LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zoreeda
(salmeterol (as xinafoate) and fluticasone propionate)

SE/H/1537/01-02/DC

This module reflects the scientific discussion for the approval of Zoreeda. The procedure was finalised on 2016-01-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Zoreeda, 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 NV, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, DE, EL, IS, LU, SK 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 approved indications, see the Summary of Product Characteristics.

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.

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. The choice to use the highest strength has been justified based on the FPM for test and reference product.

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

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.

Pharmacodynamic data in support of safety
Study PRC/CRD/02/11 was a pharmacodynamic study performed to support the safety of salmeterol using the highest strength. This was a randomised, double-blind, placebo controlled, 5-way cross-over study in healthy, adult, male human subjects (n=30) comparing two supra therapeutic doses 150/1500 mcg and 300/3000 mcg of the test and reference products. Supra therapeutic doses, 150 mcg (LD) and 300 mcg (HD) of salmeterol, were used in this study to optimise the possibility to detect a dose response between doses.

The primary endpoint was average heart rate AUC 0-4 hrs and secondary endpoints were increase in plasma glucose, decrease in serum potassium, blood pressure, maximum QTc interval (0-4 hrs). The primary and secondary endpoints and safety assessments are considered relevant since the use of LABAs at high doses are associated with cardiovascular effects including heart rate, tremor, palpitations, changes in plasma blood glucose and potassium concentrations. It is emphasised, that the most sensitive safety parameter is considered to be average heart rate.

Similarity was shown for heart rate within the equivalence limits of ± 4 bpm) following administration of 150/1500mcg and 300/3000mcg. The study was sensitive enough to pick up the difference between the two used doses since a dose related increase in heart rate was noted. The relative potency was 0.95 with a CI of 0.71-1.25.

To conclude, for the primary end-point, heart rate AUC0-4hrs, equivalence is convincingly demonstrated.

Population to be treated
The reference product Seretide is approved for adults and adolescents from 12 years of age. All three pivotal studies presented in this application are conducted with adult subjects. Extrapolation from adults to adolescents was justified based on four criteria:
1) The posology is the same in adults and adolescents
2) PK data is similar in subjects of varying ages with the reference product

3) Asthma treatment guidelines indicating that asthma treatment recommendations in adults and adolescent subjects are comparable
4) The MDI device is flow independent across both age groups.

IV.1 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 Zoreeda. The following safety concerns are listed:

Table: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions, including anaphylactic reactions • Angina pectoris • Serious respiratory-related events and death • Cardiac arrhythmias • Paradoxical bronchospasm • Systemic effects of inhaled corticosteroid (Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression) • Pneumonia in patients with COPD
Important potential risks	• Adrenal suppression • Off-label use in children • Off-label use in COPD
Important missing information	• Patients with hepatic impairment • It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk. • Information on children aged 4 to 11 years

The RMP is approved

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 25 micrograms /125 micrograms /dose pressurised inhalation, Suspension SE/H/1208/01/DC (trade name in RMS: Salmeterol Fluticason Cipla)
and
Salmeterol/Fluticasone 25 micrograms /250 micrograms /dose pressurised inhalation, Suspension SE/H/1208/02/DC (trade name in RMS: Salmeterol Fluticason Cipla)

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Zoreeda pressurised inhalation, suspension 25 µg /125 µg/dose and 25 µg /250 µg/dose 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 Zoreeda, 25/125 µg/dose and 25/250 µg/dose, pressurised inhalation, suspension was positively finalised on 2016-01-12.

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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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