26 January 2017
EMA/CHMP/148961/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rolufta

International non-proprietary name: umeclidinium

Procedure No. EMEA/H/C/004654/0000

Note

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

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List of abbreviations

Abbreviation	Description	Abbreviation	Description
ACE	Angiotensin Converting Enzyme	IHCIS	Integrated Health Care System
ACh	Acetylcholine	LABA	Long-acting beta adrenergic agonist
AE	Adverse Event	LAMA	Long-acting muscarinic antagonist
AESI	Adverse Event of Special Interest	LS	Least Square
ATC	Anatomical Therapeutic Chemical	LTOT	Long-term oxygen therapy
AUC	Area Under Curve	mcg	micrograms
BCRP	Breast Cancer Resistance Protein	MedDRA	Medical Dictionary for Regulatory Activities
BSEP	Bile Salt Export Pump	mMRC	Modified Medical Research Council Dyspnoea Scale
BOLD	Burden of Obstructive Lung Disease	N/A	Not Applicable
BPH	Benign Prostatic Hyperplasia	NDPI	Novel Dry Powder Inhaler
BPM	Beats per Minute	NHANES	National Health and Nutritional Examination Survey
CI	Confidence Interval	P-gp	P-glycoprotein
Cmax	Maximum concentration	PBO	Placebo
COPD	Chronic Obstructive Pulmonary Disease	PIL	Patient Information Leaflet
CPRD	Clinical Practice Research Datalink	PSUR	Periodic Safety Update Report
CT	Computed tomography	PT	MedDRA Preferred Term
CVD	Cardiovascular Disease	PY	Patient Years
CYP	Cytochrome	QD	Quaque Die (once-daily)
DPI	Dry Powder Inhaler	QTc(F)	Corrected QT interval using Fridericia's formula
ECG	Electrocardiogram	RMP	Risk Management Plan
EEA	European Economic Area	RR	Relative Risk
EMA	European Medicine Agency	RUQ	Right Upper Quadrant
EU	European Union	SAE	Serious Adverse Event
FEV	Forced Expiratory Volume	SMQ	Standardised MedDRA Query
FRC	Functional Residual Capacity	SmPC	Summary of Product Characteristics
FVC	Forced Vital Capacity	SOC	MedDRA System Organ Class
GI	Gastrointestinal	TBC	To be confirmed
GINA	Global Initiative for Asthma	TIO	Tiotropium
GOLD	Global Initiative of Chronic Obstructive Lung Disease	UMEC	Umeclidinium bromide
GSK	GlaxoSmithKline	UTI	Urinary Tract Infection
HV	Healthy Volunteer	VI	Vilanterol
ICH	International Conference on Harmonisation	WHO	World Health Organisation
ICS	Inhaled corticosteroid		

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services Limited submitted on 27 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Rolufta, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2012.

The applicant applied for the following indication: maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

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, quality, non-clinical and clinical data with a letter from GlaxoSmithKline Trading Services Limited allowing the cross reference to relevant quality, non-clinical and/or clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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.

This application is submitted as a multiple of Incruse authorised on 18 April 2014 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Concepcion Prieto Yerro

Co-Rapporteur: N/A

- The application was received by the EMA on 27 October 2016.
- The procedure started on 28 November 2016.
- The Rapporteurs' first Joint Assessment Report was circulated to all CHMP and PRAC members on 3 January 2017.
- During the meeting on 12 January 2017 the PRAC agreed on the PRAC Assessment Overview and Advice to

CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 16 January 2016.

- The Rapporteurs' updated Joint Assessment Report was circulated to all CHMP and PRAC members on 16 January 2017.
- During the meeting on 26 January 2017, 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 Rolufta.

2. Scientific discussion

2.1. Introduction

Rolufta (umeclidinium bromide) inhalation powder predispensed, 55 micrograms has been submitted as an informed consent application in accordance with the Article 10c of Directive 2001/83/EC.

The initial marketing authorisation application (MAA) for umeclidinium bromide was approved on 28th April 2014 under the trademark Incruse (EMEA/H/C/002809). The application for Rolufta concerns the strength of 55 micrograms inhalation powder predispensed and consists only of Module 1 information.

As a consequence, quality, efficacy and safety of Rolufta medicinal product are identical to the up-to-date quality, efficacy and safety profile of Incruse.

The Rolufta informed consent application concerns the following presentations:

- Inhaler containing 7 doses (the inhaler contains one aluminium foil laminate blister of 7 doses)
- Inhaler containing 30 doses (the inhaler contains one aluminium foil laminate blister of 30 doses)
- Multipack of 3 inhalers containing 30 doses each.

The benefit-risk of Rolufta is considered to be positive, as it is a duplicate of Incruse, in the following indication:

- Rolufta is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Umeclidinium bromide is a long acting muscarinic receptor antagonist administrated by inhalation. It is competitively inhibiting the binding of acetylcholine with muscarinic cholinergic receptors on airway smooth muscle, exerting a bronchodilatory activity. Therefore, Rolufta is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

2.2. Quality aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

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

2.3.2. Ecotoxicity/environmental risk assessment

Umeclidinium PECsurfacewater value is below the action limit of 0.01 µg/L and is not a persistent, bioaccummulative, and toxic (PBT) substance as log Kow does not exceed 4.5. Therefore umeclidinium is not expected to pose a risk to the environment. Some environmental effects studies were additionally conducted with umeclidinium and the results and associated study reports were provided in the non-clinical dossier of Incruse. For this application no additional studies, neither for the Activated Sludge, Respiration Inhibition Test (OECD 209) are required.

2.3.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted since this application is an informed consent of the Incruse application.

Umeclidinium is exempt from a full ERA as the $PEC_{SURFACEWATER}$ does not exceed the action limit of 0.01 µg/L; therefore, the Activated Sludge, Respiration Inhibition Test (OECD 209) is not required.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered there were no non-clinical objections to the granting of the authorisation of this informed consent application for Rolufta.

2.4. Clinical aspects

Since Rolufta application is an informed consent of Incruse application, the clinical data in support of the Rolufta application are identical to the up-to-date clinical data of Incruse dossier, which have been assessed and authorised (including all post-marketing procedures).

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important Identified risks	None identified
Important Potential risks	Cardio- and Cerebrovascular Disorders
	Paradoxical bronchospasm (which may be life threatening)
	Bladder outlet obstruction

	Lower Respiratory Tract Infection (incl. pneumonia)
Missing information	Safety in pregnancy and lactation
	Safety in long-term use
	Safety in severe hepatic impairment

Pharmacovigilance plan

Study / activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A Post-Authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD patients using Inhaled UMEC/VI Combination or Inhaled UMEC versus Tiotropium (Study 201038). [Category 1]	To quantify the incidence of selected cardiovascular and cerebrovascular events of interest after the start of exposure to UMEC/VI combination or UMEC in the licensed indication, in the post marketing setting, specifically in the COPD patients managed in primary care in multiple European and non-European countries and compare with the incidence of cardiovascular and cerebrovascular events of interest after the start of exposure to tiotropium (Handihaler) over 24 months follow-up.	Cardio- and Cerebrovascular Disorders LRTI (incl. pneumonia) Safety in long-term use	Planned	Final report: Q3 2024

WWE117397 (formerly WEUSKOP6679): Post-authorisation Safety Electronic Medical Records Database Cohort Study of New Users of Inhaled UMEC/VI or New Users of Inhaled UMEC in the Primary Care Setting: UK EMR Distributed Network Study [Category 3]	*Primary:* Drug utilisation review of new users of UMEC/VI and new users of UMEC compared to the COPD patients initiating long-acting bronchodilators. *Secondary:* Quantify the disease burden of COPD and estimate the incidence of selected cardiovascular and cerebrovascular events of interest among new users of UMEC/VI, new users of UMEC and a comparator (selected from new long-acting bronchodilator users) among those with no ongoing management for the events of interest at observation start.	Cardio- and Cerebrovascular Disorders LRTI (incl. pneumonia)	Started	Final report: Q4 2019
Regulatory review of the submission highlighted additional required *in vitro* drug interaction investigations. [Category 3]	Additional investigations to provide information to address: a) binding of UMEC to microsomes and recalculation of I/K_i in the gut based on free drug concentrations b) providing data for UMEC as a substrate for BCRP and BSEP c) provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers d) provide data for UMEC as a substrate of OATP1B1 and 1B3	A series of post authorisation *in vitro* studies were conducted to determine the potential for drug-drug interactions.	Completed	Final study report submitted 6th March 2015.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardio- and Cerebrovascular Disorders	Prescription-only medication. EU SmPC: "*4.4 Special warnings and precautions for use* *Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists including umeclidinium bromide. In addition, patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium bromide should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.*" 4.8 Undesirable Effects Atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, rhythm idioventricular and tachycardia included as 'uncommon' in table of adverse reactions. A patient appropriate equivalent message is included in the user tested patient information leaflet.	Not applicable
Paradoxical bronchospasm (which may be life-threatening)	Prescription-only medication. EU SmPC: "*4.4 Special warnings and precautions for use* *Paradoxical bronchospasm* *Administration of umeclidinium bromide may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.*"	Not applicable
Bladder outlet obstruction	Prescription-only medication. EU SmPC: "*4.4 Special warnings and precautions for use* *Antimuscarinic activity* *Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.*"	Not applicable
Lower respiratory tract infection (incl. pneumonia)	Prescription-only medication.	Not applicable
Pregnancy and lactation	Prescription-only medication. EU SmPC: "*4.6 Fertility, pregnancy and lactation*	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Pregnancy *There are no data from the use of umeclidinium bromide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.* *Umeclidinium bromide should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.* *Breast-feeding* *It is unknown whether umeclidinium bromide is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded.* *A decision must be made whether to discontinue breast-feeding or to discontinue INCRUSE/* Rolufta *therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.*"	
Safety in long-term use	Prescription-only medicine	Not applicable
Safety in severe hepatic impairment	Prescription-only medication. EU SmPC: "*4.2 Posology and method of administration* *Hepatic impairment* *No dosage adjustment is required in patients with mild or moderate hepatic impairment. INCRUSE/* Rolufta *has not been studied in patients with severe hepatic impairment and should be used with caution.* *5.2 Pharmacokinetic properties* *Hepatic impairment* *Subjects with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to umeclidinium bromide (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium bromide has not been evaluated in subjects with severe hepatic impairment.*"	Not applicable

Conclusion

The CHMP considered that the risk management plan version 7 above described has been revised as recommended by the PRAC to take in account the changes requested in the PSUSA procedure EMEA/H/C/PSUSA/00010263/201604 and is acceptable.

2.6. PSUR submission

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.

2.7. Pharmacovigilance

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.

2.8. Product information

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:

The MAH has included the results from the Relvar Ellipta and Anoro Ellipta user testing process as well as providing a User Bridging Report for the originator product. There are no significant changes for the proposed patient leaflet.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rolufta (Umeclidinium) is included in the additional monitoring list as a Post Authorisation Safety Study (PASS) has been imposed at the time of authorisation for Incruse (Umeclidinium) furthermore it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

Rolufta is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. The CHMP has previously reviewed data on quality, safety and efficacy of the original dossier (Incruse) and considered the benefit / risk balance favourable.

The benefit-risk of Rolufta is considered to be positive, as it is a duplicate of Incruse, in the following indication:

- Rolufta is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4. Recommendation

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

- Rolufta is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

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 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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Submission of the final clinical study report on a Post-Authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients with Rolufta compared with tiotropium (study 201038), according to a protocol agreed by the PRAC.	By Q3 2024