LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Salmeterol/Flutikason Devatis
(fluticasone propionate, salmeterol xinafoate)

SE/H/1683/03-04/X/06/G

This module reflects the scientific discussion for the approval of Salmeterol/Flutikason Devatis. The procedure was finalised on 2021-10-20. 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/Flutikason Devatis, 25 mikrogram/125 mikrogram/dos, Pressurised inhalation, suspension.

The active substance is fluticasone propionate, 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 is a grouped extension (new strength), of the previously authorised product: Salmeterol/Flutikason Devatis, 25/250 microgram/actuation, pressurised inhalation, suspension.

The extension application for Salmeterol/Flutikason Devatis, 25/125 microgram/actuation, pressurised inhalation, suspension, is submitted according to Article 10(3) of Directive 2001/83/EC and grouped with a Quality variation (B.II.d.1.e) for the previously authorised product mentioned above. The applicant, Devatis GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seretide, 25/125 microgram/actuation, pressurised inhalation, suspension, authorised in DK since 2001, with GlaxoSmithKline Pharma A/S 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 salmeterol and fluticasone propionate are well known. As salmeterol and fluticasone propionate 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)
Salmeterol/Flutikason Devatis is intended for substitution with marketed products containing the same active substance. A historical assessment has been conducted and a general consumption decrease seems to be ongoing (compared to the early to mid-2010s). It seems unlikely that there will be an increase in consumption in the near future. As such, no full phase I to Phase II ERA is considered necessary.

There are no objections to approval of Salmeterol/Flutikason Devatis from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application of the new strength of Salmeterol/Flutikason Devatis (25/125 microgram/actuation), the applicant has not submitted any pharmacokinetic or clinical/PD studies.

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, therapeutic equivalence of the developed medicinal product with the reference medicinal product is based on the comparative evaluation of in vitro data alone; i.e. in accordance with Step 1 in the OIP guideline (CPMP/EWP/4151/00 Rev. 1).

Pharmacokinetic properties of the active substance
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.

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.

Study
To support the application, the applicant has not submitted any pharmacokinetic studies.

Discussion and overall conclusion
Therapeutic equivalence can be concluded based on in vitro data. The lack of comparative pharmacokinetic data is acceptable.

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, version 2.1, signed off 03.09.20, 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/Flutikason Devatis. The summary of safety concerns has been updated according to the PRAC recommendation, following the evaluation of procedure no. PSUSA/0001455/201910 for fluticasone/salmeterol products, and all safety concerns were removed in order to harmonise the summary of safety concerns with that of the innovator product.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
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 2.1 signed 03.09.20 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 results of the user testing of the package leaflet proposed was referred to the user test report submitted for the initial DCP application for Salmeterol/Flutikason Devatis 25 microgram/250 microgram/actuation. It was concluded that this user test results could be bridged to the proposed package leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Salmeterol/Flutikason Devatis, is found adequate. There are no objections to approval of Salmeterol/Flutikason Devatis, from a non-clinical nor clinical point of view. 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 Salmeterol/Flutikason Devatis, 25 mikrogram/125 mikrogram/dos, Pressurised inhalation, suspension was positively finalised on 2021-10-20.

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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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