marketing exposure has been updated.

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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Annex 4- Specific adverse drug reaction follow-up forms	Not applicable
[redacted]	[redacted]
Annex 6- Details of proposed additional risk minimisation activities	Not applicable
[redacted]	[redacted]
[redacted]	

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
BGF	Budesonide, glycopyrronium, and formoterol fumarate
BGF MDI	Budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler
BGF MDI HFA	Budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler containing hydrofluoroalkane propellant
BGF MDI HFO	Budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler containing hydrofluoroolefin propellant
COPD	Chronic obstructive pulmonary disease
DSPC	Distearoylphosphatidylcholine or 1,2-Distearoyl-sn-glycero-3-phosphocholine
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GFF MDI	Glycopyrronium and formoterol fumarate metered dose inhaler
GVP	Good Pharmacovigilance Practices
HFA	Hydrofluoroalkane; HFA-134a, known as norflurane
HFO	Hydrofluoroolefin; HFO-1234ze(E)
ICS	Inhaled corticosteroid
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist

Abbreviation/ Special term	Definition/Explanation
MDI	Metered dose inhaler
NOAEL	No observed adverse effect level
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

I: PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Formoterol fumarate dihydrate Glycopyrronium Budesonide
Pharmacotherapeutic group(s) (ATC Code)	Adrenergics in combination with anticholinergics including triple combinations with corticosteroids. (R03AL11)
Marketing Authorisation Holder	AstraZeneca AB, Södertälje SE - 151 85, Sweden
Medicinal products to which this RMP refers	2
Invented name(s) in the EEA	Trixeo Aerosphere, 5.0/7.2/160 µg Riltrava Aerosphere, 5.0/7.2/160 µg
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Adrenergics in triple combination with anticholinergics and corticosteroids
	Summary of mode of action: Formoterol fumarate is a LABA that induces bronchodilation by causing direct relaxation of airway smooth muscle as a consequence of the increase in cyclic adenosine monophosphate through activation of adenylate cyclase. Glycopyrronium is a LAMA that induces bronchodilation through inhibition of the M3 receptor at the smooth muscle. Budesonide is an ICS that has an anti-inflammatory action in the airways.
Hyperlink to the Product Information	[eCTD link to PI]
Indication(s) in the EEA	Current: Maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA or combination of a LABA and a LAMA.
Dosage in the EEA	Current: The recommended and maximum dose is 2 inhalations twice daily (2 inhalations in the morning and 2 inhalations in the evening). The total daily dose for each component in the triple combination is as follows: 20 µg of formoterol fumarate dihydrate, 28.8 µg of glycopyrronium, and 640 µg of budesonide.

Table I-1 Product Overview

Pharmaceutical form(s) and strengths in the EEA	Current: Pressurised inhalation, suspension. Each single actuation (delivered dose, ex-actuator) contains 5 µg of formoterol fumarate dihydrate, glycopyrronium bromide 9 µg, equivalent to 7.2 µg of glycopyrronium, and budesonide 160 µg. The canister contains a co-suspension of the active substances and the following excipients: norflurane (HFA-134a) propellant (hereafter referred to as HFA), porous particles of DSPC and calcium chloride.
	Proposed: Pressurised inhalation, suspension. Each single actuation (delivered dose, ex-actuator) contains 5 µg of formoterol fumarate dihydrate, glycopyrronium bromide 9 µg, equivalent to 7.2 µg of glycopyrronium, and budesonide 160 µg. The canister contains a co-suspension of the active substances and the following excipients: HFO-1234ze(E) propellant (hereafter referred to as HFO), porous particles of DSPC and calcium chloride
Is/will the product be subject to additional monitoring in the EU?	No

II: PART II: SAFETY SPECIFICATION

II: 1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

II: 1.1 Maintenance Treatment with Triple Therapy in Patients with COPD

Part II, Module SI is not required for a Fixed combination product – no new active substance (4.b.) in accordance with *GVP, Part II, Module SI – Epidemiology of the indication and the target population* (EMA 2017) section V.C.1.1.

II: 2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II: 2.1 Summary of key safety findings from non-clinical data

Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Since each of the active components of the BGF triple combination had been extensively investigated, and were available in marketed products, a limited package of studies was conducted with the fixed-dose combination (with HFA propellant). These consisted of single-dose maximum tolerated dose studies in rats and dogs, 14-day inhalation toxicity studies in rats and dogs, and a 3-month inhalation toxicity study in dogs.

In studies in rats and dogs administered the BGF fixed dose combination, the main observed effects were those typical of a glucocorticosteroid (eg, reduced body weight, atrophy of lymphoid organs and adrenals, gastric ulcerations, decreased total white blood cell counts and lymphocytes, and increased liver glycogen). No effects attributable to glycopyrronium or formoterol were seen in these studies due to the ratio of components in the fixed-dose combination.

In separate studies at higher doses, formoterol fumarate induced the expected cardiovascular effects, such as hyperaemia and tachycardia. No significant effects related to glycopyrronium were identified at large multiples of the therapeutic dose.

Clinical experience with inhaled glucocorticosteroids and beta-2-agonists have shown that rats and dogs are more sensitive than humans to the pharmacological effects and most of the effects seen have no clinical relevance at therapeutic doses.

The new propellant, HFO, has been evaluated in a series of single (rodent) and repeat dose (rodent and non-rodent) inhalation toxicology studies. Toxicokinetics of HFO was assessed in repeat dose studies in mice, rats and dogs. In rats, an exacerbation of rodent progressive cardiomyopathy was noted at very high doses. The NOAEL obtained in the 6-month study was 4280 mg/kg/day which is >1000-fold higher than the total daily dose of HFO expected with use of BGF MDI HFO. In the 2-year rat carcinogenicity study, the incidence and severity of rodent progressive cardiomyopathy given HFO at 3918 mg/kg/day (the highest dose tested) was comparable to that observed in air control animals. There were no findings in the heart in any studies conducted in mice or dogs and there were no effects on cardiovascular function in dogs.

A 3-month toxicology study was conducted in dogs to compare BGF MDI HFO with the reference product, BGF MDI HFA. The toxicology and toxicokinetics (active ingredients) of

the drug products were equivalent, with only minor findings noted, generally reflecting glucocorticosteroid exposure.

Reproductive/developmental toxicity

No standalone studies were conducted on the BGF fixed-dose combination.

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 glycopyrrolate had no significant effects on reproduction.

HFO did not induce embryofetal toxicity in rats or rabbits. In a 2-generation reproductive performance study in rats, HFO was not associated with any effects on male or female fertility or pre- and post-natal development. There were also no effects following exposure to juvenile animals.

In a 2-generation study, a dose of HFO of approximately 23,000 mg/kg/day (19,400 parts per million for 6 hours/day) was associated with mortality in some females during the period of late lactation. Of these, occasional animals demonstrated hindlimb paralysis with or without some central nervous system pathology. The NOAEL in this study was 5763 mg/kg/day (4820 parts per million for 6 hours/day), which is approximately 1500-fold higher than the total daily dose of HFO expected with use of BGF MDI HFO. Although the specific cause of these findings is unknown, it is considered that the condition of the animals was impacted by a condition of energy depletion, secondary to the stage of lactation.

Genotoxicity

There were no key findings for the monoproducts. No standalone studies were conducted on the BGF fixed-dose combination.

HFO was not genotoxic in a range of in-vitro and in-vivo assays.

Carcinogenicity

There were no key findings of relevance to therapeutic use for the monoproducts. No standalone studies were conducted on the BGF fixed-dose combination.

HFO was not carcinogenic when evaluated in 2-year carcinogenicity studies in mice and rats.

Safety pharmacology

No standalone studies were conducted on the BGF fixed-dose combination. Safety pharmacology endpoints were included in the repeat dose toxicity studies with the fixed-dose combination (with HFA propellant).

Safety pharmacology endpoints were included in the repeat dose toxicity studies with HFO. There were no functional effects on the cardiovascular, respiratory, and central nervous systems. In addition, HFO was not a cardiac sensitiser when assessed in a single dose study in dogs.

II: 3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The clinical development programme of BGF MDI comprises clinical trials in which BGF MDI was either formulated as BGF MDI HFA or as BGF MDI HFO.

II: 3.1 BGF MDI HFO exposure

Exposure to BGF MDI HFO in patients with COPD (1 Phase III study) is summarised by duration in Table II-1, by age and gender in Table II-2 and by race in Table II-3.

Table II-1 Duration of exposure to BGF MDI HFO in patients with COPD

Duration of exposure[a]	Persons n (%)	Person time[b]
<1 month	20 (7.1)	0.99
1 to <3 months	143 (51.1)	31.72
3 to <6 months	23 (8.2)	6.36
6 to 12 months	15 (5.4)	12.67
>12 months	79 (28.2)	80.62
Total	280 (100.0)	132.35

a Months defined in 30-day intervals (eg, 3 months = 90 days).
b Person time = patient years of exposure (total exposure in days/360).
% = 100 x n/Total, within each category.
Study included: D5985C00003.

Table II-2 Exposure to BGF MDI HFO in patients with COPD by age group and gender

	Persons n (%)		Person Time[a]	
Age group	**M**	**F**	**M**	**F**
18-64 years	51 (30.4)	35 (31.3)	21.91	15.16
65-74 years	84 (50.0)	58 (51.8)	38.88	33.00
75+ years	33 (19.6)	19 (17.0)	15.02	8.39
Total	168 (100.0)	112 (100.0)	75.81	56.54

a Person time = patient years of exposure (total exposure in days/360).
% = 100 x n/Total, within each category.
Study included: D5985C00003.

Table II-3 Exposure to BGF MDI HFO in patients with COPD by race

Race	Persons n (%)	Person time[a]
Asian	0 (0.0)	NA

Table II-3 Exposure to BGF MDI HFO in patients with COPD by race

Race	Persons n (%)	Person time[a]
Black or African American	7 (2.5)	4.27
White	273 (97.5)	128.08
Other	0 (0.0)	NA
Total	280 (100.0)	132.35

a Person time = patient years of exposure (total exposure in days/360).
% = 100 x n/Total, within each category.
Study included: D5985C00003.
NA Not applicable

II: 3.2 BGF MDI exposure (formulated as BGF MDI HFA or as BGF MDI HFO)

The pooled data set includes clinical studies of BGF MDI (formulated as BGF MDI HFA or as BGF MDI HFO) in patients with COPD (1 Phase I study and 5 Phase III studies).

The duration of exposure, exposure by age group and gender, exposure by dose, and exposure by race for BGF MDI are presented in Table II-4, Table II-5, Table II-6, and Table II-7, respectively.

Table II-4 Duration of exposure to BGF MDI in patients with COPD

Duration of exposure[a]	Persons n (%)	Person time[b]
<1 month	194 (3.5)	8.36
1 to <3 months	494 (9.0)	99.37
3 to <6 months	581 (10.5)	240.00
6 to 12 months	560 (10.2)	454.19
>12 months	3685 (66.8)	3751.43
Total	5514 (100.0)	4553.35

a Months defined in 30-day intervals (eg, 3 months=90 days).
b Person time=patient years of exposure (total exposure in days/360).
%=100 x n/Total, within each category.
Note: Patients participating in more than one trial were only counted once.
Studies included: PT010005, PT010006, PT010007, PT010008, PT010018 and D5985C00003.

Table II-5 Exposure to BGF MDI in patients with COPD by age group and gender

	Persons n (%)		Person Time[a]	
Age group	**M**	**F**	**M**	**F**
18-64 years	1457 (43.3)	1113 (51.7)	1228.36	938.79
65-74 years	1464 (43.5)	854 (39.7)	1200.62	680.49
75+ years	442 (13.1)	184 (8.6)	361.84	143.26
Total	3363 (100.0)	2151 (100.0)	2790.82	1762.53

a Person time=patient years of exposure (total exposure in days/360).
%=100 x n/Total, within each category.
Note: Patients participating in more than one trial were only counted once.
Studies included: PT010005, PT010006, PT010007, PT010008, PT010018 and D5985C00003.

Table II-6 Exposure by dose of BGF MDI in patients with COPD

Dose of Exposure	Persons n (%)	Person time[a]
BGF MDI 320/14.4/9.6 µg	3383 (61.4)	2631.60
BGF MDI 160/14.4/9.6 µg	2131 (38.6)	1921.74
Total	5514 (100.0)	4553.35

a Person time=patient years of exposure (total exposure in days/360).
%=100 x n/Total, within each category.
Note: Patients participating in more than one trial were only counted once.
Studies included: PT010005, PT010006, PT010007, PT010008, PT010018 and D5985C00003.

Table II-7 Exposure to BGF MDI in patients with COPD by race

Race	Persons n (%)	Person time[a]
Asian	612 (11.1)	493.01
Black or African American	207 (3.8)	168.32
White	4527 (82.1)	3735.39
Other	168 (3.0)	156.63
Total	5514 (100.0)	4553.35

a Person time=patient years of exposure (total exposure in days/360).
%=100 x n/Total, within each category.
Note: Patients participating in more than one trial were only counted once.
Studies included: PT010005, PT010006, PT010007, PT010008, PT010018 and D5985C00003.

II: 4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Part II, Module SIV is not required for a Fixed combination product – no new active substance (4.b.) in accordance with *GVP, Part II, Module SIV – Populations not studied in clinical trials* (EMA 2017) section V.C.1.1.

II: 5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II: 5.1 Method to calculate exposure

The post-marketing patient exposure data presented here is based on TRIXEO/RILTRAVA AEROSPHERE's monthly actual ex-factory sales volume from each local affiliate. These data represent all TRIXEO/RILTRAVA AEROSPHERE formulation delivered to various distribution channels (e.g., wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of inhalers distributed containing dosages. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient took [redacted] inhalations of TRIXEO/RILTRAVA AEROSPHERE per day. Therefore, a patient-year worth of exposure is calculated by dividing the total number of doses consumed by [redacted] (ie, [redacted] inhalations per day multiplied by 365 days).

More detailed patient-level data (e.g. gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II: 5.2 Exposure

Cumulative global post-marketing patient exposure for TRIXEO/RILTRAVA AEROSPHERE since launch to 31 May 2024 has been estimated to be approximately [redacted] patient years.

The cumulative regional sales figures are presented in the table below.

Data stratified by gender or age group are not available.

Table II-8 TRIXEO/RILTRAVA AEROSPHERE cumulative sales, number of inhalers, by region

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

II: 6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for drug abuse for TRIXEO/RILTRAVA AEROSPHERE has not been studied. Based on its pharmacological properties, TRIXEO/RILTRAVA AEROSPHERE is not likely to have a potential for drug abuse and no findings during the clinical program indicate a risk for abuse, dependence, or misuse for illegal purposes.

II: 7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II: 7.1 Identification of safety concerns in the initial RMP submission

II: 7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Overview

The justification for specifying no Identified or Potential Risks and Missing Information is explained below and reflects the recent EMA 'Guidance on the Format of the Risk Management Plan (RMP) in the EU - in Integrated Format' from 30 March 2017.

BGF MDI is a combination of budesonide, glycopyrronium bromide, and formoterol fumarate dihydrate. Drugs from these classes, ICS, LAMA, and LABA, are commonly used to treat COPD, either as individual components (LAMA, LABA) or in combinations (LAMA+LABA, ICS+LABA+LAMA) (GOLD 2024). The safety profile of each drug is well established and information on class effects is included in the SmPC. Therefore, since these are well known class effects to prescribers, risks can be managed by standard clinical practice and no additional pharmacovigilance activities or risk minimisation activities are planned by AstraZeneca. No Identified or Potential risks or Missing information are proposed.

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Hypersensitivity, depression, and signs or symptoms of systemic glucocorticoid steroid effects (eg, hypofunctions of the adrenal gland).

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member State where the product is authorised):

- Anxiety, insomnia, abnormal behaviour, restlessness, agitation, nervousness, oral candidiasis, palpitations, headache, tremor, dizziness, throat irritation, cough, dysphonia, nausea, dry mouth, muscle spasms, hyperglycaemia, chest pain, urinary retention, angina pectoris, tachycardia, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles), bronchospasm, bruising, pneumonia and urinary tract infection, signs or symptoms of systemic glucocorticosteroid effects, vision blurred, angioedema.

Known pharmacological class effects that require no further characterisation and are followed up via routine pharmacovigilance:

- Beta-2-agonists: Cardiovascular effects, such as cardiac arrhythmias, eg, atrial fibrillation and tachycardia, may be seen after the administration of sympathomimetics, including formoterol. In the 24-week pivotal study PT010006 including patients with moderate to very severe COPD, the reported incidence of subjects with adverse events related to cardiovascular condition was 2.8% among patients treated with BGF MDI 160/7.2/5.0 µg. Two events of atrial fibrillation, one event of coronary artery occlusion, acute myocardial infarction and coronary artery disease were assessed as serious (0.8% of patients).

  In the 52-week pivotal study PT010005 including patients with moderate to very severe COPD, the reported incidence of subjects with adverse events related to cardiovascular conditions was 4.4% among patients treated with BGF MDI 160/7.2/5.0 µg. The most commonly reported cardiac events assessed as serious were atrial fibrillation (9), acute myocardial infarction (7), myocardial infarction (5), coronary artery disease (5) and cardiac failure congestive (5); overall, 2.0% of patients had adverse events relating to cardiovascular disorders that were assessed as serious. Frequencies were similar in the two BGF groups (160/7.2/5.0 µg and 80/7.2/5.0 µg).

  The LABA-related cardiovascular effects are well known to prescribers and managed by routine clinical practice. Cardiac manifestations such as cardiac arrhythmias and angina pectoris are included in the SmPC, Section 4.8, as uncommon events. Information is included in the SmPC, Section 4.4, stating that BGF products should be administered with caution in patients with severe cardiovascular disease. The use in the COPD population is well understood and does not impact the overall benefit-risk balance. Cardiac disorders are continuously monitored as a part of the regular routine safety surveillance activities of AstraZeneca.
- Inhaled corticosteroids: 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, cataracts, and glaucoma.

  Potential effects on bone density should be considered particularly in patients on high doses of BGF MDI for prolonged periods that have co-existing risk factors for osteoporosis. Long-term studies with inhaled budesonide in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density.

  A subset of patients in study PT0100006 continued in study PT010008 and were treated up to 52 weeks. BGF MDI 320/14.4/9.6 µg was non-inferior to GFF MDI for the primary bone mineral density and ocular endpoints.

  Systemic corticosteroid effects are well known by prescribers. Cautionary information is included in the SmPC Sections 4.4. and 4.8. Systemic corticosteroid effects are continuously monitored as a part of the regular routine safety surveillance activities of AstraZeneca. An increased risk of pneumonia in patients with COPD treated with ICS is well known to prescribers.

In study PT010006, the incidence of confirmed pneumonia was 1.9% with BGF MDI and 1.6% with GFF MDI. Eight reports of confirmed pneumonia with BGF MDI and six reports with GFF MDI were assessed as serious.

In study PT010005, the incidence of confirmed pneumonia was 4.2% (3.0% serious) with BGF MDI 160/7.2/5.0 µg, 3.5% (2.5% serious) with BGF MDI 80/7.2/5.0 µg, 2.3% (1.3% serious) with GFF MDI and 4.5% (2.4% serious) with BFF MDI. 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, and severe COPD. Cautionary information is included in the SmPC Section 4.4. Pneumonia is continuously monitored as a part of the regular routine safety surveillance activities of AstraZeneca.

- Muscarinic receptor antagonists: Potential anticholinergic effects (eg, urinary retention and narrow-angle glaucoma) are well-established class effects of LAMA, eg, glycopyrronium therapy.

  In study PT010006, one report of glaucoma, 12 reports of urinary tract infection and no reports of urinary retention were received for BGF MDI.

  In study PT010005, no reports of glaucoma, 58 reports of urinary tract infection and 11 reports of urinary retention, comprising the Medical Dictionary for Regulatory Activities preferred terms urinary retention, dysuria, pollakiuria and urinary incontinence, were received. One report of urinary retention was assessed as serious.

  Anticholinergic effects are well known to prescribers and managed by routine clinical practice. Cautionary information is included in the SmPC Sections 4.4 and 4.8. Anticholinergic effects are continuously monitored as a part of the regular routine safety surveillance activities of AstraZeneca.

- Other effects: Paradoxical bronchospasm may occur in response to exposure to any inhalation of a xenobiotic substance such as an inhaled drug, including BGF. There is no indication that treatment with BGF MDI would be characterized by an association with paradoxical bronchospasm reactions different from what would be expected with other similar treatments for the corresponding indication.

  In study PT010006, no event of paradoxical bronchospasm was reported.

  In study PT010005, one report of paradoxical bronchospasm was received.

  Paradoxical bronchospasm is well known to prescribers and managed in clinical practice. Cautionary information is included in the SmPC, Section 4.4. Paradoxical bronchospasm reactions are continuously monitored as a part of the regular routine safety surveillance activities of AstraZeneca.

II: 7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks

Not applicable.

Important potential risks

Not applicable.

Missing information

Not applicable.

II: 7.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

II: 7.3 Details of important identified risks, important potential risks and missing information

II: 7.3.1 Presentation of important identified risks and important potential risks

Not applicable.

II: 7.3.2 Presentation of missing information

Not applicable.

II: 8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II: 8.1 Summary of the safety concerns

Table II-9 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

III: PART III: PHARMACOVIGILANCE PLAN

III: 1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

As there are no safety concerns included in the TRIXEO/RILTRAVA AEROSPHERE EU RMP, there are no specific pharmacovigilance activities beyond adverse reaction reporting and signal detection.

III: 2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

No additional pharmacovigilance activities are planned by AstraZeneca.

III: 3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

No additional pharmacovigilance activities are planned by AstraZeneca.

IV: PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No additional post-authorisation efficacy studies are planned by AstraZeneca.

V: PART V: RISK MINIMISATION MEASURES

V: 1 ROUTINE RISK MINIMISATION MEASURES

As there are no important potential risks and no important identified risks or missing information included in this TRIXEO/RILTRAVA AEROSPHERE EU RMP, no relevant minimisation measures are described.

V: 2 ADDITIONAL RISK MINIMISATION MEASURES

None, see Section V: 1 above.

V: 3 SUMMARY OF RISK MINIMISATION MEASURES

None, see Section V: 1 above.

VI: PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR TRIXEO AEROSPHERE™/RILTRAVA AEROSPHERE™ (FORMOTEROL FUMARATE DIHYDRATE, GLYCOPYRRONIUM, BUDESONIDE)

This is a summary of the risk management plan (RMP) for TRIXEO/RILTRAVA AEROSPHERE. The RMP details important risks of TRIXEO/RILTRAVA AEROSPHERE and how more information will be obtained about TRIXEO/RILTRAVA AEROSPHERE's risks and uncertainties (missing information).

TRIXEO/RILTRAVA AEROSPHERE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TRIXEO/RILTRAVA AEROSPHERE should be used.

This summary of the RMP for TRIXEO/RILTRAVA AEROSPHERE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TRIXEO/RILTRAVA AEROSPHERE's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

TRIXEO/RILTRAVA AEROSPHERE is authorised for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (see SmPC for the full indication). It contains formoterol fumarate dihydrate, glycopyrronium, and budesonide as the active substances and it is given by inhalation.

Further information about the evaluation of TRIXEO/RILTRAVA AEROSPHERE's benefits can be found in TRIXEO/RILTRAVA AEROSPHERE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

TRIXEO AEROSPHERE

https://www.ema.europa.eu/en/medicines/human/EPAR/trixeo-aerosphere

RILTRAVA AEROSPHERE

https://www.ema.europa.eu/en/medicines/human/EPAR/riltrava-aerosphere

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of TRIXEO/RILTRAVA AEROSPHERE, together with measures to minimise such risks and the proposed studies for learning more about TRIXEO/RILTRAVA AEROSPHERE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of TRIXEO/RILTRAVA AEROSPHERE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TRIXEO/RILTRAVA AEROSPHERE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TRIXEO/RILTRAVA AEROSPHERE.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for TRIXEO/RILTRAVA AEROSPHERE.

LIST OF REFERENCES

EMA 2017
European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP). Module V – Risk management systems (Rev 2). EMA/838713/2011 Rev 2, 28 March 2017.

GOLD 2024
Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2024 Report). Available from: https://goldcopd.org/2024-gold-report/

[redacted]

Drug Substance	Formoterol, glycopyrronium, budesonide
Version Number	2
Data lock point for this module	15 August 2024

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for TRIXEO AEROSPHERE™, RILTRAVA AEROSPHERE™ (FORMOTEROL FUMARATE DIHYDRATE, GLYCOPYRRONIUM, BUDESONIDE)

[redacted]

Active substance(s) (INN or common name)	Formoterol fumarate dihydrate Glycopyrronium Budesonide
Product(s) concerned (brand names(s))	Trixeo Aerosphere Riltrava Aerosphere
Name of Marketing Authorisation Holder or Applicant	AstraZeneca AB, Sodertalje SE - 151 85, Sweden

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[redacted]

1 VERSION HISTORY

Version	Approval date	Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Signature Page for [redacted] System v1.0
EU Patient Risk Management Plan V2 S2

Approve: Document Level Task Verdict: Approved	[redacted]

Signature Page for [redacted] System v1.0
EU Patient Risk Management Plan V2 S2