LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Salmeterol Orifarm
(salmeterol, salmeterol xinafoate)

SE/H/2417/01/DC

This module reflects the scientific discussion for the approval of Salmeterol Orifarm. The procedure was finalised on 2023-11-22. 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 Salmeterol Orifarm, 50 microgram/dose, Inhalation powder, pre-dispensed.

The active substance is salmeterol, salmeterol xinafoate. 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 Salmeterol Orifarm, 50 microgram/dose, Inhalation powder, pre-dispensed, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Serevent Dysk, 50 micrograms/dose, inhalation powder, pre-dispensed, authorised in PL since 1999, with GlaxoSmithKline (Ireland) Limited 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

This procedure is an Article 10(3) hybrid application concerning a salmeterol xinafoate inhalation product. The proposed medical product contains 50ug salmeterol xinafoate per inhalation dose. The formulation is administered via a dry powder inhaler using a pre-dispensed dose which is a disk-type inhaler. Assuming that all quality aspects/criteria have been fulfilled (See Quality), this applied-for hybrid product does nominally not differ from the reference product (Serevent Diskus 50 by GlaxoSmithKline) regarding formulation, dosage, or medical device type ("Diskus"). Overall, pharmacodynamic, pharmacokinetic and toxicological properties of the active substance are well known (see also below). As salmeterol xinafoate is a widely used, well-known active substance, no further studies are required, and the applicant provides none. The Overview being based on literature review is, thus, appropriate. A brief non-clinical summary is provided below.

Pharmacology

The active substance, salmeterol xinafoate, is a selective β2 adrenoreceptor agonist (indicated for the regular long-term symptomatic treatment of reversible airway obstruction in patients with bronchial asthma and chronic obstructive pulmonary disease, COPD).

Pharmacokinetics

When salmeterol is administered via inhalation, some of the drug inhaled is swallowed through oropharynx and can be absorbed into the systemic circulation. As such, drug concentrations in blood come from both routes, local (respiratory tract) absorption and gastrointestinal absorption. Interspecies comparisons suggest that its more bioavailable in humans and dogs comparing to rabbits, rats, and mouse. In rat, peroral exposure (2mg/kg) gives an Tmax of 0.08-0.25h, a Cmax of 6-9ng/mL. Intravenous exposure (2mg/kg) gives a Cmax of 203-329ng/mL. In dog, peroral exposure (0.2mg/kg) gives a Tmax of 1.5h and a Cmax of 18-25ng/mL while intravenous exposure gives a 75-106ng/mL. The elimination in rats and dogs is mostly via feces (average 72-74.5% in rats, average ~59% in dog) and then urine. Different metabolites have been identified in different species. In rats, the predominant metabolic route is sulfoconjugation. Rat bile contained one major metabolite (a phenolic glucuronide coded as V) and several minor metabolites. It can be noted that in humans, feces contain predominantly one metabolite (named as metabolite IV). Chemically, it is an alpha oxidated salmeterol at the phenyl ring on the phenylbutoxy side chain.

Toxicology

The provided non-clinical overview does not provide/describe any specific toxicological inhalation exposure general toxicity tests but only covers peroral and intravenous exposure studies. The animal data indicates that dosages of 10000x higher for mouse, 2000x higher for rat, 200x higher for dogs than therapeutic dose in humans (1μg/kg) where probably not linked with any apparent toxicity. It can be noted that in isolated perfused Langendorff-heart of the rat, salbutamol induced an increase in the heart rate via a selective stimulation of the beta1 adrenoceptors. Salmeterol has demonstrated embryo-fetal risk in animal models, with delayed fetal ossification and other adverse outcomes at high doses (evidence of safety in pregnancy in humans is very limited).

Environmental Risk Assessment (ERA)

The applicant has submitted an ERA with a Phase I PECsw calculation that gives an PECsw value which is below the Phase II trigger value (<0.01ug/L). Furthermore, since Salmeterol Orifarm is a generic (hybrid) product, it is reasonable to stipulate that its usage will not lead to an increased

exposure to the environment. Based on CHMP ERA framework from 2006, a deeper (Phase II) environmental risk assessment is therefore not necessary.

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

IV. CLINICAL ASPECTS

Pharmacokinetics

Pharmacokinetic properties of the active substance
There are only limited available data on the pharmacokinetics of salmeterol due to the low plasma concentrations achieved after oral inhalation of therapeutic doses. Following inhalation, salmeterol xinafoate is dissociated in the lungs. The acid form has a half-life of approximately 10 hours.

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 sufficiently demonstrated using in vitro data, see Quality part. Thus, the absence of pharmacokinetic studies is acceptable.

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 is acceptable if 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 Salmeterol Orifarm.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
It is noted that there is no approved RMP for the nationally approved reference product. In the RMP for Seretide Diskus SE/H/0169/002 containing both fluticasone and salmeterol, all safety concerns have been removed in accordance with the definitions in Revision 2 of GVP Module V. The submitted Risk Management Plan, version 1.1 signed 13.09.2023, is thus 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 (PL) has been performed on the basis of a bridging report making reference to Seretide Diskus, SE/H/169/01-03/E03 with regards to content and Kaliumklorid Orifarm, DK/H/2347/001/DC with regards to 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, Salmeterol Orifarm, is found adequate. There are no objections to approval of Salmeterol Orifarm 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 benefit/risk is considered positive, and 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 Salmeterol Orifarm, 50 microgram/dose, Inhalation powder, pre-dispensed was positively finalised on 2023-11-22.

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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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