LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Salmeterol/Fluticasone Genetic
(fluticasone propionate, salmeterol xinafoate)

SE/H/2372/01-03/DC

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasone Genetic. The procedure was finalised on 2024-04-19. 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/Fluticasone Genetic, 50/100 microgram/dose, 50/250 microgram/dose, 50/500 microgram/dose, inhalation powder, pre-dispensed.

The active substances are fluticasone propionate and 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/Fluticasone Genetic, 50/100 microgram/dose, 50/250 microgram/dose, 50/500 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 BE, EL, IE, LU, NL and PT as concerned member states (CMS). The application was withdrawn in ES during the procedure.

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

Potential similarity with orphan medicinal products
N/A

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

The proposed medicinal product is a hybrid product containing fluticasone propionate (a glucocorticoid, dose range between 100 and 500 ug) and salmeterol xinafoate (a selective beta2-agonist, maximum dose of 50 ug). The formulation (including all excipients) and dosage is the same as in other medicinal products containing the two active substances. The reference product is Seretide Discus (mite / -- / forte, respectively, depending on the dose), marketed by GlaxoSmithKline AB (first approved in the EU in 1998).

Pharmacology/Pharmacokinetics/Toxicology
The pharmacodynamic, pharmacokinetic and toxicological properties of fluticasone propionate and salmeterol xinafoate are well known (formulation designed for inhalation). As these active substances are widely used and well-known, 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)
The provided CHMP ERA – based on the CHMP ERA guideline from 2006 (EMEA/CHMP/SWP/4447/00 Corr 2) - shows that the overall environmental exposure has declined between 2018 and 2023 for all concerned member states (based on IQVIA consumption data). As such, the absence of a Phase I assessment (and any subsequent Phase II assessment) is justified.

Overall conclusion
There are no identified issues with the pharmacodynamic, pharmacokinetic and toxicological aspects of fluticasone propionate and salmeterol xinafoate as their properties are well known (formulation designed for inhalation). There are no non-clinical objections to product approval.

IV. CLINICAL ASPECTS

According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a step-wise 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 substance
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.

Discussion and overall conclusion
Therapeutic equivalence has been demonstrated using *in vitro* data (see Quality part). 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 bioequivalence with the originator product is demonstrated, additional data is not necessary.

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/Fluticasone Genetic.

Safety specification
Table SVIII.1: Summary of safety concerns

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

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 0.1 signed 30-Jan-2023 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

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 PL was Italian.

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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Salmeterol/Fluticasone Genetic, is found adequate. There are no objections to approval of Salmeterol/Fluticasone Genetic, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk ratio 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/Fluticasone Genetic, 50/100 microgram/dose, 50/250 microgram/dose, 50/500 microgram/dose, inhalation powder, pre-dispensed, was positively finalised on 2024-04-17.

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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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