11 November 2021
EMA/622167/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Riltrava Aerosphere

International non-proprietary name: formoterol/ glycopyrronium bromide/ budesonide

Procedure No. EMEA/H/C/005311/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant applied for the following indication:

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).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information with a letter from a MAH AstraZeneca AB allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Trixeo Aerosphere authorised on 09 December 2020 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.3. Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0384/2017 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 December 2014	EMA/CHMP/SAWP/69324/2014	Nithyanandan Nagercoil, Brigitte Blöchl-Daum

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Jan Neuhauser

The application was received by the EMA on	19 August 2021
The procedure started on	13 September 2021
The CHMP and PRAC Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP and PRAC Rapporteur's updated Assessment Report was circulated to all CHMP and PRAC members on	02 November 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Riltrava Aerosphere on	11 November 2021

2. Scientific discussion

2.1. Problem statement

Riltrava Aerosphere 5 micrograms/7.2 micrograms/160 micrograms pressurised inhalation, suspension is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. For this application reference is made to Trixeo Aerosphere (EMEA/H/C/004983) including all indications, pharmaceutical forms, strengths and presentations, authorised and granted in the EU. Accordingly, the MAH of the reference product has provided consent to allow access to Module 2 to Module 5 of the initial dossier and any subsequent post-marketing procedures submitted, assessed and approved. The application for Riltrava Aerosphere consists only of Module 1 information.

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).

2.2. Type of Application and aspects on development

Scientific advice was given by the CHMP on the 18th of December 2014 (Procedure No.: EMEA/H/SA/2928/1/2014/III) for Trixeo Aerosphere with a follow up clarification on the 5th of August 2015.

The Scientific advice pertained to the following non-clinical and clinical aspects:

- Requirements for inhaled toxicology studies with the components (alone and in combination) to support clinical studies of up to 12 weeks in duration. Proposed nonclinical inhaled toxicology programme, including 3-month dog studies for BGF MDI, BFF MDI, and BD MDI, to support clinical studies of greater than 12 weeks in duration. Acceptability of the proposed nonclinical development programme to support MA of BGF MDI.
- Selection of the budesonide dose in BGF MDI for Phase III studies based upon systemic PK comparability relative to Symbicort TBH (Study PT010002). Proposed two studies; a large 1-year exacerbation study (PT010005) and a single 6-month lung function and symptom study (PT010006) to support a claim on "exacerbation benefit as well as positive effects on lung function and symptom benefits". Proposal that, if systemic exposure to budesonide administered through the BFF MDI is shown to be equivalent to or lower than that when administered through Symbicort TBH, then the safety profile of budesonide from Symbicort TBH can be extrapolated to BFF MDI and BGF MDI without the need to conduct further HPA axis, bone mineral density, and ophthalmological assessments. Acceptability to enrol patients with more severe COPD, based on history of COPD exacerbations into the study investigating COPD exacerbations in order to be able to demonstrate a difference between treatments. Endpoint selection in the Lung Function Trial. Sufficiency of proposed studies to characterize drug-drug interaction potential of the combination product vs individual components. Strategy to assess effect on QTc interval.

2.3. Quality aspects

Since this application is an informed consent of the Trixeo Aerosphere application, the quality data in support of the Riltrava Aerosphere application are identical to the up-to-date quality data of the Trixeo Aerosphere dossier, which have been assessed and approved (including all post-marketing procedures).

2.4. Non-clinical aspects

Since this application is an informed consent of the Trixeo Aerosphere application, the non-clinical data in support of the Riltrava Aerosphere application are identical to the up-to-date non-clinical data of the Trixeo Aerosphere dossier, which have been assessed and approved (including all post-marketing procedures).

2.4.1. Ecotoxicity/environmental risk assessment

Budesonide PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. However, considering that budesonide is classified as endocrine active a tailored Phase II assessment was performed on this basis. In a tailored Phase II assessment budesonide was not readily biodegradable but did not significantly absorb to solids during sewage treatment and is expected to pass into the aquatic environment. The water-sediment transformation study demonstrated budesonide not to be persistent and no bioaccumulation was seen in the fish bioconcentration assay. Therefore, budesonide does not fulfil the classification of a PBT substance.

Table 1: Summary of main study results for budesonide

Substance (INN/Invented Name): Budesonide					
CAS-number (if available): 51333-22-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.45			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0032	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 1629 ± 1734 K_d = 34.6 ± 16.6			
Ready Biodegradability Test	OECD 301	Degradation after 28 days <5%			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ =12.5 days (River); 18.1 (Pond) $DT_{50, aqueous\ phase}$ =6.45 days (River); 6.9 (Pond) $DT_{50, sediment\ system}$ =22.7 days (River); not calculable (Pond) % shifting to sediment = >10%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	7.9	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.4	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	

Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{ss}	6		BCF_L =9
Sediment dwelling organism	OECD218	NOEC	890	mg /kg	*Chironomus riparius*

Glycopyrronium Bromide PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Table 2: Summary of main study results for glycopyrrolate

Substance (INN/Invented Name): Glycopyrronium Bromide or Glycopyrrolate			
CAS-number (if available): 596-51-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-1.63	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000144	µg/L	> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)			(N)

Formoterol Fumerate PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Table 3: Summary of main study results for formoterol fumarate

Substance (INN/Invented Name): Formoterol Fumerate			
CAS-number (if available): 43229-80-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-0.837 at pH 5 0.070 at pH 7 0.895 at pH 9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC surfacewater, default or refined (e.g. prevalence, literature)	0.000096	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.4.2. Discussion on non-clinical aspects

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Riltrava Aerosphere to the environment.

The applicant commits to perform the following studies as follow-up measures:

A fish full life-cycle test is outstanding to address the potential for chronic effects of budesonide to fish. The Applicant indicated that a new fish full life-cycle study for budesonide will be performed and submitted as a post-authorisation measure for Trixeo Aerosphere.

2.4.3. Conclusion on the non-clinical aspects

The provided nonclinical package is sufficient to support the MAA for Riltrava Aerosphere

2.5. Clinical aspects

Riltrava Aerosphere (formoterol fumarate dihydrate, glycopyrronium and budesonide) 5 micrograms/ 7.2 micrograms/160 micrograms pressurised inhalation, suspension is submitted as an informed consent application of Trixeo Aerosphere (EU/1/20/1498/001-003; EMEA/H/C/004983) under Article 10(c) of Directive 2001/83/EC. The present application cross-refers to the up-to-date clinical data of the original dossier of Trixeo Aerosphere, which has been assessed and authorised. Therefore, the clinical data in support of Riltrava Aerosphere MAA are identical to the up-to-date clinical data of Trixeo Aerosphere dossier, which have been assessed and authorised by the CHMP. No new clinical data has been submitted.

2.6. Risk Management Plan

The RMP is in line with the approved EU-RMP version 1.2 of the cross-referred medicinal product Trixeo Aerosphere, 160/7.2/5.0 µg that was approved as part of the initial marketing authorisation application of Trixeo Aerosphere.

2.6.1. Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

2.6.2. Pharmacovigilance plan

As there are no safety concerns, no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection or additional pharmacovigilance activities are planned.

2.6.3. Risk minimisation measures

As there are no important potential risks and no important identified risks or missing information, no risk minimisation measures are implemented.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

2.8. Product information

The proposed product information for Riltrava is aligned with the latest approved version of the product information of the cross-referred product Trixeo Aerosphere.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

As the Patient Information Leaflet for Riltrava is identical (with the exception of the product name) to that of the reference product, the user testing of the Patient Information Leaflet for the reference product can be taken to apply equally to Riltrava.

3. Benefit-Risk Balance

The benefit-risk balance for Riltrava Aerosphere is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Riltrava Aerosphere is favourable in the following indication:

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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports 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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.