LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Salmeterol/Flutikason Devatis
(salmeterol, fluticasone propionate)

SE/H/1683/03/DC
2017-1191

This module reflects the scientific discussion for the approval of Salmeterol/Flutikason Devatis. The procedure was finalised on 2018-12-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Devatis GmbH has applied for a marketing authorisation for Salmeterol/Flutikason Devatis 25 microgram/250 microgram/actuation, pressurised inhalation, suspension. The active substances are salmeterol which is a selective long-acting beta-2 adrenergic receptor agonist (LABA) with direct beta-adrenoceptor stimulant sympathomimetic activity, and fluticasone propionate which is a corticosteroid with mainly glucocorticoid activity.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

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 xinafoate and fluticasone propionate are well known. As the combination of salmeterol/fluticasone propionate is widely used and well established in the clinic, no further non-clinical studies are required. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The product is a hybrid and intended to replace already marketed fixed-dose combination products containing the same active substances. Thus no increased exposure to the environment is expected. No further action is necessary.

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

IV. CLINICAL ASPECTS

IV.1 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. 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. 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).

Pharmacokinetics
No pharmacokinetic studies have been conducted with Salmeterol/Flutikason Devatis. Provided that the in vitro data comply with all criteria required in the OIP-guideline, the lack of comparative pharmacokinetic data is acceptable.

The known pharmacokinetic characteristics of salmeterol and fluticasone following oral inhalation are summarized below.

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.

Pharmacodynamics
No new data has been provided. This is appropriate as the pharmacodynamic properties of the beta2-agonist salmeterol and the glucocorticoid fluticasone are well known. Therapeutic similarity is not based on pharmacodynamic data in this case.

Clinical efficacy and safety
No new data has been provided. This is acceptable as the *in vitro* data comply with all criteria required in the OIP-guideline. Data on the practical use of the product and handling instructions are not warranted as the device is in use in EU with other substances.

IV.2 Risk Management Plans

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/Flutikason Devatis.

Safety specification
In response to a question posed the applicant has updated the summary of safety concerns as below.

Summary of safety concerns	
Important identified risks	• Pneumonia in patients with COPD
Important potential risks	None identified
Missing information	None identified

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 17-07-2018 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 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Salmeterol/Flutikason Devatis, was found adequate. There were no objections to approval of Salmeterol/Flutikason Devatis, from a non-clinical and clinical point of view. In vitro bioequivalence between the test and reference product were adequately demonstrated. The product information was acceptable.
The application was therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Salmeterol/Flutikason Devatis 25 microgram/250 microgram/actuation, pressurised inhalation, suspension was positively finalised on 2018-12-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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