Public Assessment Report
Scientific discussion

Salmeterol/Fluticasone Cipla
(salmeterol xinafoate, fluticasone propionate)

SE/H/1208/01-02/DC

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasone Cipla. The procedure was finalised at 2014-03-12. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Salmeterol/Fluticasone Cipla, 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, ELC Group s.r.o., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, DE, EL, IS, LU and SK as concerned member states (CMS). The application was withdrawn from CMS PL during the clock-stop period.

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 approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Salmeterol/Fluticasone Cipla is presented in the form of a pressurised inhalation, suspension containing 25 micrograms of salmeterol (as salmeterol xinafoate) and 125 or 250 micrograms of fluticasone propionate (delivered from the valve). This is equivalent to 21 micrograms of salmeterol and 110 or 220 micrograms of fluticasone propionate delivered from the actuator (delivered dose). The only excipient is Norflurane (HFA 134a). The suspension is filled in aluminium canisters with a suitable metering valve and a polypropylene actuator with dust cap having dose indicator in a sealed pouch containing desiccant.

II.2 Drug Substances

Salmeterol xinafoate has a monograph in the Ph Eur.

Salmeterol xinafoate is a white or almost white powder which is practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol and practically insoluble in methylene chloride. The structure of drug substance has been adequately proven and its physico-chemical properties sufficiently described. Relevant information is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.
Fluticasone propionate has a monograph in the Ph Eur. Fluticasone propionate is a white or almost white powder which is practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent). The structure of "drug substance" has been adequately proven and its physico-chemical properties sufficiently described. The structure of fluticasone propionate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Salmeterol/Fluticasone Cipla, 25/125 µg/dose and 25/250 µg/dose, pressurised inhalation suspension is formulated using norflurane (HFA 134a) as excipient which is controlled in accordance with a justified in-house specification. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance and the requirements in the guideline EMEA/CHMP/QWP/49313/2005 Corr for inhalation products.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30°C.

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 Pharmacokinetic data in support of efficacy and safety

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. It may be acceptable to extrapolate the results from a pharmacokinetic study on one strength to another strength if the strength investigated is considered as worst case, i.e. the strength deviating most in fine particle mass (FPM) from the reference product. 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 an adequately validated LC/MS/MS method.

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 with 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 Pharmacodynamic data in support of safety
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 and that the test product is not worse than the reference product.

IV.3 Discussion on the clinical aspects
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 and that the test product is not worse than the reference product.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns Salmeterol/Fluticasone Cipla a new 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 Salmeterol/Fluticasone Cipla 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. Based on the results from the studies, 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.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Salmeterol/Fluticasone Cipla, 25/125 µg/dose and 25/250 µg/dose, pressurised inhalation, suspension is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Salmeterol/Fluticasone Cipla, 25/125 µg/dose and 25/250 µg/dose, pressurised inhalation, suspension was successfully finalised on 2014-03-12.
Public Assessment Report – Update

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