



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

20 March 2014  
EMA/CHMP/175905/2014  
Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

Revinty Ellipta

International non-proprietary name: fluticasone furoate / vilanterol

Procedure No. EMEA/H/C/002745/0000

### Note

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



## Product information

Name of the medicinal product:	Revinty Ellipta
Applicant:	Glaxo Group Ltd Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom
Active substance:	Fluticasone furoate / vilanterol trifenate
International Nonproprietary Name	Fluticasone furoate / vilanterol
Pharmaco-therapeutic group (ATC Code):	Adrenergics and other drugs for obstructive airway diseases (R03AK10)
Therapeutic indication(s):	<p><u>Asthma Indication:</u> Revinty Ellipta is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta<sub>2</sub>-agonist and inhaled corticosteroid) is appropriate:</p> <ul style="list-style-type: none"> <li>patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting beta<sub>2</sub>-agonists.</li> </ul> <p><u>COPD Indication:</u> Revinty Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV1 &lt;70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite bronchodilator therapy.</p>
Pharmaceutical form(s):	Inhalation powder, pre-dispensed
Strength(s):	92 micrograms / 22 micrograms and 184 micrograms / 22 micrograms

Route(s) of administration:	Inhalation use
Packaging:	blister (alu)
Package size(s):	1 x 14 dose inhaler, 1 x 30 dose inhaler and 3 x 30 dose inhaler

## Table of contents

<b>1. Background information on the procedure .....</b>	<b>5</b>
1.1. Submission of the dossier.....	5
1.2. Manufacturers.....	6
1.3. Steps taken for the assessment of the product.....	6
<b>2. Scientific discussion .....</b>	<b>6</b>
2.1. Introduction.....	6
2.2. Quality aspects .....	8
2.3. Non-clinical aspects .....	8
2.3.1. Ecotoxicity/environmental risk assessment .....	8
2.4. Clinical aspects .....	12
2.5. Pharmacovigilance.....	12
2.6. Risk Management Plan .....	12
2.7. User consultation .....	19
<b>3. Benefit-Risk Balance.....</b>	<b>19</b>
<b>4. Recommendations .....</b>	<b>19</b>
Conditions and requirements of the Marketing Authorisation .....	20
Conditions or restrictions with regard to the safe and effective use of the medicinal product .....	20

# 1. Background information on the procedure

## 1.1. Submission of the dossier

The applicant Glaxo Group Ltd submitted on 24 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Revinty Ellipta, 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 24 May 2012.

The applicant applied for the following indications:

### Asthma Indication:

Revinty Ellipta is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short acting beta2-agonists.

### COPD Indication:

Revinty Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite bronchodilator therapy.

### **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 a MAH, Glaxo Group Ltd., allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Relvar Ellipta authorised on 13 November 2013 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 P/0216/2013 on the agreement of a paediatric investigation plan (PIP) for the condition “asthma”. The condition “COPD” is covered by a class waiver (CW/1/2011).

At the time of submission of the application, the PIP P/0216/2013 was not yet completed as some measures were deferred.

### ***Information relating to orphan market exclusivity***

### ***Similarity***

Not applicable.

## **Scientific Advice**

Not applicable.

## **Licensing status**

The product was not licensed in any country at the time of submission of the application. The original medicinal product Relvar Ellipta was approved in the EU on 13 November 2013.

### **1.2. Manufacturers**

#### **Manufacturer responsible for batch release**

Glaxo Operations UK Ltd. (trading as Glaxo Wellcome Operations)

Priory Street

Ware, Hertfordshire SG12 0DJ

United Kingdom

### **1.3. Steps taken for the assessment of the product**

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

**Rapporteur: Concepcion Prieto Yerro      Co-Rapporteur: David Lyons**

- The application was received by the EMA on 24 December 2013.
- The procedure started on 19 January 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 27 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 March 2014.
- The Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 13 March 2014.
- During the meeting on 20 March 2014, 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 Revinty Ellipta.

## **2. Scientific discussion**

### **2.1. Introduction**

#### **Problem statement**

Asthma is a chronic pulmonary disease characterized by airway inflammation, bronchoconstriction and increased airway responsiveness [Global Initiative in Asthma (GINA) Guideline, 2011] affecting 1%-18% of the population across different countries. The mortality, morbidity and costs associated with asthma are substantial. Inhaled corticosteroids (ICS) are considered the most effective anti-

inflammatory treatments for all severities of persistent asthma [GINA Guideline, 2011], resulting in a control of asthma symptoms, improvement in quality of life and lung function and reduction in the frequency and severity of asthma exacerbations. Add-on therapy with inhaled LABA is preferred to increasing the dose of ICS to achieve asthma control, and is associated with improvement in symptom scores, decreases in nocturnal asthma symptoms, improvement in lung function and reduction of the number of asthma exacerbations. Without concomitant ICS inhaled LABA may be associated with increased risk of serious asthma-related events (including hospitalisation, intubation and death), and therefore inhaled LABA therapy should not be used as monotherapy in asthma [GINA Guideline, 2011].

Chronic Obstructive Pulmonary Disease (COPD) is a common disease that accounts for 5% of deaths globally [World Health Organisation (WHO) 2012]. As a leading cause of morbidity and mortality worldwide, COPD produces a substantial, and growing, economic and social burden [GOLD, 2011]. COPD is characterised by persistent, usually progressive, airflow limitation associated with an enhanced inflammatory response in the airways and the lungs. Exacerbations and comorbidities contribute to the overall severity [Global Initiative for Obstructive Lung Disease (GOLD), 2011]. An exacerbation is an acute event characterised by a worsening of the symptoms of COPD that require treatment with oral corticosteroids and/or antibiotics (moderate exacerbations) or that require an inpatient hospitalization (severe exacerbations). The goals of pharmacologic therapy in COPD are the reduction in symptoms and in the frequency and severity of exacerbations, and the improvement of health status and exercise tolerance [GOLD, 2011]. Bronchodilators, such as long-acting beta<sub>2</sub> agonists (LABA), are key to improving lung function and managing symptoms in COPD. In patients not adequately controlled with a LABA, the addition of a ICS usually leads to reductions in the frequency of exacerbations, improves symptoms and quality of life and produces small improvements in lung function [GOLD, 2011].

### **About the product**

Revinty Ellipta Ellipta 92 µg/22 µg & 184 µg/22 µg inhalation powder is a pre-dispensed multi dose dry powder for oral inhalation. The active ingredients are fluticasone furoate (FF) and Vilanterol (VI) (as trifenate). FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, while VI is a selective long-acting, beta<sub>2</sub>-adrenergic agonist (LABA).

The novel dry powder inhaler (NDPI), called Ellipta, incorporates two blister strips, one containing a blend of micronised FF and lactose monohydrate and the other containing a blend of micronised VI, lactose monohydrate and magnesium stearate. Upon actuation, the inhaler delivers the contents of one blister containing FF blend and one blister containing VI blend.

Revinty Ellipta is a novel ICS/LABA fixed dose combination for oral inhalation administered from a Novel Dry Powder Inhaler (NDPI). It contains fluticasone furoate (FF; GW685698X), an ICS, and vilanterol (VI; vilanterol trifenate; GW642444M), an inhaled LABA. Neither FF nor VI is currently available as an individual component for oral inhalation. However, FF is the active substance in Avamys, an intranasal corticosteroid authorised via the Centralised Procedure.

The Applicant applied for the following two indications:

#### Asthma

Revinty Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta<sub>2</sub>-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta<sub>2</sub>-agonists.

#### COPD (Chronic Obstructive Pulmonary Disease)

Revinty Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV<sub>1</sub><70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

In asthma, the posology requested is one inhalation of Revinty Ellipta 92 µg/22 µg once daily (OD). If patients are inadequately controlled on Revinty Ellipta 92 mcg/22 µg OD, the dose of Revinty Ellipta 184 µg/22 µg should be considered.

In COPD, the posology requested is one inhalation of Revinty Ellipta 92 mcg/22 µg OD. Revinty Ellipta 184 µg/22 mcg is not recommended in COPD, due to lack of superior efficacy compared to the lower dose, and increase in risk of pneumonia and other adverse events.

## **2.2. Quality aspects**

Since this application is an informed consent of the Relvar Ellipta application, the quality data in support of the Revinty Ellipta application are identical to the up-to-date quality data of the Relvar Ellipta dossier, which has been assessed and approved.

## **2.3. Non-clinical aspects**

No non-clinical data have been submitted in the Revinty Ellipta dossier, since this application is an informed consent of the Relvar Ellipta application: the non-clinical data in support of the Revinty Ellipta application are identical to the up-to-date non-clinical data of the Relvar Ellipta dossier, which have been assessed and approved.

### **2.3.1. Ecotoxicity/environmental risk assessment**

An environmental Risk Assessment(ERA) has been provided, which is identical to the one that was submitted for Relvar Ellipta.

The ERA was prepared in compliance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/4447/00). The two active substances fluticasone furoate and vilanterol have been assessed separately. Predicted environmental concentrations were significantly below the threshold value of 0.01 µL, indicating that no a Phase II – Tier A is needed for both active substances.

#### **Fluticasone furoate (GW685698)**

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of fluticasone furoate. The log K<sub>ow</sub> was determined according to study OECD 117 with a value of 2.61. Based on the log K<sub>ow</sub> value being below 3, fluticasone furoate is not expected to be a bio-accumulative substance. The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSE_{\text{ai}} \cdot F_{\text{pen}}}{WASTEW_{\text{inhab}} \cdot DILUTION}$$

The following values were used for the calculation:

$$DOSE_{\text{ai}} = 0.200 \quad (\text{mg patient}^{-1} \text{ d}^{-1})$$

$$F_{\text{pen}} = 0.01 \quad (\text{patient inh}^{-1})$$

$$WASTEW_{\text{inhab}} = 200 \quad (\text{L inh}^{-1} \text{ d}^{-1})$$

DILUTION = 10 (-)

PEC<sub>surfacewater</sub> is 0.001 µg/L.

The PEC<sub>surfacewater</sub> is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Fluticasone furoate is a glucocorticoid, hence it should be considered as a potential endocrine disruptor. Therefore the potential endocrine activity of this compound should be investigated. In the context of the obligation of the Applicant to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

- An OECD 210 modified extended early life-stage study in fish using fluticasone furoate should be conducted to complete the Environmental Risk Assessment. Once the results are available, the Environmental Risk Assessment should be updated accordingly.

The results from this additional study were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that these applications comply with Article 6 of Regulation 726/2004 having regard to the requirements of Article 8(3) of Directive 2001/83.

**Table 1. Summary of main study results for fluticasone furoate**

<b>Substance (INN/Invented Name): GW685698 /</b>					
<b>CAS-number (if available):</b>					
<b>PBT screening</b>		<b>Result</b>		<b>Conclusion</b>	
Bioaccumulation potential- log K <sub>ow</sub>		OECD117 ...		2.61	
				Potential PBT (N)	
<b>PBT-assessment</b>					
<b>Parameter</b>		<b>Result relevant for conclusion</b>		<b>Conclusion</b>	
Bioaccumulation		log K <sub>ow</sub>		2.61	
Persistence		DT50 or ready biodegradability		≈ 3% in 64 days	
Toxicity		NOEC or CMR		4.2 µg/L (unfiltered 48 h) 0.012 µg/L (filtered 48 h)	
				not B Considered to be persistent. Report not provided No significant toxicity Report not provided	
<b>PBT-statement :</b>		The compound is not considered as PBT nor vPvB			
<b>Phase I</b>					
<b>Calculation</b>		<b>Value</b>		<b>Unit</b>	
PEC <sub>surfacewater</sub> , default or refined (e.g. prevalence, literature)		0.001		µg/L	
				> 0.01 threshold (N)	
<b>Phase II Physical-chemical properties and fate</b>					
<b>Study type</b>		<b>Test protocol</b>		<b>Results</b>	
Adsorption-Desorption		OECD 106		Koc = 3,800 to 16,000mL/g (mean 9,600mL/g) Kocdes = 5,400 to 22,000mL/g (mean 13,000mL/g)	
Ready Biodegradability Test		OECD 302C		Not inherently Biodegradable	
				Report not provided	
<b>Phase IIa Effect studies</b>					
<b>Study type</b>		<b>Test protocol</b>		<b>Endpoint</b>	
Algae, Growth Inhibition Test/ <i>Species</i>		OECD 201		NOEC	
				value	
				Unit	
				Remarks	
				4.2 (unfiltered 48h) 0.012 (filtered 48h)	
				µg/L	
				Species: Daphnia Report not provided	

Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1,000	µg/L	Report not provided
<b>Phase IIb Studies</b>					
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	>1,000	mg/kg	LC <sub>50</sub> (14 days) = 1,000 mg/kg Report not provided

### Vilanterol (GW64244)

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of vilanterol. The log K<sub>ow</sub> was determined according to study OECD 107 with a value of 1.354. Based on the log K<sub>ow</sub> value being below 3, vilanterol is not expected to be a bio-accumulative substance. The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSE_{\text{ai}} \cdot F_{\text{pen}}}{WASTEW_{\text{inhab}} \cdot DILUTION}$$

The following values were used for the calculation:

$$DOSE_{\text{ai}} = 0.025 \text{ (mg patient}^{-1} \text{ d}^{-1}\text{)}$$

$$F_{\text{pen}} = 0.01 \text{ (patient inh}^{-1}\text{)}$$

$$WASTEW_{\text{inhab}} = 200 \text{ (L inh}^{-1} \text{ d}^{-1}\text{)}$$

$$DILUTION = 10 \text{ (-)}$$

PEC<sub>surfacewater</sub> is 0.00013 µg/L.

The PEC<sub>surfacewater</sub> is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Table 2. Summary of main study results for vilanterol trifenate

<b>Substance (INN/Invented Name): GW642444M</b>						
<b>CAS-number (if available):</b>						
<b>PBT screening</b>		<b>Result</b>		<b>Conclusion</b>		
Bioaccumulation potential- log $K_{ow}$		OECD107 ...		0.092 (to pH 5) 1.354 (to pH 7) 1.390 (to pH 9)		Potential PBT (N)
<b>PBT-assessment</b>						
<b>Parameter</b>		<b>Result relevant for conclusion</b>		<b>Conclusion</b>		
Bioaccumulation		log $K_{ow}$		0.092 (to pH 5) 1.354 (to pH 7) 1.390 (to pH 9)		not B
<b>PBT-statement :</b>		The compound is not considered as PBT nor vPvB				
<b>Phase I</b>						
<b>Calculation</b>		<b>Value</b>	<b>Unit</b>		<b>Conclusion</b>	
PEC <sub>surfacewater</sub> , default or refined (e.g. prevalence, literature)		0.00013	µg/L		> 0.01 threshold (N)	
<b>Phase II Physical-chemical properties and fate</b>						
<b>Study type</b>		<b>Test protocol</b>	<b>Results</b>		<b>Remarks</b>	
ND		ND	ND		NA	
<b>Phase II a Effect studies</b>						
<b>Study type</b>		<b>Test protocol</b>	<b>Endpo int</b>	<b>value</b>	<b>Unit</b>	<b>Remarks</b>
Algae, Growth Inhibition Test/ <i>Species</i>		OECD 202	NOEC	Yield (72 hr) EyC <sub>50</sub> = 910 NOEC = 95.4 Growth Rate (72 hr) ErC <sub>50</sub> = 5910 NOEC = 977 Biomass (72 hr) EbC <sub>50</sub> = 1080 NOEC = 95.4	µg/L	Species: <i>Pseudokirchneriell a subcapitata</i> Report not provided
<i>Daphnia</i> sp. Reproduction Test		OECD 211	NOEC	Reproduction (21 days) EC <sub>50</sub> > 12500 LOEC > 12500 NOEC = 12500 Reproduction (21 days) EC <sub>50</sub> > 12500 LOEC = 12500 NOEC = 6250	µg/L	Report not provided
Fish, Early Life Stage Toxicity Test/ <i>Species</i>		OECD 210	NOEC	Hatching LOEC > 10000 NOEC (28 day) = 10000 Larvae Survival EC <sub>50</sub> (28 days) > 10000 LOEC > 10000 NOEC (28	µg/L	Species: <i>Pimephales promelas</i> Report not provided

			days)= 10000 <u>Length and</u> <u>Weight</u> LOEC = 1111 NOEC (28 day)= 370		
<b>Phase II b Studies</b>					
ND	ND	ND	ND	NA	NA

## **2.4. Clinical aspects**

No new clinical data has been provided within this application. The clinical data in support of the Revinty Ellipta application is identical to the up-to-date clinical data of the Relvar Ellipta dossier which have already been assessed and approved by the CHMP.

## **2.5. Pharmacovigilance**

### **Detailed description of the pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

## **2.6. Risk Management Plan**

RMP version 6.2 was provided with this submission. This RMP version 6.2 is identical to the RMP approved for Relvar Ellipta, no further assessment was needed and therefore no PRAC Advice was sought.

Below is a short overview of the content of the Risk Management Plan which is identical to Relvar Ellipta:

## Safety concerns

**Table 3. Summary of the Safety Concerns**

Summary of safety concerns	
Important identified risks	Pneumonia in patients with COPD and Asthma
Important potential risks	Serious cardiovascular events Asthma-related intubations and deaths Growth retardation in children Decreased bone mineral density and associated fractures Hypersensitivity Adrenal suppression Corticosteroid associated eye disorders Off label use in <12 years of age Off label use of the 200/25 dose in patients with COPD
missing information	Safety in pregnancy and lactation Long-term use > 1 year in both asthma and COPD Safety in adolescent asthmatic patients treated with the 200/25 strength

## Pharmacovigilance plans

**Table 4. On-going and planned studies in the Post-authorisation Pharmacovigilance Development 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)
Salford Study (COPD) (H2C115151)  Interventional 1	H2C115151: A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) compared with the existing COPD maintenance therapy alone in subjects with COPD.	Pneumonia in patients with COPD and Asthma	<i>Started</i>	3Q2015
Salford Study (Asthma)	A 12-month, open	Pneumonia in patients	<i>Started</i>	

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)
(HZA115150) Interventional 1	label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) compared with the existing Asthma maintenance therapy alone in subjects with Asthma.	with COPD and Asthma.		2Q2016
SUMMIT Study (HZA113782) Interventional 3	Clinical Outcomes Study to compare the effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg, or the Monotherapy components with placebo on Survival in Subjects with moderate Chronic Obstructive Pulmonary Disease (COPD) and a history of or at increased risk for cardiovascular disease.	Pneumonia in patients with COPD  Serious cardiovascular events  Reduced Bone Mineral Density and associated fractures  Hypersensitivity  Eye disorders	<i>Started</i>	2Q2017
Paediatric knemometry study in Asthma (HZA107112) Interventional 3	Evaluate the effect on short-term lower-leg of two weeks treatment with inhaled fluticasone furoate versus placebo once daily using a knemometer	Growth Retardation	<i>Planned</i>	4Q2016
Paediatric growth velocity study in Asthma (HZA114971) Interventional 3	Determine if there is an effect on the growth velocity of in pre-pubescent paediatric subjects following administration of inhaled fluticasone furoate (FF) for one year	Growth Retardation	<i>Planned</i>	2Q2020
Bone mineral density study in COPD patients (HZA102792) Interventional 3	The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density assessed at the total hip by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.	Decreased Bone Mineral Density and associated fractures	<i>Planned</i>	2Q2019
Drug utilization study of	A retrospective	Off Label Use of 200/25	<i>Planned</i>	40 months

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)
new users of fluticasone furoate / vilanterol (FF/VI) in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study	longitudinal noninterventional observational study of patients identified based on new prescriptions for FF/VI from an electronic medical records (EMR) database. Patients will be stratified by indication (e.g. asthma, COPD, neither diagnosis) followed for a one year study period following FF/VI initial prescription, and compared with the asthma and COPD populations treated with maintenance therapy identified during this period.	dose in COPD		<i>from initiation, dependent on date of licence approval</i>

\*Category 1 are imposed activities considered key to the benefit risk of the product.  
Category 2 are specific obligations  
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

**Risk minimisation measures**

**Table 5. Summary table of Risk Minimisation Measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pneumonia in patients with COPD and Asthma	Section 4.4 Warnings and Precautions: Pneumonia in patients with COPD An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal (see section 4.8). 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 receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m <sup>2</sup> and patients with a (forced expiratory volume) FEV <sub>1</sub> <50%	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>predicted. These factors should be considered when fluticasone furoate/vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs.</p> <p>Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of systemic corticosteroid-related adverse reactions (see section 4.8). The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified.</p> <p>The event will be listed in section 4.8 Adverse Events: Pneumonia</p> <p>In an integrated analysis of the two replicate one year studies in COPD with an exacerbation in the preceding year (n = 3255), the number of pneumonia events per 1000 patient years was 97.9 with FF/VI 184/22, 85.7 in the FF/VI 92/22 and 42.3 in the VI 22 group. For severe pneumonia the corresponding number of events per 1000 patient years were 33.6, 35.5, and 7.6 respectively, while for serious pneumonia the corresponding events per 1000 patient/years were 35.1 for FF/VI 184/22, 42.9 with FF/VI 92/22, 12.1 with VI 22.</p> <p>Finally, the exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 184/22 versus 1.5 for FF/VI 92/22 and 0 for VI 22.</p> <p>In an integrated analysis of 7 studies in COPD (n = 4236), the number of pneumonia events per 1000 patient years was 92.3 with FF/VI 184/22, 77.7 in the FF/VI 92/22, 42.2 in the VI 22 group and 18.0 with placebo. For severe pneumonia the corresponding events per 1000 patient years were 33.8, 28.7, 12.0 and 0, respectively, while for serious pneumonia the corresponding events per 1000 patient years were 35.1 for FF/VI 184/22, 35.9 with FF/VI 92/22, 15.7 with VI 22 and 6.0 for placebo. Finally, the exposure-adjusted cases of fatal pneumonia were 7.8 for FF/VI 184/22 versus 1.2 for FF/VI 92/22 and 0 for VI 22 and placebo.</p>	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia per 1000 patient/years was 18.4 for FF/VI 184/22 versus 9.6 for FF/VI 92/22 and 8.0 in the placebo group.</p>	
Asthma-related intubations and deaths	<p>Section 4.4:  <i>"Asthma-related adverse events and exacerbations may occur during treatment with Relvar Ellipta. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on fluticasone furoate/vilanterol"</i></p>	Not applicable
Serious Cardiovascular events	<p>Section 4.4:  <i>"Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular, tachycardia and extrasystoles may be seen with sympathomimetic medicinal products, including Relvar Ellipta. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease".</i></p>	Not applicable
Growth retardation in children	<p>Section 4.4:  <i>"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).</i></p>	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Decreased bone mineral density	<p>Section 4.4:  <i>"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).</i></p>	Not applicable
Hypersensitivity	<p>The EU SmPC contraindicates against patients with a known allergy:  <i>Hypersensitivity to fluticasone furoate or vilanterol or to any of the excipients listed in section 6.1.</i></p>	Not applicable
Adrenal suppression	<p>Section 4.4:  <i>"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).</i></p>	Not applicable
Steroid associated eye disorders	<p>Section 4.4:  <i>"Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).</i></p>	Not applicable
Off Label Use of the 200/25 dose in COPD	<p>Section 4.2 :  <i>Relvar Ellipta 184 micrograms/22 micrograms is not indicated for patients with COPD. There is no</i></p>	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>additional benefit of the 184/22 microgram dose compared to the 92/22 microgram dose and there is an increased risk of corticosteroid related adverse reactions (see sections 4.4 and 4.8)</i></p> <p>Section 4.4 :  <i>Relvar Ellipta 184 micrograms/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is an increased risk of corticosteroid related adverse reactions (see section 4.8)</i></p>	
Off Label Use in children <12 years of Age	<p>The indication in asthma is in Adults and adolescents aged 12 years and over  For Children aged under 12 years:  The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the Indication for Asthma.</p>	Not applicable

The CHMP confirmed that no changes are needed for this Risk Management Plan of Revinty Ellipta.

## 2.7. 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 Applicant provided the report on the results from the user consultation done for Relvar Ellipta. The CHMP considered it acceptable to refer to the user consultation done for Relvar Ellipta as the package leaflet is identical and no separate user testing for this informed consent application is considered necessary.

## 3. Benefit-Risk Balance

The application has been submitted in accordance with Article 10c of Directive 2001/83/EC as amended (Informed consent Application) under automatic access to the centralised procedure.

Revinty Ellipta is identical to Relvar Ellipta previously approved by the CHMP. The quality, non-clinical, efficacy and safety data for Revinty Ellipta is therefore considered satisfactorily and the benefit-risk profile for Revinty Ellipta is positive.

## 4. Recommendations

### Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Revinty Ellipta in:

- the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta<sub>2</sub>-agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short acting beta<sub>2</sub>-agonists).
- the symptomatic treatment of patients with COPD with a FEV1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

### ***Conditions and requirements of the Marketing Authorisation***

- **Periodic safety update reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

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

<b>Description</b>	<b>Due date</b>
Submission of final clinical study report for the interventional post-authorisation safety study to further investigate the risk of pneumonia with Revinty Ellipta compared with other ICS/LABA FDC in the treatment of COPD, according to a protocol agreed by the Committee.	30 September 2015
Submission of final clinical study report for the interventional post-authorisation safety study to further investigate the risk of pneumonia with Revinty Ellipta compared with other ICS/LABA FDC in the treatment of asthma, according to a protocol agreed by the Committee	30 June 2016

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

Not applicable.

***Paediatric Data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0216/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

## ***Divergent Position***

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Revinty Ellipta for the following indications:

### Asthma Indication:

Revinty Ellipta is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta<sub>2</sub>-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting beta<sub>2</sub>-agonists.

### COPD Indication:

Revinty Ellipta is indicated for symptomatic treatment of adults with COPD with a FEV<sub>1</sub> <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

The reasons for divergent opinion were as follows:

In asthma, the superiority of the fixed dose combination (FDC) to the mono components on bronchodilatory effect and symptomatic improvement has not been sufficiently demonstrated (Guideline on Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1)). None of the mono components have been previously approved for the treatment of asthma, and non-inferiority of the FDC compared with established LABA/ICS FDC therapies, or superiority of the FDC compared with established LABA or ICS mono therapies in asthma has not been proven.

Regarding the COPD indication, no clear symptomatic benefit of the FDC versus placebo was apparent on dyspnoea scores, and the chosen active comparator (VI) for the exacerbation studies is not considered optimal as it is not an authorised LABA for the treatment of patients with COPD. Therefore, the magnitude of the symptomatic effect (dyspnoea, exacerbations) of the FDC in COPD is uncertain. The issue is hampered by the lack of comparisons with established COPD therapies.

In relation to safety issues, the risk of pneumonia seems to be a common and serious adverse event, with 6 fatal cases of pneumonia observed in the COPD studies, which are of special concern. This risk cannot be fully characterized due to methodological limitations of the clinical studies with regard to the assessment of pneumonia.

London, 20 March 2014

---

Pieter de Graeff

---

Pierre Demolis

---

Kristina Dunder

---

Harald Enzmann

---

Hubert Leufkens

---

Daniela Melchiorri

---

Ivana Mikacic

---

Jan Mueller-Berghaus

---

Concepcion Prieto Yerro

Bruno Sepodes

---