LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Salmeterol/ Fluticasone Wellnex (salmeterol xinafoat/fluticasone propionate)

SE/H/1856/01/DC

This module reflects the scientific discussion for the approval of Salmeterol/ Fluticasone Wellnex. The procedure was finalised on 2019-09-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Wellnex GmbH has applied for a marketing authorisation for Salmeterol/ Fluticasone Wellnex 50/500 µg, Inhalation powder, pre-dispensed. 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.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC 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

Pharmacodynamic, pharmacokinetic and toxicological properties of salmeterol xinafoate and fluticasone propionate are well known. As salmeterol xinafoate and fluticasone propionate are widely used, well-known active substances, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since Salmeterol/ Fluticasone Wellnex is a hybrid product intended to replace marketed products containing the same active substances, it will not lead to an increased exposure to the environment. However, fluticasone is considered to be a potential endocrine disruptor. The Applicant has committed to submit a tailored ERA for fluticasone propionate post approval. There are no objections to approval of Salmeterol/Fluticasone Wellnex from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Salmeterol/ Fluticasone Wellnex 50/500 µg is a pre-dispensed inhalation powder containing fluticasone propionate and salmeterol xinafoate for inhalation use. The application comprises one strength corresponding to the highest strength of the reference product. The low and middle strength (50/100 µg and 50/250 µg) from the same Applicant have been approved via a separate application (SE/H/1797/001-002/DC).

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, equivalence was not demonstrated based on pharmaceutical data alone and thus pharmacokinetic studies were performed.

IV.2 Pharmacokinetics

To support the application, the applicant has submitted one pivotal pharmacokinetic study with the applied strength:
Study 4852/17, which was a 4-way-crossover-study where test and reference product were administered with and without activated charcoal.

Pharmacokinetic properties of the active substances
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.

Study 4852/17 with 50 microgram/500 microgram/dose strength

Methods

This was a single-dose, four-way crossover study conducted in 60 healthy volunteers, comparing Salmeterol/Fluticasone 50 microgram/500 microgram/dose, inhalation powder with Seretide Accuhaler 50 microgram/500 microgram/dose pre-dispensed inhalation powder by Glaxo Wellcome UK from the UK market under fasting conditions with and without administration of activated charcoal. A single dose of 2 inhalations was administered. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose (for fluticasone propionate up to 30 hours post-dose). Plasma concentrations of salmeterol and fluticasone propionate were determined with LC/MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 4th and 31st December 2017.

Results

The results from the pharmacokinetic and statistical analysis are presented in the tables below.

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone propionate, n=53 (administration with charcoal) /54 (administration without charcoal).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test with charcoal (A)	**1669.38±430.34**	**176.43±45.69**	**1.25 (0.50-3.00)**
Reference with charcoal (B)	**1867.13±518.74**	**225.65±69.49**	**1.25 (0.33-3.00)**
Test without charcoal (C)	**1719.00±398.23**	**179.09±41.57**	**1.25 (0.17-3.00)**
Reference without charcoal (D)	**1839.91±477.83**	**213.56±63.70**	**1.25 (0.33-3.00)**
***Ratio (90% CI) (with charcoal; A vs B)**	-	-	-
***Ratio (90% CI) (without charcoal; C vs D)**	**95.26 (90.26-100.54)**	**86.28 (81.29-91.58)**	-

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*

Table 2: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for salmeterol, n=53 (administration with charcoal) /54 (administration without charcoal).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test with charcoal (A)	**471.19±124.28**	**439.87±119.03**	**0.07 (0.03-0.10)**
Reference with charcoal (B)	**455.88±156.54**	**470.39±163.28**	**0.07 (0.03-0.10)**
Test without charcoal (C)	**637.35±213.06**	**463.34±127.47**	**0.07 (0.03-0.10)**
Reference without charcoal (D)	**589.24±199.13**	**466.18±165.56**	**0.07 (0.03-1.25)**
***Ratio (90% CI) (with charcoal; A vs B)**	**104.67 (98.07-111.70)**	**94.33 (88.12-100.97)**	-
***Ratio (90% CI) (without charcoal; C vs D)**	**109.82 (103.81-116.19)**	**103.27 (95.78-111.35)**	
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*

Administration without charcoal: 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 salmeterol and fluticasone propionate.

Administration with charcoal: 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 salmeterol. This comparison was not performed for fluticasone propionate.

Discussion and overall conclusion

The pivotal study was performed with and without activated charcoal blockade. However, bioequivalence assessment was done both with and without charcoal for salmeterol, but for fluticasone bioequivalence assessment was only done without activated charcoal.

For fluticasone, the contribution of intestinal absorption to systemic exposure is negligible, and thus a study without activated charcoal would have been sufficient for both efficacy and safety comparisons. It is considered acceptable that no test/reference comparison has been performed for fluticasone following administration with charcoal, since this was pre-specified in the protocol and since the contribution of intestinal absorption to systemic exposure is negligible for fluticasone and that administration with activated charcoal thus would not have been necessary for fluticasone.

The pharmacokinetic study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). Both test and reference products were administered with and without activated charcoal blockade, in order to investigate therapeutic equivalence regarding both efficacy and safety. However, the test/reference comparison with charcoal was only performed for salmeterol and not for fluticasone as discussed above. There was frequent early sampling which is crucial in order to catch salmeterol C_{max}. The bioanalytical methods were adequately validated. T_{max} was similar for test and reference product. The batches of test and reference product were representative for the intended product and the reference product on the market. Extrapolation of results from the PK study performed with healthy volunteers to the patient population is acceptable since the test and reference products have similar flow rate dependency.

In conclusion, therapeutic equivalence has been demonstrated based on pharmacokinetic data.

IV.3 Pharmacodynamics/Clinical efficacy/Clinical safety

No studies are conducted as therapeutic equivalence is documented based on pharmacokinetics. There are no studies regarding efficacy and safety in children for this applied product, therefore, this product cannot have indication in individuals under the age of 12.

IV.4 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/ Fluticasone Wellnex 50 µg/500 µg/dose.

Safety specification

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

The MAH has submitted an RMP, including a Summary of safety concerns that is now identical to the one of the reference product, i.e. empty. The RMP now includes all products from the MAH, containing salmeterol/fluticasone.

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 0.3 signed 8 March 2019 is considered acceptable, as the applicant has made the required updates.

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 an RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The layout of 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.

A bridging to the reference product regarding the content has been proposed. This is accepted. The user test for the reference product Seretide Diskus was accepted in SE/H/169/01-03/E03.

A user consultation with target patient groups on the content of the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Seretide Diskus, SE/H/169/01-03/E03. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product, Salmeterol/Fluticasone Wellnex is found adequate. There are no objections to approval of Salmeterol/Fluticasone Wellnex, from a non-clinical and clinical point of view. Therapeutic equivalence can be concluded based on pharmacokinetic data. 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/EC in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
1.6.1 Environmental Risk Assessment - Update for fluticasone propionate will be submitted	Q2 2021

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

N/A

VII. APPROVAL

The Decentralised procedure for Salmeterol/ Fluticasone Wellnex 50/500 µg, Inhalation powder, pre-dispensed was positively finalised on 2019-09-19.

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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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