22 February 2018
EMA/155337/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trydonis

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

Procedure No. EMEA/H/C/004702/0000

Note

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

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
ADR	Adverse Drug Reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APSD	aerodynamic particle size distribution
AST	aspartate aminotransferase
ATS	American Thoracic Society
BMI	body mass index
BUD	budesonide
CAT	COPD Assessment Test
CDLM	Capacity of Daily Living during the Morning
CEC	Clinical Endpoint Committee
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Database
CRF/eCRF	case report form/electronic case report form
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
ECG	electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERS	European Respiratory Society
EXACT-RS	Exacerbations of Chronic Pulmonary Disease Tool
EXT	Extension (Population)
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FF	fluticasone furoate
FOR	formoterol
FP	fluticasone propionate
FVC	forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation

ICS	inhaled corticosteroid
IND	Investigational New Drug
ITT	Intent-to-Treat (Population)
LABA	long-acting beta$_2$ receptor agonist
LAMA	long-acting muscarinic receptor antagonist
LRTI	lower respiratory tract infection
LS	least square
MACE	Major Adverse Cardiac Event
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mMRC	modified Medical Research Council
NHANES	National Health and Nutrition Examination Survey
PD	pharmacodynamic
PK	pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient-reported outcomes
PT	Preferred Term
QTc(F)	corrected QT interval using Friedicia's formula
RAP	Reporting and Analysis Plan
RMP	Risk Management Plan
SAE	serious adverse event
SALM	salmeterol
SAR	serious adverse report
SD	standard deviation
SDAP	Summary Document Analysis Plan
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD
SMQs	Standardised MedDRA Queries
SS	Serial Spirometry (Population)
TDI	Transitional Dyspnoea Index
TDI-SAC	Transitional Dysponea Index-self administered computerised version
TIO	tiotropium
UMEC	umeclidinium bromide
URTI	upper respiratory tract infection
VI	vilanterol
WM	weighted mean

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Chiesi Farmaceutici S.p.A. submitted on 24 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Trydonis, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 10 November 2016. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

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 (for effects on symptoms control and prevention of exacerbations see section 5.1).

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 the MAH of Trimbow, Chiesi Farmaceutici S.p.A, allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Trimbow authorised on 17 July 2017 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

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.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 February 2013 and 10 April 2013. The Scientific Advice pertained to non-clinical and clinical aspects of the development and on the Phase III studies' design

as part of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	24 November 2017
The procedure started on	25 December 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2018
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 Trydonis on	22 February 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COPD is strongly linked to tobacco smoking, particularly cigarette smoking and is a male predominant condition, in COPD clinical trials in developed countries generally about two thirds of included patients are male and for both males and females the average age tends to be in the early sixties. In poor countries the male predominance is not as marked as women may develop COPD as a result of cooking over open fires. The prevalence is quite variable on a local basis with higher prevalence linked to lower affluence and social status. Screening would be possible by mass measurement of lung function which is cheap, easy, and non-invasive, but is not done in practice. There have been no substantial trials of the value of screening for COPD. Tobacco smoking cessation or non/never smoking is an effective measure and societal efforts have been made in that direction rather than into screening programmes.

2.1.2. Biologic features

COPD is characterised by cough, excess sputum production, airways narrowing leading to air trapping and hyperinflation of the chest, and loss of lung tissue (emphysema). In its more advanced stages it causes strain and eventually failure, of the cardiac right ventricle.

2.1.3. Clinical presentation, diagnosis and stage / prognosis

Clinical presentation tends to be as cough and breathlessness in a heavy cigarette smoker and is unusual before approximately the age of forty.

Exacerbations in COPD are driven by episodes of acute inflammation, usually following a viral or bacterial infection. While current maintenance therapies prevent exacerbations in many COPD patients, exacerbation events in others remain poorly controlled, resulting in frequent use of oral corticosteroids and antibiotics and, in many cases, recurrent hospital admissions. This is particularly exemplified in a sub-population of patients termed frequent exacerbators. Despite treatment, some patients do not regain their baseline lung function following an exacerbation and repeated events can lead to an accelerated decline in lung function, resulting in a worsening overall quality of life for patients and a significant burden on healthcare resources.

The prognosis in terms of morbidity and mortality is directly linked to the extent of lung damage.

2.1.4. Management

Management is through smoking cessation, pharmacological intervention with bronchodilators and anti-inflammatory agents and, when necessary treatment of respiratory infections, physical rehabilitation is aimed primarily at muscle strengthening, and in advanced cases long term domiciliary oxygen administration is helpful and has a proven benefit on lung function. Some patients are suitable for lung volume reduction surgery to reduce non-gas exchanging thoracic space. Once developed the condition is only partly reversible so more treatment options are always welcome.

About the product

This is an informed consent application in accordance with article 10c of Directive 2001/83/EC.

The product of this application is a duplicate with identical composition and documentation as Trimbow 87 micrograms /5 micrograms /9 micrograms pressurised inhalation, authorized on 17 July 2017, marketing-authorisation holder, Chiesi Farmaceutici S.p.A.

Approval was granted for the following indication:

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 (for effects on symptoms control and prevention of exacerbations see section 5.1).

Type of Application and aspects on development

Trydonis 87 micrograms /5 micrograms /9 micrograms pressurised inhalation, the medicinal product of this marketing authorisation application, is a duplicate of Trimbow 87 micrograms /5 micrograms /9 micrograms pressurised inhalation. Trydonis 87 micrograms /5 micrograms /9 micrograms pressurised inhalation have the same qualitative and quantitative composition in terms of active substance, and the same pharmaceutical form as the reference product Trimbow 87 micrograms /5 micrograms /9 micrograms pressurised inhalation.

The MAH for the authorised medicinal product and for the product applied for in the informed consent application is the same, Chiesi Farmaceutici S.p.A.

A letter of consent to grant full and permanent access to the dossier (module 1 to 5) of the reference product Trimbow to fulfil its obligations as MAH as described in Directive 2001/83/EC has been provided with this submission.

2.2. Compliance with GLP, GMP, GCP

GLP

All pivotal non-clinical studies were performed to GLP

GMP inspection(s)

No GMP inspection is requested based on this application.

GCP

With respect to GCP compliance the Applicant stated within the MAA that the clinical studies were conducted in compliance with local regulation and guidance, with the International Conference on Harmonisation (ICH) guidelines and with Good Clinical Practice (GCP) regulations. Study subjects/patients were accorded all rights granted by the Declaration of Helsinki.

2.3. Quality aspects

Since this application is an informed consent of the Trimbow application, the quality data in support of the Beclometasone / Formoterol / Glycopyrronium bromide Chiesi Farmaceutici S.p.A. application are identical to the up-to-date quality data of the Trimbow dossier, which have been assessed and approved (including all post-marketing procedures).

2.4. Non Clinical aspects

Trydonis is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to TRIMBOW (EMEA/H/C/004257, EU/1/17/1208). The applicant refers to module 4 of the TRIMBOW MA. Therefore, the non-clinical data in support of the Trydonis MAA are identical to the up-to-date non-clinical data of TRIMBOW dossier, which have been assessed and authorised by the CHMP. No new non-clinical data has been submitted.

The Applicant provided an environmental risk assessment in accordance with the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2). The PEC values in Phase I for all active ingredients (beclometasone dipropionate (BDP), formoterol fumarate dehydrate (FF), and glycopyrronium bromide (GB)) are below the action limit of 0.01 µg/L. For the active substances FF and GB no assessment in Phase II Tier A is required. BDP and its active metabolite beclometasone monopropionate (B17MP) are glucocorticoids. Glucocorticoids play a role in many physiological processes and act as endocrine disruptors. Therefore, according to the EMA guideline (EMEA/CHMP/SWP/4447/00), a tailored environmental risk assessment strategy should be followed to address its specific mechanism of action irrespective of the action limit of 0.01 µg/L.

The Applicant provided acceptable experimental values on log K_{OW} of -0.02 and -1.35 for FF and GB, respectively. No further PBT assessment is required. For B17MP an experimental value of 3.49 is available

and accepted by the assessor. The potential to bioaccumulate should be considered in Phase II Tier B for this active ingredient.

Table 1: ***Summary of main study results***

Substance (INN / Invented Name): Formoterol fumarate dihydrate			
CAS-number (if available): 183814-30-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	-0.02	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.02	not B
	BCF	not available	
Persistence	DT50 or ready biodegradability	not available	
Toxicity	NOEC or CMR	not available	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00012	µg/L	> 0.01 threshold (N)

Substance (INN / Invented Name): glycopyrronium bromide			
CAS-number (if available): 51186-83-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	-1.35	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-1.35	not B
	BCF	not available	
Persistence	DT50 or ready biodegradability	not available	
Toxicity	NOEC or CMR	not available	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00025	µg/L	> 0.01 threshold (N)

2.5. Clinical

This application concerns an informed consent application in accordance with article 10(c) of directive 2001/83/EC. All clinical information is cross-referred to the up-to-date module 5 of the original dossier of Trimbow, which has been assessed and authorised. Therefore, the conclusions drawn for the clinical data of the Trimbow application, apply also for Trydonis. No additional studies have been provided.

2.6. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.7. Risk management plan

The applicant declares that the submitted EU-RMP version is the same as the approved EU-RMP version 4.0 (dated 17 May 2017) TRIMBOW, except for the addition of the invented name Trydonis.

The applicant identified the following safety concerns in the RMP version 4.0 (dated 17 May 2017):

Table 2: *Summary of the Safety Concerns*

Important Identified Risks	- Electrocardiogram QT prolonged, tachycardia, tachyarrhythmia - Atrial fibrillation - Increased risk of pneumonia in COPD patients - Risk of increased systemic exposure of Glycopyrronium bromide at therapeutic doses when used in patients with severe renal impairment
Important Potential Risks	- Cardio- and cerebrovascular events
Missing information	- Off label use in paediatric population in asthma indication - Use in patients with hepatic impairment - Use in pregnancy and lactation

The safety concerns as proposed by the applicant are acceptable.

Table 3: *Summary Table of the Risk Minimisation Measures*

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Electrocardiogram QT prolonged, tachycardia, tachyarrhythmia	Text in SmPC section 4.4, 4.5, 4.8 Prescription only medicine	None
Atrial fibrillation	Text in SmPC section 4.4, 4.8 Prescription only medicine	None
Increased risk of pneumonia in COPD patients	Text in SmPC section 4.4, 4.8 Prescription only medicine	None
Risk of increased systemic exposure of Glycopyrronium bromide at therapeutic doses when used in patients with severe renal impairment	Text in SmPC section 4.2, 4.4, 5.2	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine	
Important Potential Risks		
Cardio-and cerebrovascular events	Text in SmPC section 4.4, 4.8 Prescription only medicine	None
Missing Information		
Off label use in paediatric population in asthma indication	Text in SmPC section 4.2, 5.1 Prescription only medicine	None
Use in patients with hepatic impairment	Text in SmPC section 4.2, 4.4, 5.2 Prescription only medicine	None
Use in in pregnancy and lactation	Text in SmPC section 4.6, 5.3 Prescription only medicine	None

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.8. Product information

The Labelling of the present duplicate dossier cross-refers to the up-to-date Labelling of the original dossier (TRIMBOW), which has been assessed and authorised, with the logical changes included in the medicinal product specific data (i.e.: invented name).

The Package Leaflet of the present duplicate dossier cross-refers to the up-to-date Package Leaflet of the original dossier (TRIMBOW), which has been assessed and authorised, with the logical changes included in the medicinal product specific data (i.e.: invented name).

Consultation with target patient groups

The submitted report refers to the consultation performed on the reference product TRIMBOW Package Leaflet. No change to the authorised Package Leaflet for TRIMBOW is introduced for Trydonis, with the exception of the Invented Name and the Local Representatives for Italy and Spain. Therefore, the applicant´s justification to not undertake further consultation with target patient groups, is considered acceptable.

Braille

The applicant confirms that the name of the medicinal product will be printed in Braille format on the carton box in accordance with article 56a of Directive 2001/83/EC as amended. For the multipack presentations (i.e.

2 canisters of 120 actuations and 3 canisters of 120 actuations), the product name in Braille will be printed both on outer packaging and inner boxes.

3. Overall conclusion and benefit risk assessment

Trydonis 87 micrograms /5 micrograms /9 micrograms pressurised inhalation, solution (beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium) is submitted under an informed consent application, article 10(c) of directive 2001/83/EC.

The reference product for this application is TRIMBOW 87 micrograms /5 micrograms /9 micrograms pressurised inhalation, solution (EMEA/H/C/004257, EU/1/17/1208).

Trydonis and TRIMBOW have the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form. Therefore, the benefit-risk of Trydonis is considered to be positive in the following indication:

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 (for effects on symptoms control and prevention of exacerbations see section 5.1)

4. Recommendations

Outcome

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

Trydonis 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 β2-agonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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

Not applicable.