

Public Assessment Report

Scientific discussion

Relanio
(salmeterol xinafoate/ fluticasone propionate)

SE/H/972/01-02/DC

This module reflects the scientific discussion for the approval of Relanio. Please note that the marketing authorisation was first approved with the name “Salmeterol/Fluticasone Pharos” and therefore this name is used throughout the document. The procedure was finalised at 2011-05-04. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

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

II. QUALITY ASPECTS

II.1 Introduction

Salmeterol/Fluticasone Pharos 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 One double-blister strip is withdrawn from the canister, loaded into the inhaler and the upper foil is removed as to reveal the dose.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/Fluticasone Pharos, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose 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

According to the OIP guideline, pharmacokinetic documentation may be used to support efficacy and safety. The applicant has submitted one pulmonary deposition study, where the bioequivalence of the test and reference products is investigated during concomitant administration of active charcoal to block drug absorption from the intestine. This study is usually used to support efficacy but may also be used to support safety for substances with a low oral bioavailability.

Pharmacokinetics supporting efficacy

Equivalent efficacy of both fluticasone and salmeterol is supported by PK data.

Bioequivalence was observed between the 50-500µg 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. The result may be extrapolated to the 50/250 strength based on the quality documentation.

Pharmacokinetics supporting safety

For fluticasone, the results of the pulmonary deposition study also supports systemic safety as the oral bioavailability of fluticasone is very low.

The oral availability of salmeterol is unknown even though results of a DDI study with ketoconazole indicate that it may be low. As it is the larger particles which may be subject to oral deposition, the applicant was asked to provide data supporting equivalence on these particles. Equivalence with regard to this particle size has been shown (See quality aspects above).

Clinical efficacy and safety

The clinical efficacy and safety assessment mainly relies on the pharmacokinetic and pharmaceutical quality documentation. However, the applicant has performed two single dose handling studies in support of the application. For fixed combination inhalation products two co-primary variables, one for each component, are recommended to be used to evaluate efficacy. However, in this case the two performed single dose studies are considered to be handling study and not crucial pivotal clinical studies on which the therapeutic equivalence is based on. The primary efficacy endpoint was the 12-hour average FEV1 [area under the FEV1 versus time curve divided by 12 (FEV1 AUC0-12/12) which is considered to reflect the effect of the salmeterol component. The chosen non-inferiority range (CI) was rather wide with respect to the clinical endpoint. Nevertheless, the results showed that the CI range was narrower than proposed and close to 100%. Thus, the results from the study clearly show that the test product can be handled correctly by the patients. Few adverse events were reported, paradoxical bronchospasms was reported for three patients in the second handling study. No unexpected adverse events were observed. The clinical safety data from this small study is of limited value in drawing any more far-reaching conclusions. The clinical data is limited but sufficient since the therapeutic equivalence is supported by pharmaceutical and pharmacokinetic data.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Benefit risk assessment

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/ Fluticasone PharOS 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 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.

A pulmonary deposition study, which is a bioequivalence study where oral absorption has been blocked with active charcoal, has been performed in healthy volunteers. Equivalence was shown, supporting efficacy for both fluticasone and salmeterol, as well as systemic safety related to fluticasone. Salmeterol safety is adequately supported by pharmaceutical data, i.e. comparative *in vitro* data on the larger, orally available particles.

The Applicant has also submitted two small single dose handling studies in patients with mild to moderate persistent asthma 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 patients. Few adverse events were reported. No unexpected adverse events were observed. The clinical 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.

In conclusion, the risk/benefit ratio is considered positive and Salmeterol/Fluticasone Pharos, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose 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 language used for the purpose of user testing the PIL was English.

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.

VI. APPROVAL

The Decentralised procedure for Salmeterol/Fluticasone Pharos, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose, was successfully finalised on 2011-05-04.

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)