LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Duohal
(salmeterol (as xinaofate) and fluticasone propionate)

SE/H/1599/01-02/DC

This module reflects the scientific discussion for the approval of Duohal. The procedure was finalised on 2016-12-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Duohal, 25/125 µg/dose and 25/250 µg/dose, pressurised inhalation, suspension, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Cipla Europe (EU) Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, FR as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seretide Evohaler, 25/125 µg/dose and 25/250 µg/dose, pressurised inhalation, suspension, authorised in UK since 2000, with Glaxo Wellcome UK Limited as marketing authorisation holder.

The reference product used in the bioequivalence/pharmacokinetic studies is Seretide Evohaler, 25/250 µg/dose, pressurised inhalation, suspension from UK with Glaxo Wellcome UK Limited as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

According to the guideline "*Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents"* (CPMP/EWP/4151/00 rev 1 guideline) a step-wise approach should be considered when demonstrating therapeutic equivalence. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data. Since all criteria for pharmaceutical properties cannot be fulfilled, pharmacokinetic, and or pharmacodynamic, clinical efficacy and safety data is required to establish therapeutic equivalence.

IV.1 Pharmacokinetics

In total three pivotal pharmacokinetic studies have been submitted. All studies were conducted with the 25 µg/250 µg strength, comparing the test Salmeterol/Fluticasone pMDI 25 µg/250 µg per actuation with the reference Seretide Evohaler 25 µg/250 µg per actuation, both administered as 2 inhalations in healthy volunteers under fasting conditions. The choice to use the highest strength has been justified based on the FPM for test and reference product. The in vitro data show that both strengths are similar with almost no deviation in fine particle mass from the reference product. Further, data has been provided to show that the batches used are representative for the product applied for and for the reference product on the market.

The studies were conducted in healthy volunteers which is acceptable as there is no flow-rate dependency for an inhalation spray.

In all studies salmeterol and fluticasone was analysed using adequately validated LC/MS/MS methods.

Study PRC/CRD/07/10 was a two-way, single-dose, crossover bioequivalence study conducted without active charcoal blockade to evaluate total systemic safety of both active substances. Given the negligible oral bioavailability of fluticasone the study could also be used in the efficacy evaluation of fluticasone. For fluticasone bioequivalence was demonstrated for both AUC and Cmax. For salmeterol bioequivalence was demonstrated regarding AUC but not for Cmax. Hence, the results show similarity in both safety and efficacy for fluticasone. For salmeterol, an additional pharmacodynamic equivalence study has been conducted to support safety given the higher Cmax obtained with the test product in the bioequivalence study.

Study PRC/CRD/13/11 was a two-treatment, four-period, single-dose, crossover bioequivalence study using the Aero Chamber and the Volumatic Spacer. The study was conducted without active charcoal. The exposure of salmeterol was increased 2-fold and the exposure of fluticasone was increased by approximately 60% after administration with the Volumatic spacer compared to the Aerochamber. Similar results were obtained for the test and the reference product and bioequivalence was demonstrated with both spacers.

Study PRC/CRD/03/12 was a two-treatment, four-period, single-dose, replicate crossover bioequivalence study conducted without active charcoal in order to evaluate similarity in lung-deposition in support of efficacy of salmeterol. Bioequivalence was shown.

PK summary and conclusion
Salmeterol: Bioequivalence was demonstrated when administered with active charcoal and hence similarity in lung-deposition, which reflects efficacy, can be concluded. When administered without active charcoal bioequivalence was only demonstrated for AUC but not for Cmax. Additional PD-data have been submitted to support systemic safety given the higher Cmax. Bioequivalence was also demonstrated when using the AeroChamber Plus VHC or a Volumatic spacer (administration without active charcoal).

Fluticasone: Bioequivalence was demonstrated after administration without active charcoal blockade. Given the negligible oral bioavailability of fluticasone the main part of the dose will be absorbed via the lungs and similarity regarding both safety and efficacy can be concluded in the study without charcoal blockade. Bioequivalence was also demonstrated when after the AeroChamber Plus VHC or a Volumatic spacer (administration without active charcoal).

The pharmacokinetic documentation is sufficient.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Duohal.

The applicant has submitted an RMP (Version 1) with DLP 1 October 2015 and final sign off, 6 November 2015. The following safety concerns are listed:

Summary of safety concerns	
Important identified risks	• Hoarseness/dysphonia • Arthralgia • Myalgia • Headache • Candidiasis of the mouth and throat • Bronchitis • Pneumonia • Hypokalemia
Important potential risks	• Tremors • Palpitations • Cardiac arrhythmias • Paradoxical bronchospasm • Adrenal suppression • Systemic effects in paediatric population
Important missing information	• No studies of the effect on the ability to drive and use machines have been performed. • There are no data available for use of Salmeterol and Fluticasone propionate pressurised inhalation suspension in patients with hepatic impairment • There are no data in humans regarding effect of Salmeterol and Fluticasone propionate pressurised inhalation suspension on fertility. • It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

The RMP is approved.

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 RMS;
- 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 dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Salmeterol/Fluticasone Cipla (Seroflo) SE/H/1208/01-02/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns Duohal a pressurised metered dose inhaler (pMDI) containing the active products fluticasone propionate and salmeterol xinafoate and a propellant Norflurane (HFA-134a) at two different strengths, 25/125 µg/dose and 25/250 µg/dose.

The application for Duohal is a hybrid application and evaluated in a step-wise approach according to the guideline CPMP/EWP/4151/00 Rev.1 (OIP-guideline). The base in the evaluation is the pharmaceutical properties. Comparative *in vitro* studies of the applied product and the reference product have been performed however the data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based on *in vitro* data, and *in vivo* studies are needed for demonstration of therapeutic equivalence.

To support this application with respect to clinical aspects, the Applicant has submitted three pharmacokinetic studies and one pharmacodynamic study. All studies were performed with the 25/250 µg/dose strength. Extrapolation of the results to the lower strength of 25 µg/125 µg is acceptable based on the FPM for test and reference product. Furthermore, the batches (both test and reference products) used in the three pharmacokinetic studies and the pharmacodynamic study are representative for the product applied for and for the reference product on the market.

According to the OIP-guideline, pharmacokinetic data may be used to support efficacy and safety. Efficacy is supported by a pulmonary deposition study, which means a bioequivalence study with concomitant charcoal. A bioequivalence study without active charcoal is needed to support total systemic safety. For substances with negligible oral bioavailability, like fluticasone, a study without active charcoal is sufficient to support both efficacy and safety.

Salmeterol: Bioequivalence was demonstrated when administered with active charcoal and hence similarity in lung-deposition, which reflects efficacy, can be concluded. When administered without active charcoal bioequivalence was only demonstrated for AUC but not for Cmax. Additional PD-data have been submitted to support systemic safety given the higher Cmax. Bioequivalence was also demonstrated when using the AeroChamber Plus VHC or a Volumatic spacer.

Fluticasone: Bioequivalence was demonstrated after administration without active charcoal blockade. Given the negligible oral bioavailability of fluticasone the main part of the dose will be absorbed via the lungs and similarity regarding both safety and efficacy can be concluded in the study without charcoal blockade. Bioequivalence was also demonstrated when using the AeroChamber Plus VHC or a Volumatic spacer.

A pharmacodynamic study was performed to support the safety of salmeterol. The highest strength comparing two supra therapeutic doses 150/1500 mcg and 300/3000 mcg was used of the test and reference products to optimise the possibility to detect a dose response between doses. From a clinical safety point of view it is acceptable to use the highest strength is the

pharmacodynamic study. For the primary end-point, heart rate AUC0-4hrs, equivalence is convincingly demonstrated. Heart rate is the most sensitive safety parameter for picking up the pharmacodynamic effects of salmeterol. The other safety parameters (secondary endpoints) are not as sensitive as heart rate but show further support that the test and reference products are equivalent. Thus, with regard to safety of salmeterol it can be concluded that the test products is equivalent to the reference product.

To summarise, therapeutic equivalence has been convincingly demonstrated.

In the proposed indication, which is supported, adults and adolescents 12 years and older are included.
This application concerns a new pressurised metered dose inhaler (pMDI). The pMDI device has no resistance to airflow and asthma subjects of all ages are able to generate flow rates of 30-60 L/min, a range over which the *in vitro* performance of the test and reference product are comparable. Furthermore, the handling of the test spray and the originator spray is similar. The posology recommendation is the same in adults and adolescents 12 years and older which supports the approval of adolescents 12 years and older for the test product. The PK studies and the PD study were conducted in healthy volunteers which is reasonable when considering the adolescent group (12 years and older). With respect to fluticasone it is children below 12 years who are the most vulnerable individuals when considering the risk of growth retardation and this group of children (below 12 years) is not included. In addition, there are precautionary statements in the SmPC regarding the risk of growth retardation which cover this aspect. Thus, an indication including adults and adolescents 12 years and older is recommended.

To conclude, the product is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Duohal, 25 µg /125 µg/dose and 25 µg /250 µg/dose, pressurised inhalation suspension, was positively finalised on 2016-12-08.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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