LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Serefarm
(salmeterol xinafoate, fluticasone propionate)

SE/H/2116/01-03/DC

This module reflects the scientific discussion for the approval of Serefarm. The procedure was finalised on 2022-04-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Serefarm, 50 microgram/100 microgram/dose, 50 microgram/250 microgram/dose, 50 microgram/500 microgram/dose, inhalation powder, pre-dispensed.

The active substances are salmeterol xinafoate and fluticasone propionate. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Serefarm, 50 mcg/100 mcg/dose, 50 mcg/250 mcg/dose, 50 mcg/500 mcg/dose, inhalation powder, pre-dispensed, is submitted according to Article 10(3) ("bioequivalence cannot be demonstrated through bioavailability studies") of Directive 2001/83/EC. The applicant, Orifarm Generics A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seretide Diskus mite/Seretide Diskus/Seretide Diskus Forte, 50 mcg/100 mcg/dose, 50 mcg/250 mcg/dose, 50 mcg/500 mcg/dose inhalation powder, pre-dispensed authorised in Sweden since 1998, with GlaxoSmithKline AB as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of fluticasone propionas and salmeterolum, are well known. As fluticasone propionas and salmeterolum are widely used, well-known active substances, no further studies are required, and the applicant provides none. A non-clinical overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
While fluticasone is a likely endocrine active substance, since Serefarm is a generic product, it will not lead to an increased exposure to the environment. A full (phase I and II) environmental risk assessment is therefore not deemed necessary under the framework of the presently active CHMP ERA guideline from 2006.

Conclusion
There are no objections to approval of Serefarm from a non-clinical point of view.

IV. CLINICAL ASPECTS

According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a stepwise approach should be considered when demonstrating therapeutic equivalence for an orally inhaled product. 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. In the current application, pharmaceutical data alone was used to demonstrate equivalence and no pharmacokinetic studies were performed.

Pharmacokinetics
Pharmacokinetic properties of the active substances
Salmeterol
There are only limited available data on the pharmacokinetics of salmeterol in asthmatic patients due to the low plasma concentrations achieved after oral inhalation of therapeutic doses. Peak concentrations are in general obtained in about 5 min after inhalation. Salmeterol is a racemic mixture of the two optical isomers, (R)- and (S)-, of salmeterol.

Fluticasone propionate
The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5-11% of the nominal dose depending on the inhalation device used. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. Due to pre-systemic metabolism, the oral availability is less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose. The terminal half-life is approximately 8 hours. Plasma protein binding is 91%. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the CYP3A4.

Biowaiver
No pharmacokinetic studies have been submitted as the applicant claims that therapeutic equivalence can be concluded based on *in vitro* data only.

Discussion and overall conclusion
Therapeutic equivalence has been demonstrated using in vitro data (see Quality part). Thus, the absence of pharmacokinetic studies can be accepted in line with the OIP guideline.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that therapeutic equivalence with the originator product is demonstrated, additional data is not necessary. The age limit (4 years of age) is acceptable as therapeutic equivalence is established based on *in vitro* data.

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 Serefarm.

Safety specification
On request all proposed items were removed from the safety specification. This is appropriate according to GVP module V rev 2 as all safety concerns are well characterised and there are no outstanding additional pharmacovigilance activity or additional risk minimisation measure.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 15.10.2021 is considered acceptable.

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 Seretide Diskus, SE/H/169/01-03/E03 regarding content and Kaliumklorid Orifarm, DK/H/2347/001 regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Serefarm, is found adequate. There are no objections to approval of Serefarm, from a non-clinical and clinical point of view. Therapeutic equivalence between the test and reference product has been adequately demonstrated using in vitro data. The product information is acceptable. The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Serefarm, 50 microgram/100 microgram/dose, 50 microgram/250 microgram/dose, 50 microgram/500 microgram/dose, inhalation powder, pre-dispensed was positively finalised on 2022-04-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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