23 July 2015
EMA/499766/2015
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/WS0708

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Relvar Ellipta	FLUTICASONE FUROATE / VILANTEROL	EMEA/H/C/002673/WS0708/0011
Revinty Ellipta	FLUTICASONE FUROATE / VILANTEROL	EMEA/H/C/002745/WS0708/0007

Worksharing applicant (WSA): Glaxo Group Ltd

Note

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

Assessment Timetable/Steps taken for the assessment

Timetable	Dates
Start of procedure:	22 February 2015
CHMP Rapporteur Assessment Report	30 March 2015
CHMP comments	13 April 2015
Rapporteur Revised Assessment Report	n/a
Request for Supplementary information	23 April 2015
CHMP Rapporteur Assessment Report	9 July 2015
CHMP comments	13 July 2015
Rapporteur Revised Assessment Report	23 July 2015
Opinion	23 July 2015

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd submitted to the European Medicines Agency on 4 February 2015 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 4.2 of the SmPC to clarify the information to prescribers on the initial dose of Relvar/Revinty based on the corticosteroid dose equivalence.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics.

1.2. Rationale for the proposed change

Relvar/Revinty Ellipta has been marketed in several countries and during this time the MAH has received feedback from prescribers regarding the wording of the Section 4.2, Posology and method of administration of the Summary of Product Characteristics (SmPC). Prescribers consider that the Section 4.2 of the SmPC, as currently worded, does not provide clear guidance as to which dose of Relvar/Revinty Ellipta should be initiated depending on the dose of inhaled corticosteroid the patient is currently receiving.

The purpose of this submission is to update the wording in the Relvar/Revinty Ellipta SmPC to address the feedback from prescribers.

2. Scientific discussion

2.1. Introduction

Relvar and Revinty Ellipta 100 µg/25 µg & 200 µg/25 µg inhalation powder are a pre-dispensed multi dose dry powder for oral inhalation. The active ingredients are fluticasone furoate (FF) and Vilanterol (VI) (as trifenatate). FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, while VI is a selective long-acting, beta2-adrenergic agonist (LABA).

Relvar Ellipta was approved in the EU on 13th November 2013 and the duplicate licence, Revinty Ellipta, approved in the EU on 2nd May 2014 for the following indication:

"regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal 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".

Due to the feedback received from prescribers about the unclear information included in Section 4.2 of the SmPC (See Section 1.2 of this AR, Rationale for the proposed change) some wording changes to the SmPC have been proposed by the MAH in order to clarify the patients in which to initiate Relvar/Revinty Ellipta.

2.2. Clinical Efficacy aspects

During the review of the Relvar Ellipta Marketing Authorisation Application (MAA), the applicant was asked to amend the wording of equivalence of fluticasone fuorate (FF) dosing in line with other inhaled corticosteroid/long-acting beta2-agonists (ICS/LABAs).

The MAH states now that there is no longer comparable wording regarding corticosteroid dose equivalence in either the Seretide Accuhaler/Diskus SmPC or the SmPCs for any other ICS/LABAs. The wording in the Seretide Mutual Recognition (MR) SmPC was removed in August 2014 at the request of the Medicines and Healthcare products Regulatory Agency (MHRA) as a post approval commitment following a duplicate licence procedure. Across the approved SmPCs for ICS containing medicines, there is common language that patients should be treated with the dose of the corticosteroid appropriate to the severity of their disease but the description of identification of the appropriate patients varies across the labels. However the MAH recognises the need for information in the SmPC to guide prescribers to the appropriate patients to initiate Relvar/Revinty Ellipta and proposes a change in the wording in the Relvar/Revinty Ellipta SmPC to minimise confusion and enable prescribers to initiate Relvar/Revinty Ellipta in appropriate patients, which would be reflective of the inclusion criteria of the Phase III studies (Table 1).

Table 1. Summary of Prior ICS Inclusion Criteria for Phase III Studies

Study	Daily dose of ICS prior to study	FF/VI dose
Lower dose studies		
HZA106827 (Bleecker, 2014)	200-500 mcg/day FP or equivalent	FF/VI 92/22
Higher dose studies		
HZA106829 (O'Byrne, 2014)	1000 mcg/day FP or equivalent	FF/VI 184/22

Therefore, following changes have been proposed in Section 4.2 (deletions ~~strikethrough~~, additions in **bold**).

Current	Proposed
Adults and adolescents aged 12 years and over One inhalation of Relvar/Revinty Ellipta 92/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar/Revinty Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief. A starting dose of Relvar/Revinty Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta2-agonist. If patients are inadequately controlled on Relvar/Revinty Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional	Adults and adolescents aged 12 years and over One inhalation of Relvar/Revinty Ellipta 92/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar/Revinty Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief. A starting dose of Relvar/Revinty Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta2-agonist. If patients are inadequately controlled on Relvar/Revinty Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional

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In response to CHMP request the company was asked to provide further justification for amending section 4.2. The full justification is detailed below:

The MAH agreed that prescribers should be aware that the potency of fluticasone furoate (FF) is not equivalent to fluticasone propionate (FP) and that this is particularly important as the similar names of both active principles may lead to the assumption that the two compounds are the same. As a consequence additional wording is proposed in Section 4.2 and 5.1 of the SmPC to make this clearer.

However, the company did not agree with the proposed wording describing FF 100 mcg once daily as a 'mid' dose only and considers that there are efficacy and safety data to support its description as a 'low/mid dose' which are discussed below.

The MAH view is that FF100 mcg once daily should be considered a starting dose of FF to be used in combination with VI for patients uncontrolled on low to mid dose ICS (plus SABA), as supported by clinical pharmacology and clinical data. The efficacy of FF 50 mcg has been tested on a number of occasions and was not established as an efficacious dose, therefore FF100 mcg once daily is the lowest effective dose.

Although similar bronchodilatory effects were seen for FF100 mcg once daily and FP250 mcg twice daily, and for FF200 mcg once daily and FP 500 mcg twice daily, from a safety perspective a much higher dose of FF would need to be administered (FF 644 mcg/daily) to achieve a similar degree of cortisol suppression to that seen with FP 500 mcg twice daily; thus FF 200 mcg once daily should not be considered a high dose corticosteroid from a systemic safety perspective.

Since FF monotherapy is not available the MAH believed that the clearest way to inform prescribers of the correct strength of RELVAR to use is by the insertion of a table. This table includes the relevant doses of the most commonly used inhaled corticosteroids (ICS) (FP and budesonide) plus short acting beta agonists (SABA) and reflects the patient population recruited to the pivotal RELVAR asthma clinical studies; its purpose is not to promote switching from other ICS/LABAs to RELVAR but to ensure patients not adequately controlled with ICS and 'as needed' SABA are initiated on the most appropriate dose of RELVAR.

Rationale

- Treatment Guidelines

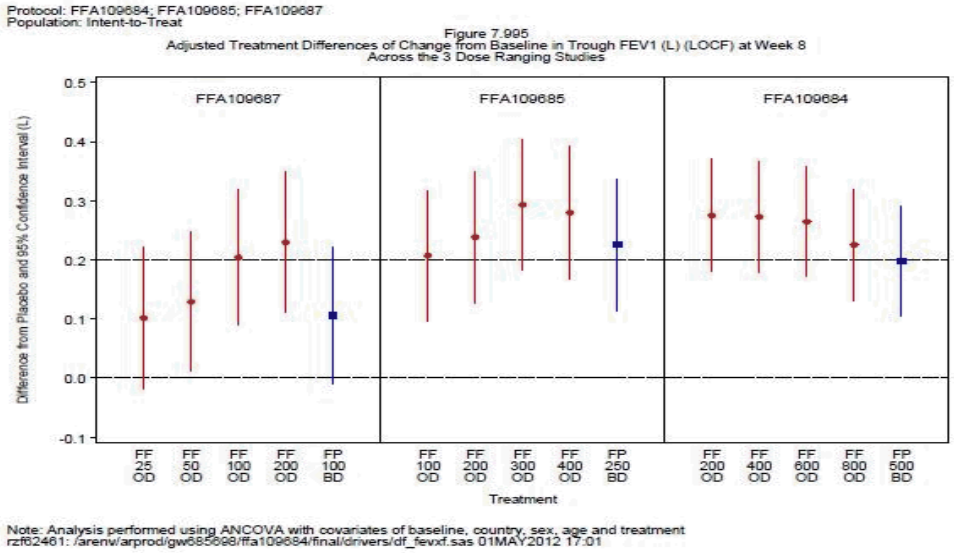
Current global asthma treatment guidelines developed by the Global Initiative for Asthma (GINA) (GINA, 2015) position low dose ICS as doses that are effective without significant risk of side-effects and high doses as those achievable with an acceptable systemic side-effect profile. GINA also classifies the various ICS formulations into low, mid and high doses. High doses are doses of ICS that, with prolonged use, are associated with increased risk of systemic side effects. However, this does not mean ICS doses within each classified category are therapeutically equivalent, although this is often assumed and has lead to the incorrect assertion that efficacy and safety cannot be separated. In clinical practice, the selection of dose should be based on symptom control and patients should be monitored to assess their response to treatment and any side effects. The ICS dose should be titrated to the minimum dose that will maintain good symptom control and minimise exacerbation risk and potential for side effects. The available clinical data, discussed below, support that FF 100 mcg, in combination with the long acting beta agonist, vilanterol (VI), is the lowest effective dose of RELVAR. As only two strengths of FF have been developed in combination with a long acting beta agonist (LABA) and three strengths of FP/salmeterol are available; it is not possible to directly equate one strength of FF/VI as equivalent to one strength of FP/salmeterol. Consistent with this, it is noted that the current version of GINA has 5 steps with ICS/LABA at steps three and four. Thus there is recognition that there are not three strengths of all ICS/LABA combinations available or required.

- Lowest Effective Dose of FF is 100 mcg

One aim of the FF clinical development program was to identify doses of FF that would achieve an acceptable level of clinical efficacy, for both lung function and symptomatic parameters, without compromising the safety profile. Although the dose response to ICS for improved lung function is shallow, it was considered that a single ICS strength would not meet the needs of all asthma patients. Consequently a wide range of FF doses were evaluated to identify the optimal FF doses. Three Phase IIb dose-ranging studies were conducted in subjects symptomatic on short-acting beta2-agonists (FFA109687), low dose ICS (FFA109685) and medium doses of ICS ([FFA109684) and tested a range of doses of FF (from 25 mcg to

800 mcg once daily, dosed in the evening). In these dose-ranging studies, FF was well tolerated at doses up to 600 mcg, while at 800 mcg significant urinary cortisol suppression was observed. Results for different FF doses on trough FEV1 from the three dose ranging studies in subjects with varying severity of asthma are summarised in Figure 1 and show substantial efficacy (>200 mL improvement in trough FEV1) with FF 100 mcg once daily and near maximal efficacy with FF 200 mcg once daily.

Figure 1. Adjusted Treatment Differences From Placebo of Change from Baseline in Trough FEV1 (L) (LOCF) at Week 8 Across FF Dose-Ranging Studies in Asthma



In FFA109687, the FF 50 mcg group failed to meet the pre-defined 200 mL difference from placebo (129 mL [95% CI: 11, 247]), although this difference was statistically significant. A post hoc analysis by baseline lung function confirmed that in subjects with more severe asthma (FEV1 ⩽65% of predicted normal) trough FEV_1 improvements relative to placebo were substantially lower at 50 mcg (36 mL [95% CI: -181, 253]) than at 100 mcg (267 mL [95% CI: 70, 463]) or 200 mcg (190 mL [95% CI: -6, 386]). Based on these data it was concluded that FF 50 mcg once daily is not an adequate dose for patients who are candidates for treatment with an ICS/LABA combination.

The ineffectiveness of FF 50 mcg was confirmed in the FF monotherapy phase III development program. Two studies were conducted with FF 50 mcg once daily (FFA115283 and FFA115285). Both studies were placebo-controlled, parallel group, randomised studies that recruited patients on SABA only or on non ICS controller medication. FFA115283 was a 12 week study comparing FF50 mcg once daily with placebo. FFA115285 was a 24 week study comparing FF50 mcg once daily with placebo and it also included an FP100 mcg twice daily arm. In both studies the primary endpoint was trough FEV1 and the powered secondary endpoint was rescue free 24 hour periods. In FFA115283 statistically significant differences for FF 50 mcg relative to placebo were observed in trough FEV1 (120 mL; p=0.012) and in percentage of rescue-free 24-hour periods over Weeks 1-12 (11.6%; p=0.004) (O'Byrne, 2014). However in FFA115285 the difference in trough FEV1 for FF 50 mcg once daily relative to placebo was 37mL and was not statistically significant (p = 0.430) nor was the difference in the percentage of rescue-free 24-hour periods for FF 50 mcg once daily relative to placebo over Weeks 1-24 significant (treatment difference was 7.8%, p =0.084) (Busse, 2014). In contrast in FFA115285 the difference between FP100 mcg twice daily and placebo was statistically significant for both trough FEV1 (treatment difference 102mL, p=0.030) and rescue- free 24 hour periods (treatment difference 10.6%, p=0.020). The failure to replicate the efficacy of FF 50 mcg once daily in studies FFA115283 and FFA115285 has confirmed that the lowest effective dose of FF in adults and adolescent subjects with asthma is FF100 mcg once daily. Consequently from an efficacy point of view FF/VI

100/25 mcg once daily is a suitable starting dose in adults/adolescents not adequately controlled with ICS and 'as needed' SABA.

- Impact of Pharmacological Differences Between Corticosteroids

It is acknowledged that the potential for confusion in understanding the posology for FF relative to FP may arise due to similarity in their names and not recognising the differences in their pharmacological and physicochemical properties. FF and FP are not pro-drug esters of fluticasone and their efficacy is dependent on the intact molecules. The two molecules have distinct properties with the furoate moiety in FF being responsible for enhanced glucocorticoid receptor binding affinity and longer lung retention compared to FP and other ICS molecules (Daley-Yates, 2015). These features allow FF to be effective when given once daily, at low delivered dose relative to other ICS.

The structural features of FF that give rise to high potency also result in lower systemic exposure. Enhanced potency leads to greater lipophilicity (since the molecular structural features that confer greater potency also confer greater lipophilicity), slower dissolution and absorption of inhaled drug particles with longer retention times in the airways. Once absorbed, more potent ICS such as FF have higher plasma protein binding, lower unbound fractions in plasma and larger volumes of distribution. Such molecules are also good substrates for drug metabolising enzymes and have high systemic clearance, high first pass metabolism and low oral bioavailability of the swallowed dose. All these factors, together with the lower dose that greater potency affords, favour low systemic drug concentrations, thereby providing better targeting of the drug to the site of action and improving the therapeutic index (Daley-Yates, 2015).

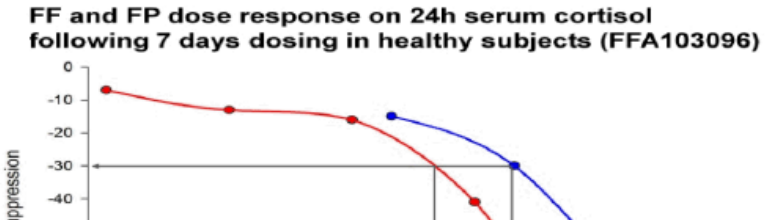
- Systemic Effects of ICS

An HPA axis safety study, in subjects with asthma, showed that both FF 100 mcg once daily and 200 mcg once daily, both in combination with the LABA, vilanterol (VI), had no significant effects on 24 hour serum cortisol, and hence are not high doses of ICS in terms of systemic effects (Allen, 2013b). In a clinical pharmacology study comparing the effect of FF and FP on cortisol supression in healthy subjects (which represents worst case scenario as greater systemic exposure occurs in healthy subjects than in asthmatic subjects), a dose response for cortisol suppression was seen for both FF and FP. FF 100 mcg once daily and 200 mcg once daily resulted in 7% and 13% cortisol suppression, respectively, compared with 15% and 30% cortisol suppression for FP 250 mcg twice daily and 500 mcg twice daily, respectively (Figure 2). The study concluded that a nominal dose of FF 644 mcg/day was equivalent to FP 1000 mcg/day in terms of cortisol suppression (Figure 2).

In addition, a pharmacokinetic/pharmacodynamic model of cortisol suppression has been established over a wide range of systemic FF exposures representing the therapeutic and supratherapeutic range in both patients and healthy subjects (Allen, 2013a). The PK/PD model predicted an FF AUC24 of 1,000 pg • h/mL, several times the exposure associated with FF doses of 100 or 200 mcg/day, would be required to reduce 24-h serum cortisol by 20%. This finding is in agreement with the data from study FFA103096 shown in Figure 2. Therefore the totality of the cortisol suppression data demonstrate that despite its higher potency, FF 200 mcg has similar systemic effects compared with FP 250 mcg twice daily and lower systemic effects compared with FP 500 mcg twice daily and that even the highest FF dose should not be regarded, as a high dose ICS in terms of systemic effects. Furthermore, FF 100 mcg once daily can be deemed a low dose ICS in terms of its systemic effects due to its very low potential for cortisol suppressive effects.

In summary, the dose of FF shown to produce equivalent cortisol suppression to FP 1000 mcg daily was 644 mcg daily which is more than three times the highest licensed dose of FF used in combination with VI.

Figure 2. Comparative dose responses for FF and FP on 24h cortisol suppression



- Patient Populations Recruited to Pivotal Studies

The table proposed for inclusion in the SPC reflects the population recruited to the pivotal studies. In study HZA106827 all subjects had to be using a low to mid dose ICS or a low dose ICS/ LABA for at least 12 weeks prior to Visit 1 and maintained on a stable ICS dose (FP 100–250 mcg twice daily or equivalent) for at least 4 weeks prior to Visit 1 to be eligible for enrolment.

Table 1 provides details of doses of commonly prescribed ICS combination medication which were permitted per protocol prior to enrolment into HZA106827.

These doses are appropriate for asthma patients with mild to moderate disease. During run-in, the most commonly used ICS was FP (55%) with a mean total daily dose of 334.3 mcg, followed by budesonide (24%) with a mean total daily dose of 482.7 mcg and beclomethasone dipropionate (14%) with a mean total daily dose of 267.3 mcg.

Table 1. ICS entry medication in HZA106827

Asthma Therapy	Entry Medication HZA106827 Total Daily Dose
ICS	
Fluticasone propionate CFC/HFA MDI	200mcg to 500mcg
Fluticasone propionate DPI	200 to 500mcg
Beclomethasone dipropionate DPI	400 to 800mcg
Beclomethasone dipropionate HFA MDI (QVAR)	200mcg to 400mcg
Beclomethasone dipropionate HFA MDI (Clenil)	400mcg to 1000mcg
Budesonide DPI/MDI	400 to 800mcg
Flunisolide	1000mcg to 2000mcg
Flunisolide HFA MDI	320 to 640mcg
Triamcinolone acetonide MDI	1000 to 2000mcg
Mometasone furoate DPI	200 to 400mcg
Ciclesonide HFA MDI	100mcg to 400mcg

In study HZA106829 all subjects had to be using high dose ICS (or mid dose ICS/LABA) for at least 12 weeks prior to Visit 1 and as a consequence subjects on ICS only were maintained on a stable ICS dose (FP 500mcg twice daily or equivalent) for 4 weeks prior to Visit 1. Table 2 provides details of doses of commonly prescribed ICS medication which were permitted per protocol prior to enrolment into HZA106829. These doses are appropriate for asthma patients with moderate to severe disease. The most frequently used ICS

during the run-in period of the study was FP with 61% of subjects overall. The mean daily dose of FP was similar over the three groups (ranging from 551.1 mcg in the FF 200 group to 583.2 mcg in the FF/VI 200/25 group).

Table 2. ICS entry medication in HZA106829

Asthma Therapy	Entry Medication HZA106829 Total Daily Dose
ICS	
Fluticasone propionate CFC/HFA MDI	≥1000mcg
Fluticasone propionate DPI	≥1000mcg
Beclomethasone dipropionate DPI	≥1200mcg
Beclomethasone dipropionate HFA MDI (QVAR)	≥800mcg
Beclomethasone dipropionate HFA MDI (Clenil)	≥1200mcg
Budesonide DPI/MDI	≥1600mcg
Flunisolide	>2000mcg
Flunisolide HFA MDI	>640mcg
Triamcinolone acetonide MDI	≥1750mcg
Mometasone furoate DPI	≥800mcg
Ciclesonide HFA MDI	≥800mcg

MAH's conclusion

GSK believed that FF100 mcg once daily should be considered a starting dose of FF to be used in combination with VI for patients uncontrolled on low to mid dose ICS (plus SABA), as supported by clinical pharmacology and clinical data. The efficacy of FF 50 mcg has been tested on a number of occasions and was not established as an efficacious dose in adults and adolescents, therefore FF100 mcg once daily is the lowest effective dose. Although similar bronchodilatory effects were seen for FF100 mcg once daily and FP250 mcg twice daily, and for FF200 mcg once daily and FP 500 mcg twice daily, from a safety perspective a much higher dose of FF would need to be administered (FF 644 mcg/daily) to achieve a similar degree of cortisol suppression to that seen with FP 500 mcg twice daily; thus FF 200 mcg once daily should not be considered a high dose corticosteroid from a systemic safety perspective.

GSK agrees with the Agency that prescribers should be aware of the potency differences between FF and FP. Since FF monotherapy is not available in the EU the company proposes to include a table instructing prescribers as to which strength of FF/VI is appropriate for eligible patients to step up to if they are not adequately controlled on ICS and 'as needed' SABA. This table includes the relevant doses of the most commonly used inhaled ICS plus SABA and reflects the patient population recruited to the pivotal RELVAR asthma clinical studies. The purpose of the table is not to promote switching from other ICS/LABAs to RELVAR, but to ensure patients not adequately controlled with ICS and 'as needed' SABA are initiated on the most appropriate dose of the combination, and has been revised to address the Agency's concerns. In consideration of both the efficacy and safety (cortisol suppression) data provided herein, GSK has proposed additional changes to the posology section (with supportive data provided in Section 5.1). These changes are based on the data generated in the Relvar program and are intended to aid prescribers in dose selection, while also addressing the concerns raised by the Agency.

Proposed amendments to the SmPC by MAH

Following amendments have been proposed (New text is shown in *italics*, deleted text in ~~strikethrough~~)

Section 4.2. Dosage and Administration

~~A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long acting beta2 agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.~~

~~Patients should be regularly reassessed by a healthcare professional so that the strength of fluticasone furoate/vilanterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.~~

~~Relvar Ellipta 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting beta2-agonist.~~

The maximum recommended dose is Relvar Ellipta 184/22 micrograms once daily. Patients with asthma should be given the strength of Relvar Ellipta containing the appropriate fluticasone furoate (FF) dosage for the severity of their disease *(see Table 1). If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.*

Table 1 Recommended dose of Relvar Ellipta for patients uncontrolled on an inhaled corticosteroid and a short acting beta2-agonist

For patients uncontrolled on fluticasone propionate 100 micrograms to 250 micrograms twice daily or equivalent (budesonide 200-400 micrograms twice daily) plus short acting $beta_2$-agonist	One inhalation of Relvar Ellipta 92/22 micrograms once daily
For patients uncontrolled on fluticasone propionate 500 micrograms twice daily or equivalent (budesonide 600-800 micrograms twice daily) plus short acting $beta_2$-agonist	One inhalation of Relvar Ellipta 184/22 micrograms once daily

Patients should be regularly reassessed by a healthcare professional so that the strength of fluticasone furoate/vilanterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Prescribers should be aware that fluticasone furoate is a novel inhaled corticosteroid with different dosing requirements to other inhaled corticosteroids including fluticasone propionate (see Section 5.1)

Prescribers should be aware that in patients with asthma, *in terms of effects on lung function and symptomatic endpoints,* fluticasone furoate *92* micrograms once daily is *similar* to fluticasone propionate 250 micrograms twice daily, while *fluticasone furoate 184* micrograms once daily is *similar to fluticasone propionate 500 micrograms twice daily. In terms of cortisol suppression, fluticasone furoate 184 micrograms once daily is similar to fluticasone propionate 250 micrograms twice daily (see Section 5.1).*

Section 5.1. Pharmacodynamic Effects

Fluticasone furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent antiinflammatory activity. The precise mechanism through which fluticasone furoate affects asthma and COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines involved in inflammation). *In vitro the binding affinity of fluticasone furoate for the human glucocorticoid receptor is approximately 30 times that of dexamethasone and 1.7 times that of fluticasone propionate. Fluticasone furoate also has a greater cellular accumulation and a slower rate of cellular efflux compared with other glucocorticoids including fluticasone propionate, consistent with greater tissue retention. This higher glucocorticoid receptor binding affinity and longer tissue retention results in a greater topical efficacy in the airways for fluticasone furoate compared with fluticasone propionate. In clinical studies, fluticasone furoate 92 micrograms once daily was similar to fluticasone propionate 250 micrograms twice daily and fluticasone furoate 184 micrograms once daily was similar to fluticasone propionate 500 micrograms twice daily in terms of improvements in lung function and symptom control. In patients with asthma or COPD fluticasone furoate 92 and 184 micrograms once daily did not produce detectable cortisol suppression. In healthy subjects, where greater systemic exposure occurred, fluticasone furoate 100 and 200 micrograms once daily produced a dose-related decrease in 24hour serum cortisol of 7% and 13%, respectively. A greater effect was seen with fluticasone propionate 250 and 500 micrograms twice daily which reduced 24 hour serum cortisol by 15% and 30%, respectively.*

2.2.1. Discussion

It is acknowledged that the current wording of Section 4.2 may require some amendments. However, the new text proposed by the MAH is not agreed and some modifications should be included in order to reflect clearly the patients in which to initiate Relvar/Revinty Ellipta.

It is stated that *"a starting dose of Relvar/Revinty Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta2-agonist. If patients are inadequately controlled on Relvar/Revinty Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control".* However, a few lines below, the following statement: *"prescribers should be aware that in patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily, while FF 200 micrograms once daily is approximately equivalent to FP 500 micrograms twice daily"* has been included. It should be noted that these doses are equivalent to medium to high daily doses of inhaled corticosteroids *(Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014*), which is not consistent with the previous statement. As no appropriate RELVAR "low-dose" strength of fluticasone furoate is currently available for initial treatment of asthma when a ICS/LABA combination is indicated, starting with the medium ICS dose in RELVAR instead of starting with a low dose ICS available in other ICS/LAMA combinations may pose a risk of overtreatment and pneumonia. In summary, "low to mid" should be replaced by "medium" according to the established equivalences with FP as follows:

A starting dose of Relvar/Revinty Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a ~~low to mid~~ ***medium*** *dose of inhaled corticosteroid in combination with a long-acting beta2-agonist. If patients are inadequately controlled on Relvar/Revinty Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.*

The deletion of the equivalence between FF and PF is not agreed, since prescribers should be aware that in patients with asthma, potency of this new steroid product is not equivalent to fluticasone propionate. This is particularly important regarding the similarity in the name of both active principles that may lead to the assumption that the two compounds are the same. On the other hand, the indication approved for RELVAR LABA/ICS combination is "for patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta2-agonists", but not for patients not adequately controlled with other inhaled corticosteroids. Therefore, the correspondence included in section 4.2 should be restricted to the equivalence in potency with doses of ICS in both directions (not only from other ICSs to RELVAR), and the inclusion of a table with a "switching procedure" from any ICS to RELVAR is not endorsed.

~~For patients uncontrolled on fluticasone propionate 100 micrograms to 250 micrograms twice daily or equivalent (budesonide 200-400 micrograms twice daily)~~	~~Relvar/Revinty 92/22~~
~~For patients uncontrolled on fluticasone propionate 500 micrograms twice daily or equivalent (budesonide 600-800 micrograms twice daily)~~	~~Relvar/Revinty 184/22~~

The following amended statement may contribute to minimize possible medication errors and consequently, it should be maintained and completed as follows:

"Prescribers should be aware that in patients with asthma, fluticasone furoate (FF) 100 micrograms once daily ***(medium dose)*** *is approximately equivalent to* ***medium doses of*** *fluticasone propionate (FP) (250 micrograms twice daily)* ***or equivalent (budesonide 400-800 micrograms twice-daily)****, while FF 200 micrograms once daily* ***(high dose)*** *is approximately equivalent to* ***high doses of*** *FP* ***(****500 micrograms twice daily****) or equivalent (budesonide 800-1600 micrograms twice-daily). Currently there are no RELVAR dose strengths containing low doses of fluticasone furoate and no equivalence with low doses of other ICS can be established."*

The MAH proposal to consider FF 100 mcg once daily as a "low/mid" dose instead of a "mid dose" is not accepted due to the following considerations:

Data from a head to head comparison between FF/VI 100/25 and FP/salmeterol 250/50 BD (previously classified as medium dose by the GINA) in a 6 month parallel group phase III study (HZA113091, Woodcock A et al. Chest 2013) submitted during the evaluation of Relvar (See EPAR), which randomised 806 patients uncontrolled on mid dose ICS (FP 250 mcg bid or equivalent) showed that the efficacy of once-daily FF/VI was similar to bid FP/SAL in improving lung function in patients with persistent asthma. Both treatments resulted in an improvement in lung function from baseline over 24 h, with a LS mean increase from baseline in weighted mean FEV1 (primary efficacy endpoint) of 341 mL for the FF/VI group and 377 mL for the FP/salmeterol group. The adjusted mean treatment difference of -37 mL between the groups was not statistically significant (p=0.162). Trough FEV1 was measured as a secondary endpoint at 24 hours after the last dose of FF/VI and 12 hours after the last dose of FP/salmeterol. Subjects in the FP/salmeterol group achieved a LS mean change from baseline in trough FEV1 of 300 mL and subjects in the FF/VI group 281 mL, the difference in adjusted mean of 19 mL was not statistically significant (p=0.485). There was no statistically significant difference in the "Other" endpoints of AQLQ score (adjusted treatment difference 0.09; 95% CI -0.03, 0.21; p=0.130) or ACT score (adjusted treatment difference 0.2; 95% CI -0.2, 0.7; p=0.310). The incidence of asthma exacerbations was low and similar across the treatment groups, with the highest percentage of on-treatment events in the FP/salmeterol group (12 subjects, 3%) compared with the FF/VI group (10 subjects, 2%). One subject in the FF/VI group vs. 2 subjects in the FP/salmeterol group were hospitalised due to their asthma exacerbations.

The incidence and type of on-treatment AEs with FF/VI (213 subjects [53%]) was similar compared with FP/salmeterol (198 subjects [49%]). Of these, AEs for 19 subjects [5%] in the FF/VI group were considered related to treatment; in the FP/salmeterol group 15 subjects [4%] had AEs considered drug-related. No clinically relevant effects on 24-h urine cortisol excretion were found. Analysis of urine cortisol excretion for showed that the FF/VI to FP/salmeterol urine cortisol ratio of 0.85 was not statistically significant (p=0.075).

Overall, data from the direct comparison between FF/VI 100/25 OD versus FP/salmeterol 250/50 BD (considered medium dose of CSI) showed similar efficacy and safety profiles.

Moreover, recruited population in the pivotal study HZA106827 corresponds to uncontrolled patients with low to mid doses of CSI. According to the step-wise approach reflected in the GINA as well as the authorized indication for Relvar, FF 100 mcg OD can't be considered as a low dose.

Based on it, consideration of FF 100 mcg once daily as "a low dose" is not supported and Section 4.2 should be maintained as previously proposed (See PI, document attached).

Additionally, the MAH states that although similar bronchodilatory effects were for FF200 mcg once daily and FP 500 mcg twice daily, from a safety perspective a much higher dose of FF would need to be

administered (FF 644 mcg/daily) to achieve a similar degree of cortisol suppression to that seen with FP 500 mcg twice daily; thus FF 200 mcg once daily should not be considered a high dose corticosteroid from a systemic safety perspective (Figure 2). Taking into consideration this data, new changes in Section 5.1 have been proposed.

This information is not considered to provide relevant information to the prescribers (Guideline on Summary of Product Characteristics, Volume 2C NTA) and data comes from a single phase I study (FFA103096) in which FF 100 mcg once daily and 200 mcg once daily resulted in 7% and 13% cortisol suppression, respectively, compared with 15% and 30% cortisol suppression for FP 250 mcg twice daily and 500 mcg twice daily (See figure 2).

Results from HZA106829 phase III study with uncontrolled patients on moderate to high doses of ICS (See table 2) which would constitute the target population of Relvar 200 mcg FF, confirmed that 24-hour, free cortisol urinalysis found no significant differences, with ratios to baseline of 0.91, 0.98 and 0.84 for FF 200 OD, FF/VI 200/25 OD and FP 500 BD, respectively. Furthermore, as all subjects entered the study on moderate to high doses of ICS, a decrease in free cortisol versus baseline is not expected (HZA106829 study report).

Consequently, the text included under Section 5.1 as well as the comparisons in terms of cortical suppression under Section 4.2 should be removed.

Conclusions

- Consideration of FF 100 mcg once daily as "a low dose" is not supported and Section 4.2 should be maintained as previously proposed with some minor changes.
- New information included in Section 5.1 is not accepted since it is not considered to provide relevant information to the prescribers and data comes from a single phase I study.

The MAH disagreed with the CHMP recommendation for minor changes to section 4.2 of the SmPC to reflect that the 100 mcg FF dose should not be considered as 'low-to-mid' but as 'medium' instead and with all the consequential PI changes (see above discussion).

In conclusion the CHMP adopted a negative opinion for this worksharing application.

3. Overall conclusion and impact on the benefit/risk balance

Consideration of fluticasone furoate (FF) 100 mcg once daily as a low dose is not supported; relevant changes to section 4.2 of the SmPC are not accepted.

Newly proposed information in section 5.1 of the SmPC is not accepted, either, since it is not considered to provide relevant information to the prescribers and data comes from a single phase I study.

The benefit-risk balance of Relvar Ellipta, Revinty Ellipta, remains positive in the approved indication.

4. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation refused		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	n/a

Update of section 4.2 of the SmPC to clarify the information to prescribers on the initial dose of Relvar/Revinty based on the corticosteroid dose equivalence.

☒ is not recommended for approval.

This worksharing procedure leads to no amendments to the Product Information.

Grounds for refusal:

The proposed update to the section 4.2 of the SmPC including the reference to the fluticasone furoate (FF) 100 mcg once daily as "a low dose" and the addition of table with recommended dose of Relvar/Revinty Ellipta for patients uncontrolled on an inhaled corticosteroid and a short acting beta2-agonist is not supported.

The MAH proposal to consider FF 100 mcg once daily as a "low/mid" dose instead of a "mid dose" is not accepted due to the following considerations:

The recruited population in the pivotal study HZA106827 corresponds to uncontrolled patients with low to mid doses of CSI. According to the step-wise approach reflected in the GINA as well as the authorized indication for Relvar, FF 100 mcg OD can't be considered as a low dose.

New information on fluticasone furoate pharmacodynamic properties included in the section 5.1 is not accepted since it is not considered to provide relevant information to the prescribers and comes from a single phase I study (FFA103096) in which FF 100 mcg once daily and 200 mcg once daily resulted in 7% and 13% cortisol suppression, respectively, compared with 15% and 30% cortisol suppression for FP 250 mcg twice daily and 500 mcg twice daily.

Results from HZA106829 phase III study with uncontrolled patients on moderate to high doses of ICS which would constitute the target population of Relvar 200 mcg FF, confirmed that 24-hour, free cortisol urinalysis found no significant differences, with ratios to baseline of 0.91, 0.98 and 0.84 for FF 200 OD, FF/VI 200/25 OD and FP 500 BD, respectively. Furthermore, as all subjects entered the study on moderate to high doses of ICS, a decrease in free cortisol versus baseline is not expected (HZA106829 study report).

Additionally, clinical data from the direct comparison between FF/VI 100/25 OD versus FP/salmeterol 250/50 BD (considered medium dose of CSI) showed similar efficacy and safety profiles.

Consequently, FF100mcg once daily is considered to be a "mid dose" of corticosteroids.