26 April 2019
EMA/299628/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Temybric Ellipta

International non-proprietary name:fluticasone furoate / umeclidinium / vilanterol

Procedure No. EMEA/H/C/005254/0000

Note

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

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic obstructive pulmonary disease
EC	European Community
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
MAA	Marketing Authorisation Application
NA	Not applicable
SmPC	Summary of Product Characteristics.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo SmithKline Trading Services submitted on 6 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Temybric Ellipta, 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 15 December 2015.

The product of this application is a multiple with identical composition and documentation of Trelegy Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed (fluticasone furoate/umeclidinium/vilanterol), authorised on the 15 November 2017 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Temybric Ellipta 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 or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom 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 Trelegy, Glaxo SmithKline Trading Services, allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Trelegy authorised on 15 November 2017 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The MAH for the authorised medicinal product and for the product applied for in the informed consent application is the same, GlaxoSmithKline Trading Services.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2011 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.

New active Substance status

The applicant indicated the active substance fluticasone furoate / umeclidinium / vilanterol contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received Scientific advice from the CHMP on the development for the indication from the CHMP on 21 March 2013 (EMEA/H/SA/2498/1/2012/II) and 24 October 2013 (EMEA/H/SA/2498/1/FU/1/2013/II and EMEA/H/SA/2498/2/2013/I). The Scientific advice pertained to the following *clinical* aspects:

- Adequacy of the chronic triple combination toxicology study in addition to full non-clinical study packages available for the individual substances to support MAA
- Design and adequacy of the clinical pharmacology programme: drug-drug-interaction studies, PK in special populations and need for definitive QTc study.
- Plans for population PK analysis in Phase 3 programme
- Appropriateness to start Phase 3 programme based on completed Phase 1 studies and available data from dual combinations FF/VI and UMEC/VI and UMEC alone
- Appropriateness of dose selection for the triple fixed dose combination based on data emerging from the dual combinations of FF/VI and UMEC/VI in COPD
- Appropriateness of the designs of planned confirmatory studies: study population in relation to potential indications, sample size/power considerations, assay sensitivity measures, choice of primary and secondary efficacy endpoints, use of symptom scales, choice of comparator, statistical analysis plan including type-1-error control for hierarchy of pre-specified secondary efficacy endpoints, number of confirmatory studies at the time of MAA, plans for pre-specified subgroup analyses to investigate responder characteristics, safety monitoring and safety database.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Peter Kiely.

The application was received by the EMA on	6 February 2019
The procedure started on	26 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	29 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 March 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2019
The Rapporteurs circulated the updated CHMP Assessment Report on	18 April 2019
The Rapporteurs circulated the updated PRAC Assessment Report on	18 April 2019
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 Temybric Ellipta on	26 April 2019

2. Scientific discussion

2.1. Problem statement

Temybric Ellipta is submitted under an informed consent application, article 10(c) of directive 2001/83/EC with reference made to Trelegy Ellipta (EU/1/17/1236).

Trelegy Ellipta (resp. Temybric Ellipta) is a pre-dispensed inhalation powder which is administered using the Ellipta inhaler. It is indicated as a once-daily maintenance therapy to prevent and relieve symptoms of COPD in adult patients.

Trelegy Ellipta (resp. Temybric Ellipta) contains a corticosteroid (fluticasone furoate), a long acting muscarinic receptor antagonist (umeclidinium bromide) and a long-acting β_2 agonist (vilanterol trifenatate) in a fixed dose combination.

Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide equivalent to 55 micrograms umeclidinium and 22 micrograms vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate).

2.1.1. Epidemiology

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

Fluticasone furoate (FF)/umeclidinium bromide (UMEC)/vilanterol (VI) Inhalation Powder (hereafter referred to as FF/UMEC/VI) is a triple combination of an inhaled corticosteroid, a long-acting muscarinic receptor antagonist, and a long- acting beta$_2$-adrenergic receptor agonist. The product is a fixed dose combination of 100 mcg FF, 62.5 mcg UMEC, and 25 mcg VI for oral inhalation administered via a single inhaler (ELLIPTA). These doses are the same as used in the dual combinations of FF/VI and UMEC/VI and UMEC monotherapy, all administered once-daily via the ELLIPTA inhaler, which have already been licensed for the treatment of chronic obstructive pulmonary disease (COPD) in the European Union (EU).

Type of Application and aspects on development

Temybric Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed (fluticasone furoate/umeclidinium/vilanterol) is submitted under an informed consent application, article 10(c) of directive 2001/83/EC with reference made to Trelegy Ellipta (EU/1/17/1236).

The MAH for the authorised medicinal product and for the product applied for in the informed consent application is the same, Glaxo SmithKline Trading Services.

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

The product of this application is a duplicate with identical composition and documentation as Trelegy Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed (fluticasone furoate/umeclidinium/vilanterol), authorised on the 15 November 2017.

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 fluticasone furoate / umeclidinium / vilanterol, marketed by GlaxoSmithKline Trading Services (Trelegy Ellipta EMEA/H/C/4363, EU/1/17/1236), the quality data in support of the Temybric Ellipta application are identical to the up-to-date quality data of the Trelegy Ellipta dossier, which have been assessed and approved (including all post-marketing procedures).

2.4. Non-clinical aspects

2.4.1. Introduction

Temybric Ellipta is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Trelegy Ellipta (EMEA/H/C/4363, EU/1/17/1236). For complete information please refer to the EPAR of Trelegy Ellipta which contains the full scientific assessment of the data related to Trelegy or Temybric applications.

No new nonclinical data have been provided in this submission. 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).

2.4.2. Ecotoxicity / environmental risk assessment

An updated Environmental Risk Assessment has been provided in the application as follows:

Fluticasone Furoate (FF), Umeclidinium (UMEC) and Vilanterol (VI) have partition coefficients (2.61, 1.256 and 1.354, respectively) which are less than 4.5 .

For FF, UMEC and VI, the Phase I Predicted Environmental Concentration values of 0.0005 μg/L, 0.0003125 μg/L, and 0.000125 μg/L, respectively, are significantly less than the nominal trigger value of 0.01 μg/L. Therefore, no Phase II standard fate and effects analysis is required for FF, UMEC or VI.

A tailored Phase II Tier A environmental risk assessment was provided for the active ingredient fluticasone furoate to evaluate its potential as an endocrine disruptor (Table 1).

Table 1: Summary of main study results

Substance (INN / Invented Name): Fluticasone furoate (GW685698)			
CAS-number (if available): 397864-44-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	2.61	Potential PBT (N)

PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	2.61			not B
Persistence	OECD 304 A	DT50 > 137 d (12°C)			P
Toxicity	NOEC	0.29 µg/L			T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$	0.0011	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)	Fluticasone furoate is a glucocorticoid and, as such, is considered a potential endocrine disruptor and therefore the potential endocrine activity of this compound was investigated in an appropriate chronic test system with relevant endpoints				(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc = 3,800 to 16,000mL/g (mean of 4 soils and 1 sediment: 9,600mL/g) Koc_{des} = 5,400 to 22,000mL/g (mean of 4 soils and 1 sediment: 13,000mL/g)			Report provided
Inherent Biodegradability Test	OECD 302 C	Not inherently biodegradable			Report provided
Inherent biodegradability in Soil	OECD 304 A	DT50 > 64d 3% mineralization in 64d			Reliable Report provided FF considered as P
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Acute toxicity to *Daphnia magna*	OECD 202	NOEC	4.2 (unfiltered 48h) 0.012 (filtered 48h)	mg/L	Report provided Not valid and not relevant for this ERA.
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	0.29	µg/L	Report provided
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	Report provided
Phase IIb Studies					
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/kg	Eisenia fetida LC_{50} (14 days) = 1,000 mg/kg Report provided

2.4.3. Discussion on non-clinical aspects

The updated data for the ERA are acceptable and do not pose an additional risk for the environment.

2.4.4. Conclusion on the non-clinical aspects

The CHMP considers that the non clinical data including the updated ERA support administration in humans and the proposed indication.

2.5. Clinical aspects

Temybric Ellipta is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Trelegy Ellipta (EMEA/H/C/4363, EU/1/17/1236). All clinical information is cross-referred to the up-to-date module 5 of the original dossier of Trelegy Ellipta, which has been assessed and authorised. Therefore, the conclusions drawn for the clinical data of the Trelegy Ellipta application, apply also for Temybric Ellipta. No additional studies have been provided which is appropriate for applications under this legal basis.

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 has submitted a Risk Management Plan (RMP) that is the same RMP as the currently approved RMP for Trelegy Ellipta.

Safety concerns

Summary of safety concerns	
Important identified risks	Pneumonia
Important potential risks	Serious Cardiovascular Events
	Decreased bone mineral density and associated fractures
Missing information	None

Pharmacovigilance plan

There are no on-going or planned additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Pneumonia	**Routine risk minimisation measures:** Section 4.4 and section 4.8 of the SmPC (also Section 4 of Product Leaflet). **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted Follow Up Questionnaire **Additional pharmacovigilance activities:** None
Serious cardiovascular events	**Routine risk minimisation measures:** Section 4.4 and section 4.8 of the SmPC (also Section 4 of Product Leaflet). **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Decreased Bone Mineral Density and Associated Fractures	**Routine risk minimisation measures:** Section 4.4 and section 4.8 of the SmPC (also Section 4 of Product Leaflet). **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.1 is acceptable.

2.8. 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.

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.

2.9. New Active Substance

The CHMP, based on the available data, considers that fluticasone furoate / umeclidinium / vilanterol is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union contained in the marketing authorisation of Trelegy Ellipta which was authorised in the European Union on 15 November 2017.

2.10. Product information

The PI of the present duplicate dossier cross-refers to the up-to-date approved PI of the original dossier (Trelegy Ellipta) which has been assessed and authorised.

Consultation with target patient groups

The submitted report refers to the consultation performed on the reference product Trelegy Package Leaflet. No change to the authorised Package Leaflet for Trelegy Ellipta is introduced for Temybric Ellipta. Therefore, the applicant´s justification to not undertake further consultation with target patient groups is considered acceptable.

Braille

The applicant confirms that the product name will be included in Braille on the outer packaging in line with Article 56a of Directive 2001/83/EC as amended.

3. Overall conclusion and Benefit-Risk Balance

Temybric Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed (fluticasone furoate/umeclidinium/vilanterol) is submitted under an informed consent application, article 10(c) of directive 2001/83/EC.

The authorised medicinal product in this application is Trelegy Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed (fluticasone furoate/umeclidinium/vilanterol) (EMEA/H/C/4363, EU/1/17/1236).

Temybric Ellipta and Trelegy Ellipta have the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form. Therefore, the benefit-risk of Temybric Ellipta is considered to be favourable 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 β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom 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 Temybric Ellipta is favourable 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 β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom 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.