

Public Assessment Report

Scientific discussion

Salmeterol/Fluticasone Wellnex (salmeterol xinafoat/fluticasone propionate)

SE/H/1797/01-02/DC

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasone Wellnex. The procedure was finalised on 2019-05-02. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Wellnex GmbH has applied for a marketing authorisation for Salmeterol/Fluticasone Wellnex, 50/100 µg and 50/250 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 50/100 µg and 50/250 µg is a pre-dispensed inhalation powder containing fluticasone propionate and salmeterol xinafoate for inhalation use. The application comprises two strengths corresponding to the low and middle strength of the reference product. A higher dose strength (50/500 µg) from the same Applicant has been approved via a separate application SE/H/1856/001/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 two pivotal pharmacokinetic studies, one with each applied strength, comparing Salmeterol/Fluticasone Wellnex with the reference product Seretide Diskus/Seretide Accuhaler.:

Study 4157/16 with 50 microgram/100 microgram/dose strength

Study 3678/15 with 50 microgram/250 microgram/dose strength

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 4157/16 with 50 microgram/100 microgram/dose strength

Methods

This was a single-dose, four-way crossover study conducted in 60 healthy volunteers, comparing Salmeterol/fluticasone propionate 50 microgram/100 microgram/dose, inhalation powder with Seretide Accuhaler 50 microgram/100 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 3 inhalations was administered. Blood samples for concentration analysis were collected pre-dose and up to 36 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 10th September and 24th October 2016.

Results

The results from the pharmacokinetic and statistical analysis are presented in

Table 1 below for fluticasone propionate and in Table 2 for salmeterol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for fluticasone propionate, n=58 (administration with charcoal) /59 (administration without charcoal).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test with charcoal (A)	449.06$\pm$106.69	86.56$\pm$25.45	0.50 (0.07-2.00)
Reference with charcoal (B)	433.13$\pm$105.85	72.91$\pm$20.06	0.50 (0.07-3.00)
Test without charcoal (C)	462.92$\pm$123.66	90.79$\pm$27.82	0.33 (0.10-1.25)
Reference without charcoal (D)	442.44$\pm$111.35	76.72$\pm$21.41	0.50 (0.10-2.00)
*Ratio (90% CI) (with charcoal; A vs B)	104.31 (100.45-108.31)	118.36 (112.34-124.69)	-
*Ratio (90% CI) (without charcoal; C vs D)	104.08 (98.96-109.48)	117.10 (109.45-125.28)	-
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 $\pm$ SD, t_{max} median, range) for salmeterol, n=58 (administration with charcoal) /59 (administration without charcoal).

Treatment	AUC _{0-t} pg*h/ml	C _{max} pg/ml	t _{max} h
Test with charcoal (A)	451.34 $\pm$ 144.43	368.99 $\pm$ 104.91	0.07 (0.03-0.17)
Reference with charcoal (B)	430.58 $\pm$ 154.76	332.30 $\pm$ 108.14	0.07 (0.03-0.13)
Test without charcoal (C)	665.03 $\pm$ 249.22	380.09 $\pm$ 124.17	0.07 (0.03-0.10)
Reference without charcoal (D)	663.51 $\pm$ 278.02	344.42 $\pm$ 108.22	0.07 (0.03-0.12)
*Ratio (90% CI) (with charcoal; A vs B)	105.56 (101.20-110.10)	113.08 (107.22-119.26)	-
*Ratio (90% CI) (without charcoal; C vs D)	101.23 (95.87-106.89)	109.56 (102.98-116.56)	-

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*

For fluticasone propionate, following 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%. Following administration without charcoal, for AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% but for C_{max} the 90% confidence interval for the ratio of the test and reference products was slightly outside the conventional acceptance range of 80.00-125.00% (upper limit 125.28).

The applicant submitted an additional analysis for fluticasone in response to questions raised, where fluticasone data with and without charcoal was pooled (see Table 3 below). The 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 3: Pharmacokinetic parameters AUC_{0-t} and C_{max} for fluticasone propionate administration with and without charcoal pooled, n=59 (normal scale results of log-transformed values; geometric means, ratios and associated 90% confidence intervals)

Treatment	AUC _{0-t} pg*h/ml	C _{max} pg/ml
Test (A)	442.08	84.73
Reference (B)	424.04	71.98
*Ratio (90% CI) (A vs B)	104.25 (100.83 - 107.79)	117.72 (113.03 - 122.60)
AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours		
C _{max} maximum plasma concentration		

For salmeterol, following administration with and 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%.

Study 3678/15 with 50 microgram/250 microgram/dose strength

Methods

This was a single-dose, four-way crossover study conducted in 60 healthy volunteers, comparing 50 microgram/250 microgram/dose, inhalation powder with Seretide Diskus, 50 microgram/250 microgram/dose, inhalation powder by Glaxo Smith Kline BV from the Dutch 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 36 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 21st Dec 2016 and 19th Jan 2017.

Results

The results from the pharmacokinetic and statistical analysis are presented in **Table 4** below for fluticasone propionate and in **Table 5** for salmeterol.

Table 4: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone propionate, n=57 (comparison with charcoal)/n=58 (comparison without charcoal).

Treatment	AUC _{0-t} pg*h/ml	C _{max} pg/ml	t _{max} h
Test with charcoal (A)	748.90±261.38	87.90±28.25	1.25 (0.25-3.00)
Reference with charcoal (B)	818.75±216.01	95.09±26.05	1.25 (0.33-3.00)
Test without charcoal (C)	819.44±246.75	97.18±29.42	1.00 (0.17-3.00)
Reference without charcoal (D)	866.22±227.34	102.52±29.34	1.13 (0.25-3.00)
*Ratio (90% CI)	87.58 (81.53-94.07)	90.82 (84.99-97.05)	-

(with charcoal, A vs B)			
*Ratio (90% CI) (without charcoal, C vs D)	93.50 (88.68-98.59)	94.60 (88.69-100.90)	-
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 5: Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for salmeterol, n=58.

Treatment	AUC _{0-t} pg*h/ml	C _{max} pg/ml	t _{max} h
Test with charcoal (A)	243.11 $\pm$ 89.88	215.31 $\pm$ 79.18	0.07 (0.03-0.10)
Reference with charcoal (B)	212.85 $\pm$ 72.10	206.78 $\pm$ 65.31	0.07 (0.03-0.12)
Test without charcoal (C)	357.53 $\pm$ 119.72	237.86 $\pm$ 76.86	0.07 (0.03-0.10)
Reference without charcoal (D)	337.20 $\pm$ 126.86	224.19 $\pm$ 74.79	0.07 (0.03-0.10)
*Ratio (90% CI) (with charcoal, A vs B)	111.37 (103.19-120.20)	102.12 (94.63-110.21)	-
*Ratio (90% CI) (without charcoal, C vs D)	107.57 (101.42-114.11)	107.21 (100.39-114.50)	-
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*

Following administration with and 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 both fluticasone propionate and salmeterol.

Discussion and overall conclusion

The pivotal studies were performed with and without activated charcoal blockade. For salmeterol, the contribution of intestinal absorption to systemic exposure is not negligible and

thus a study with activated charcoal is adequate in order to assess equivalence regarding both efficacy and safety. For fluticasone, the contribution of intestinal absorption to systemic exposure is negligible, and thus a study without activated charcoal might have been used for both efficacy and safety comparisons. However, since this is a combination product, it is relevant to compare both substances with and without charcoal.

The pharmacokinetic studies 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. 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.

50 microgram/100 microgram/dose strength

Therapeutic equivalence can be concluded regarding both efficacy and safety for salmeterol.

For fluticasone propionate, C_{max} appears to be slightly higher for test than reference (point estimate 1.17 in the comparison without charcoal and 1.18 in the comparison with charcoal), but the results with charcoal are just inside the acceptance criteria while the results without charcoal are just outside the acceptance criteria.

The applicant has submitted pooled results for fluticasone with and without charcoal from study 4157/16 as recommended by the RMS, and the results for both AUC and C_{max} are then within the conventional acceptance criteria.

The approach to pool fluticasone data with and without charcoal is considered relevant, considering that the oral contribution to the total systemic exposure following inhalation of fluticasone propionate is considered to be negligible. This can also be seen in the results from the current study, where the AUC values are very similar with and without activated charcoal administration (2-3% difference). In the study with the higher strength, the applicant has assessed the effect of charcoal on the administration of fluticasone, and the results are within the conventional acceptance criteria for bioequivalence. Thus, in principle, therapeutic equivalence for fluticasone regarding efficacy and safety could be established either with or without charcoal administration, since the administration of charcoal is not expected to significantly affect the results.

Thus, based on the pooled results for fluticasone with and without charcoal, therapeutic equivalence can be concluded also for fluticasone for this strength.

50 microgram/250 microgram/dose strength

Therapeutic equivalence can be concluded regarding both efficacy and safety for both active substances.

In conclusion, therapeutic equivalence can be concluded based on pharmacokinetic data for both strengths.

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 propionate Wellnex 50 /100 µg/dose and 50/250 µg/dose.

Safety specification

Table SVIII.1: Summary of safety concerns

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.

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 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 for both strengths.

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, 50/100 µg and 50/250 µg, Inhalation powder, pre-dispensed was positively finalised on 2019-05-02.

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)