LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Salmex
(salmeterol (as xinafoate) and fluticasone propionate)

SE/H/1590/01-03/DC

This module reflects the scientific discussion for the approval of Salmex. The procedure was finalised on 2017-11-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Salmex, 50 microgram/100 microgram/dose, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose, inhalation powder, pre-dispensed, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Glenmark Phamraceuticals Europe Ltd, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, NO and IS 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, 50mcg/100 mcg, inhalation powder, pre-dispensed, authorised in SE since 1998, with GlaxoSmithKline AB, as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

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, therapeutic equivalence was demonstrated based on pharmacokinetic data. The applicant submitted two pharmacokinetic studies, one with and one without activated charcoal blockade. Both pharmacokinetic studies were performed with the 50 microgram/500 microgram strength.

IV.1 Pharmacokinetics

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.

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.

For fluticasone, the contribution of intestinal absorption to systemic exposure is negligible, and thus a study without activated charcoal can be used for both efficacy and safety comparisons. For salmeterol, the contribution of intestinal absorption to systemic exposure is not negligible. Thus, it is adequate that studies with and without activated charcoal have been submitted, in order to demonstrate equivalence regarding efficacy and safety for both salmeterol and fluticasone propionate.

Study 03SX2016 without activated charcoal blockade

Study 03SX2016 was an open, randomised, two-treatment, four-period, two-sequence (TTRR and RRTT), replicated, single-dose crossover study conducted in 44 healthy volunteers under fasting conditions without concomitant administration of activated charcoal, comparing Salmex, 50 microgram /500 microgram/inhalation, inhalation powder with Seretide Dysk, 50

microgram /500 microgram/inhalation, inhalation powder. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable, although a longer sampling time would have been advisable. Plasma concentrations of salmeterol and fluticasone propionate were determined with validated LC/MS/MS methods. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both salmeterol and fluticasone propionate. T_{max} was similar for test and reference.

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for salmeterol, n=84 (test)/83 (ref) without activated charcoal.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**224.99±69.19**	**205.53±64.54**	**0.083 (0.05-0.17)**
Reference	**199.33±74.57**	**185.27±72.68**	**0.083 (0.05-0.083)**
***Ratio (90% CI)**	**114.60 (108.84-120.66)**	**113.46 (105.75-121.74)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2:Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone propionate, n=84 (test)/83 (ref) without activated charcoal.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**977.47±240.33**	**90.26±25.46**	**2 (0.17-4)**
Reference	**955.32±271.77**	**98.52±31.68**	**2 (0.13-4)**
***Ratio (90% CI)**	**103.06 (97.79-108.62)**	**92.31 (87.32-97.58)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

<u>Study 04SX2016 with activated charcoal blockade</u>

Study 04SX2016 was an open, randomised, two-treatment, four-period, two-sequence (TTRR and RRTT), replicated, single-dose crossover study conducted in 44 healthy volunteers under fasting conditions with concomitant administration of activated charcoal, comparing Salmex, 50 microgram /500 microgram/inhalation, inhalation powder with Seretide Dysk, 50 microgram /500 microgram/inhalation, inhalation powder. Blood samples were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of salmeterol and fluticasone propionate were determined with validated LC/MS/MS methods. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both salmeterol and fluticasone propionate. T_{max} was similar for test and reference.

Activated charcoal was only administered on one occasion, 30 minutes before drug inhalation, at a dose of 1 g. In the method described by Borgstrom and Nilsson (Pharm Res 1990) and

validated for salmeterol by Ward et al (Am J Respir Crit Care Med 1997) activated charcoal is administered at higher doses and the administration is repeated several times post inhalation. It is noted that the AUC results for salmeterol in the studies with and without charcoal are very similar. Although this is a between-study comparison, the studies are very similar in design and performed at the same clinical and bioanalytical site and with the same bioanalytical method. Thus, this indicates that the method used for administration of activated charcoal may be insufficient to block gastrointestinal absorption of salmeterol. However, for salmeterol, as an alternative to a study with activated charcoal, it may be possible to use $AUC_{0\text{-}30}$ min in a study without activated charcoal as a surrogate for efficacy, since salmeterol has a very early t_{max}. The applicant submitted analysis of 90% CI for $AUC_{0\text{-}30\ min}$ in the study without activated charcoal (03SX2016), and the results were within the conventional acceptance limits of 80.00-125.00. It is noted that this was also the case for study 04SX2016 and for the pooled analysis of both studies. Although this is a post-hoc analysis, therapeutic equivalence for efficacy and safety is considered sufficiently demonstrated for test compared to reference.

Table 3:Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for salmeterol, n=82 (test)/73 (ref).

Treatment	$AUC_{0\text{-}t}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**217.78±80.54**	**213.30±82.15**	**0.05 (0.05-0.133)**
Reference	**186.72±66.79**	**184.42±63.24**	**0.083 (0.017-0.133)**
***Ratio (90% CI)**	**113.02 (104.99-121.67)**	**109.85 (101.52-118.88)**	**-**
$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 4:Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone propionate, n=82 (test)/75 (ref).

Treatment	$AUC_{0\text{-}t}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**920.70±290.60**	**89.42±26.25**	**2 (0.5-4)**
Reference	**851.33±237.08**	**93.43±29.09**	**2 (0.5-3)**
***Ratio (90% CI)**	**110.34 (99.10-122.85)**	**99.03 (89.99-108.98)**	**-**
$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Pharmacokinetic conclusion

Therapeutic equivalence between Salmex 50 microgram /500 microgram/inhalation, inhalation powder and Seretide Diskus 50/500 microgram, inhalation powder has been sufficiently demonstrated based on pharmacokinetic data.

The results with the 50 microgram /500 microgram formulation CAN be extrapolated to the other strengths 50 microgram/250 microgram and 50 microgram/100 microgram.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary. Salmex is suggested to be indicated for adults and children from 4 years in line with the reference product. There are no pharmacokinetic or clinical studies conducted in children as similarity is shown by means of *in vitro* data for parameters of relevance for children i.e. lowest strength at 30 and 60 l /min.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (Version 1.0), 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 Salmex. The data lockpoint for this RMP was 27 November 2015.

Safety specification

On request the summary of safety concerns were updated in line with the RMP for the reference product as detailed in the table below.

Summary of safety concerns	
Important identified risks	Pneumonia in COPD and asthma patient populations
	Respiratory-related events or deaths
	Cushing's syndrome and adrenal suppression
	Growth retardation in paediatrics
	Drug interaction with CYP450 3A4 inhibitors
	Hypersensitivity reactions including anaphylactic reactions
	Arrhythmias
	Angina
Important potential risks	None
Missing information	Patients with hepatic impairment
	Breastfeeding women
	Use in children <4 years of age

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 RMP is approved.

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 Salmex is found adequate. There are no objections to approval of Salmex, from a non-clinical and clinical point of view. The bridge to the reference product is confirmed for all age groups and Salmex can therefore be approved for the same age span as the reference product i.e. 4 years of age. The product information is acceptable.
The application is 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 Salmex, 50 microgram/100 microgram/dose, 50 microgram/250 microgram/dose, 50 microgram/500 microgram/dose, inhalation powder, pre-dispensed was positively finalised on 2017-11-29

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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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