COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Salmeterol/Fluticasonpropionaat Elpen 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose inhalation powder, pre-dispensed

(salmeterol xinafoate/fluticasone propionate)

NL/H/5709/002-003/DC

Date: 6 February 2023

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasonpropionaat Elpen 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose inhalation powder, pre-dispensed. The procedure was finalised at 22 May 2013 in Sweden. After a transfer on 22 November 2022, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

ELPEN Pharmaceutical Co. has applied for a marketing authorisation for Salmeterol/Fluticasonpropionaat Elpen 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose inhalation powder, pre-dispensed claiming essential similarity to Seretide Diskus, inhalation powder, pre- dispensed, 50 microgram/250 microgram/ dose, marketed in Sweden by Glaxo Smithkline AB. The product contains salmeterol xinafoate/fluticasone propionate as active substances. For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Salmeterol/Fluticasonpropionaat Elpen is presented in the form of inhalation powder, pre-dispensed containing salmeterol xinafoate corresponding to 50 microgram salmeterol and fluticasone propionate 250 or 500 microgram per dose. Lactose monohydrate is used as excipient. The system consists of an inhalation device and Al/Al double-blister strips containing fluticasone propionate blended with lactose in one blister and salmeterol xinafoate blended with lactose in a second blister. One double-blister strip is withdrawn from the canister, loaded into the inhaler and the upper foil is removed as to reveal the dose. The dose is subsequently emitted when the patient inhales through the mouthpiece of the device.

II.2 Drug Substance

Both salmeterol xinafoate and fluticasone propionate have a monograph in the Ph Eur.

Salmeterol xinafoate is a white or almost white powder which is soluble in ethanol and practically insoluble in water. The structure has been adequately proven and its physico-chemical properties sufficiently described. 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 is a white or almost white powder which is slightly soluble in alcohol and practically insoluble in water. The structure has been adequately proven and its physico-chemical properties sufficiently described. 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/Fluticasonpropionaat Elpen 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose inhalation powder, pre-dispensed is formulated using one excipient which is described in the current Ph Eur. Lactose used in the product is of animal origin. TSE declaration is submitted confirming that the milk used is from healthy animals.
The product development has taken into consideration the physico-chemical characteristics of the active substance.
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 25°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

IV.1 Introduction

According to the OIP guideline, a step-wise approach should be considered when demonstrating therapeutic equivalence. The quality data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based solely on *in vitro* data and *in vivo* studies are needed for demonstration of therapeutic equivalence. As a second step, pharmacokinetic documentation may be used to support efficacy and safety.

IV.2 Pharmacokinetics supporting efficacy

Equivalent efficacy of both fluticasone and salmeterol is supported by PK data. Bioequivalence was demonstrated between the 50 µg/500µg test formulation and the reference Seretide when administered as a 50-500µg/inhalation single-dose together with active charcoal in healthy volunteers. The choice to perform the study in healthy volunteers is satisfactory as

the FPD of the formulations are not flow-dependent within the 30-90 L/min range. It is acceptable to extrapolate the results from a pharmacokinetic study on one strength to another strength if the strength investigated is considering as worst case, i.e. the strength deviating most in FPD from the reference product. With this approach, the result may be extrapolated to the 50 µg /250 µg strength based on the quality documentation.

IV.3 Pharmacokinetics supporting safety

Equivalent safety of both fluticasone and salmeterol is supported by PK data. For salmeterol bioequivalence was demonstrated between the 250 µg/50 µg strength test formulation and Seretide in a study without charcoal blockade performed in asthmatic patients. For fluticasone,

the results of the pulmonary deposition study also supports systemic safety as the oral bioavailability of fluticasone is very low. Similarity in cortisol suppression was also shown in the study without active charcoal, which could be seen as a further support of similar fluticasone safety. Given the similarity in FPD between the 250 µg/50 µg and the 500 µg/50 µg strength, the results with the 250 µg/50 µg can be extrapolated to the highest strength of 500 µg/50 µg.

IV.4 Clinical efficacy and safety

The Applicant has also submitted two small single handling studies in adult patients with mild to moderate persistent asthma since the inhalation device is not the same as the originator device. The studies were two single dose studies using the 50 µg/250 µg and 50 µg/500 µg formulations, respectively. To use the new inhalation device, the patient needs to take one double-blister strip from the canister, load into the inhaler, remove the upper foil and then inhale the dose through the mouthpiece of the device. There are already other inhalations devices on the market which also requires the patient to load the dose before inhalation. The results from both handling studies show for that the test product can be handled correctly by the adult patients. Few adverse events were reported and no unexpected adverse events were observed. The clinical safety data from these two small studies can only be considered to be very limited and too restricted to draw any well-founded conclusions. The clinical data is limited but sufficient since the therapeutic equivalence is supported by pharmaceutical and pharmacokinetic data for the two higher strengths (50 µg/250 µg and 50 µg/500 µg).

To conclude, therapeutic equivalence has been demonstrated.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applied product consists of an inhalation device and Al/Al double-blister strips containing fluticasone propionate blended with lactose in one blister and salmeterol blended with lactose in a second blister. One double-blister strip is withdrawn from the canister, loaded into the inhaler and the upper foil is removed as to reveal the dose. The dose is subsequently emitted

when the patient inhales through the mouthpiece of the device. The reference product, Seretide Diskus is an inhalation device with fluticasone propionate and salmeterol blended with lactose.

The application for Salmeterol/Fluticasonpropionaat Elpen 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose inhalation powder, pre-dispensed is a hybrid application and evaluated in a step-wise approach according to the guideline CPMP/EWP/4151/00 Rev.1. The base in the evaluation is the pharmaceutical properties. Comparative *in vitro* studies of the applied product and the reference product have been performed on both strengths and statistical analysis is provided. The data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based solely on *in vitro* data and *in vivo* studies are needed for demonstration of therapeutic equivalence.

As a second step, pharmacokinetic documentation may be used to support efficacy and safety. Equivalent efficacy has been shown for salmeterol and fluticasone through the demonstration of bioequivalence between the 50 µg/500µg test formulation and the reference Seretide in a pulmonary deposition study in healthy volunteers. To support equivalent safety for salmeterol, the applicant has submitted *in vitro* equivalence data on particles likely to deposit in the oral cavity being eligible to oral absorption. In addition, equivalent total systemic safety has been shown for salmeterol through demonstration of bioequivalence between the 50 µg /250 µg test formulation and Seretide in a study without charcoal blockade. For fluticasone, the results of the pulmonary deposition study also support systemic safety as the oral bioavailability of fluticasone is very low. Similarity in cortisol suppression was also shown in the study without active charcoal, which could be seen as a further support of similar fluticasone safety. Given the similarity in FPD between the two strengths, the results with the 50 µg/250 µg strength can be extrapolated to the strength of 50 µg 500 µg and vice versa.

The Applicant has also submitted two small single dose studies in adult patients with mild to moderate persistent asthma using the 50 µg/250 µg and 50 µg/500 µg formulations, respectively. These two small studies are in our view considered to be two small handling studies to assure that the patients can correctly use the inhalations device since the inhalation device is not the same as the originator device. To use the new inhalation device, the patient needs to take one double-blister strip from the canister, load into the inhaler, remove the upper foil and then inhale the dose through the mouthpiece of the device. There are already other inhalations devices on the market which also requires the patient to load the dose before inhalation. The results from both handling studies show for that the test product can be handled correctly by the adult patients. Few adverse events were reported and no unexpected adverse events were observed. The clinical safety data from these two small studies can only be considered to be very limited and too restricted to draw any well-founded conclusions. The clinical data is limited but sufficient since the therapeutic equivalence is supported by pharmaceutical and pharmacokinetic data for the two strengths (50 µg/250 µg and 50 µg/500 µg).

To conclude, therapeutic equivalence has been sufficiently demonstrated.

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 the parent PL Relanio SE/H/972/01-02/DC, also a discussion regarding layout was presented and accepted.

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

The risk/benefit ratio is considered positive and Salmeterol/Fluticasonpropionaat Elpen 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose inhalation powder, pre-dispensedis recommended for approval.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-