LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fusacomb Easyhaler (fluticasone propionate, salmeterol xinafoate)

SE/H/1701/01-02/DC

This module reflects the scientific discussion for the approval of Fusacomb Easyhaler. The procedure was finalised on 2018-03-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Orion Corporation has applied for a marketing authorisation for Fusacomb Easyhaler, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose, inhalation powder. The active substances are fluticasone propionate and salmeterol xinafoate.

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 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

IV.1 Introduction

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. An overview of the clinical studies is shown in Table 1.

Table 1: Summary of studies in the clinical development programme of Salmeterol/fluticasone EH

Pivotal study	
Study ID	Objective
SAULI 3106010	The objective of the study is to demonstrate therapeutic equivalence (non-inferiority in total systemic exposure and BE in lung deposition) between at least one Salmeterol/fluticasone EH test product and Seretide Diskus.
Supportive study	
Study ID	Objective
SALIF 3106002	To characterise inspiratory flow parameters across the EH and Diskus inhalers in patients with asthma and COPD
Other studies	
Study ID	Objective
SALTON 3106001	To compare the PK of salmeterol and fluticasone after administration of 4 different Salmeterol/fluticasone EH product variants and Seretide Diskus with concomitant charcoal (pulmonary absorption)
SALSA 3106004	To compare the PK of salmeterol and fluticasone propionate after administration of 2 different Salmeterol/fluticasone EH product variants and Seretide Diskus with and without concomitant charcoal (pulmonary and total systemic absorption)
SALLI 3106005	To compare the PK of salmeterol and fluticasone propionate after administration of 4 different Salmeterol/fluticasone EH product variants and Seretide Diskus with concomitant charcoal (pulmonary absorption)
SALBLOCK 3106006	To assess whether the used charcoal block method prevents the absorption of salmeterol from the gastrointestinal (GI) tract

SALME 3106007	To demonstrate equivalent pulmonary deposition and total systemic exposure of Salmeterol/fluticasone EH with Seretide Diskus
SALENA 3106008	To demonstrate equivalent pulmonary deposition and total systemic exposure of Salmeterol/fluticasone EH with Seretide Diskus
SAMPO 3106009	To demonstrate therapeutic equivalence (non-inferiority in total systemic exposure and BE in lung deposition) between at least one Salmeterol/fluticasone EH test product and Seretide Diskus.

Several pharmacokinetic studies were performed during the development work of Salmeterol/fluticasone Easyhaler. Based on the results from the studies, the product development work continued with product variants differing both regarding powder formulation (FPD and ratio of different lactose grades) and inhaler. In the pivotal study, SAULI 3106010, one of the test products was the final proposed Salmeterol/fluticasone EH product submitted in this application.

IV.2 Pharmacokinetics

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.

Pharmacokinetic studies aim at demonstrating similar pulmonary deposition and similar total systemic exposure between a hybrid inhalation product and the originator. According to the OIP guideline, bioequivalence studies with charcoal blockade could be used to compare pulmonary deposition as a surrogate for efficacy. In addition, bioequivalence studies without charcoal blockade could be used to compare systemic exposure as a surrogate for safety. For some inhaled medicinal products, the contribution of intestinal absorption to systemic exposure is negligible (<5%) and a single dose PK study without charcoal can be used for both efficacy and safety comparisons. According to the Q&A document published by the Pharmacokinetic Working Party, in case the contribution of intestinal absorption to systemic exposure is not negligible but if the absorption of the drug in the lung is very quick (e.g., $t_{max} \leq$ 5 min) and absorption occurs before the contribution of gastrointestinal absorption is significant (e.g., salbutamol/albuterol, salmeterol), $AUC_{0\text{-}30\ min}$ might be acceptable as a surrogate for efficacy and $AUC_{0\text{-}t}$ for safety. Thus, also in this case, one study without active charcoal blockade is sufficient.

Pilot studies

The 3 initial pilot studies (**SALTON 3106001**, **SALSA 3106004**, **SALLI 3106005**) compared salmeterol and fluticasone propionate PK after administration of several different product variants of Salmeterol/fluticasone EH dmDPI (test) and Seretide Diskus DPI (reference). None of the test products in the pilot studies showed bioequivalent lung deposition (and non-inferior total systemic exposure in SALSA 3106004) for all primary parameters in comparison to the reference product. Product development was continued based on these results to establish the correct formulation for fulfilling BE criteria.

Pivotal-scale PK studies

Two Easyhaler product variants were studied in the pivotal-scale studies **SALME 3106007** and **SALENA 3106008** (one in each study). The EH variant was compared to the reference product after administration with and without charcoal in both studies. These studies showed that the EH variants yielded lower salmeterol and fluticasone propionate plasma concentrations in comparison with the reference product.

The **SAMPO 3106009** study was conducted to compare 3 different Salmeterol/fluticasone EH products against the reference product in a pivotal-scale PK trial with an adaptive design. In Part I study treatments were administered without concomitant charcoal. One successful EH product was selected for Part II and tested for BE of salmeterol lung deposition after administration with charcoal. Salmeterol lung deposition was lower for the EH test product and the BE criteria were not met. Therefore, none of the EH products tested in SAMPO 3106009 were therapeutically equivalent with Seretide Diskus.

Further product development was performed between and after the three studies based on the study results.

Pivotal pharmacokinetic study: SAULI 3106010

SAULI 3106010 was an open (laboratory-blinded) single-dose, four-treatment, four-period, four-sequence crossover study conducted in 65 healthy volunteers, comparing three different versions of Salmeterol/fluticasone Easyhaler (A, B and C), 50 microgram/500 microgram/inhalation, inhalation powder, with Seretide Diskus, 50 microgram/500 microgram/inhalation, inhalation powder under fasting conditions and without concomitant administration of activated charcoal. A single dose of 2 inhalations was administered. The study was conducted between 20th July and 23rd November 2016. Blood samples were collected pre-dose and up to 34 hours post-dose. In the original protocol, the intention was to have a part II of the study where administration with activated charcoal was performed (as in study SAMPO 3106009), but in an amendment to the study protocol this part was omitted and replaced with calculation of $AUC_{0\text{-}30\ min}$ (together with C_{max}) for assessment of salmeterol efficacy. For fluticasone propionate, 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 but the absorption of the drug in the lung is very quick (median t_{max} was 4 minutes in the study). Thus, the use of $AUC_{0\text{-}30\ min}$ as a surrogate for salmeterol efficacy in a study without activated charcoal can be accepted. There was frequent early sampling which is crucial in order to catch salmeterol C_{max}. The study design is considered acceptable. Plasma concentrations of salmeterol and fluticasone propionate were determined with an adequately validated LC/MS/MS method.

The results are presented below.

Fluticasone propionate

Table 2: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for fluticasone propionate, n=61.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test A	1516.67 ± 388.82	130.63 ± 35.47	2.00 (0.3 - 4.0)
Test B	1879.72 ± 440.28	172.90 ± 44.41	1.50 (0.1 - 4.0)
Test C	1560.39 ± 379.64	134.48 ± 35.39	2.00 (0.3 - 4.0)
Reference	1885.41 ± 439.55	164.50 ± 48.46	2.00 (0.1 - 4.0)
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		

Table 3: Bioequivalence evaluation of fluticasone propionate

	$AUC_{(0-t)}$		C_{max}	
	Geometric Mean Ratio (Test/Reference)	**90% Confidence interval**	**Geometric Mean Ratio (Test/Reference)**	**90% Confidence interval**
Test **A**	0.8005	0.7675 - 0.8350	0.7952	0.7548 - 0.8377
Test **B**	0.9980	0.9568 - 1.0410	1.0594	1.0057 - 1.1161
Test **C**	0.8258	0.7917 - 0.8614	0.8225	0.7807 - 0.8665
	Geometric Mean Ratio (Test/Reference)	**95% Confidence interval**	**Geometric Mean Ratio (Test/Reference)**	**95% Confidence interval**
Test **B**	0.9980	0.9491 - 1.0495	1.0594	0.9956 - 1.1274
Test **C**	0.8258	0.7853 - 0.8684	0.8225	0.7729 - 0.8752
	Geometric Mean Ratio (Test/Reference)	**96.7% Confidence interval**	**Geometric Mean Ratio (Test/Reference)**	**96.7% Confidence interval**
Test **B**	0.9980	0.9448 - 1.0542	1.0594	0.9901 - 1.1336

For AUC_{0-t} and C_{max} the multiplicity corrected 96.7% confidence interval for the ratio of the test and reference products for fluticasone propionate fell within the conventional acceptance range of 80.00-125.00% for test product B. The applicant has adequately corrected the results for multiplicity. Thus, the relevant point estimate and confidence interval for AUC_{0-t} is 0.9980 (0.9448 - 1.0542) and for C_{max} 1.0594 (0.9901 - 1.1336).

Salmeterol

For salmeterol, a non-inferiority approach was used for AUC_{0-t} and C_{max} (surrogate for safety) and a bioequivalence approach was used for $AUC_{0-30\ min}$ and C_{max} (surrogate for efficacy).

Table 4: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for salmeterol, n=59.

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-30\ min}$ pg*h/ml	C_{max} pg/ml	t_{max} min
Test A	443.32 ± 195.14	76.36 ± 22.75	297.12 ± 104.07	4.00 (2.0 - 15.0)
Test B	499.22 ± 144.56	94.90 ± 24.96	375.10 ± 115.88	4.00 (4.0 - 6.0)
Test C	427.53 ± 143.80	76.54 ± 19.79	295.86 ± 93.08	4.00 (2.0 - 6.0)
Reference	446.15 ± 148.73	82.88 ± 27.16	338.25 ± 125.07	4.00 (2.0 - 6.0)

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

Table 5: Non-inferiority evaluation of salmeterol in SAULI 3106010

	$AUC_{(0-t)}$		C_{max}	
	Geometric Mean Ratio (Test/Reference)	**Confidence limit Upper 95%**	**Geometric Mean Ratio (Test/Reference)**	**Confidence limit Upper 95%**
Test **A**	0.9752	1.0221	0.8834	0.9419
Test **B**	1.1286	1.1829	1.1266	1.2012
Test **C**	0.9590	1.0051	0.8836	0.9420

Test A, Test B or Test C = Easyhaler test products in SAULI 3106010

Table 6: Bioequivalence evaluation of salmeterol in SAULI 3106010

Pharmacokinetic Parameter	Geometric Mean Ratio (Test/Reference)	90% Confidence Intervals
AUC_{30min}	1.1605	1.0989, 1.2255
C_{max}	1.1266	1.0567, 1.2012

Test = Easyhaler test product B in SAULI 3106010

For AUC_{0-t} and C_{max} the upper limit of the one-sided 95% confidence interval for the ratio of the test and reference products fell below 125.00% for all three test products.

For $AUC_{0-30\ min}$ 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 test product B. No multiplicity correction was performed in this step and a question was raised regarding this in the primary round. However, the applicant has demonstrated that using the more conservative CIs (98.3% CI for non-inferiority evaluation and 96.7% CI for bioequivalence evaluation), the results show therapeutic equivalence of salmeterol between Salmeterol/fluticasone Easyhaler and Seretide Diskus, excluding a possible inflation of type I error.

It was questioned in the primary round that subjects not having data from all four periods were excluded from the statistical analysis. As a sensitivity analysis, a reanalysis was performed where only the data from test B and reference was included (all subjects having data from both

test B and reference was included) and where the estimation of variance was based on only test B and reference. The confidence grade was as for the already performed analysis (e g 96.7 % for the fluticasone propionate comparison). The results of the sensitivity analyses were also within the standard acceptance criteria for bioequivalence.

Pharmacokinetic conclusion
Based on the submitted pivotal bioequivalence study, the applied version of Salmeterol/fluticasone Easyhaler 50/500 microgram (EH B in the study) is considered therapeutically equivalent with Seretide Diskus 50/500 microgram.

Based on the in vitro dose proportionality studies, the results of study SAULI 3106010 with 50/500 microgram formulation CAN be extrapolated to the other strength 50/250 microgram.

Pharmacodynamics/Clinical efficacy/Clinical safety
Data are provided on device functioning *in vivo* (inhalatory flow) have been submitted. No other studies are conducted as therapeutic similarity is documented based on pharmacokinetics.

SALIF 3106002 -Inspiratory flow parameters with placebo dry powder inhalers, Easyhaler and Diskus; an open, randomised, multicentre study in patients with asthma or COPD.

This was an open, randomised, multicentre crossover study with placebo EH and Diskus inhalers. Two inhaler versions of the EH were investigated. The Diskus inhaler studied was the one used for Seretide Diskus products. All intended patient populations of the Salmeterol/fluticasone EH including asthmatic children, adults and elderly as well as COPD patients were recruited into the study (a range of different severities for both diseases).
The primary objective of the study was to characterise the inspiratory flow parameters across 2 EH inhaler versions and 1 Diskus inhaler in patients with asthma (including children, adults, and the elderly) and in patients with COPD.
The secondary objective of the study was to build a prediction model for estimating PIF rates and inspiratory volume through the EH and Diskus based on anthropometric and lung function measurements.

The mean PIF rates measured through EH type B device were lowest in all subgroups and the PIF rates measured through Diskus device were highest in all subgroups except in COPD patients where EH type A device provided the highest value. Variation was greatest with Diskus device in all subgroups.

The device EH type A is the device to be marketed. It is already available on the market with other substances and thus Study SALIF 3106002 is not regarded pivotal for this application.

Similar in vitro flow rate dependency between the test and the reference product was shown with the flow rate range achievable by the intended patient population. Therefore, pharmacokinetic findings obtained in healthy volunteers can be extrapolated to intended patient populations of Salmeterol/fluticasone Easyhaler.

Paediatric population
Notably, the lowest age of treatment is proposed to 12 years of age, i.e. the product is intended also for adolescents although the pivotal pharmacokinetic study was conducted in adults. According to the OIP guideline (CHMP/EWP/4151/00 Rev. 1) studies should be performed in the intended patient population (i.e. including adolescents) and adolescents could then be

included as a specific sub-population. However, following praxis developed over time and detailed in a Q&A document, it is found more appropriate to recruit healthy adult volunteers to studies as these are less variable than patients. In addition, patients may be less discriminatory since lung depositions are mostly central due to bronchoconstriction. In the current application efficacy and safety is supported by means of pharmacokinetics in healthy adult volunteers. Adolescents have not and may not be included in such studies. Nevertheless, it is acceptable to waive data in in adolescents as these have a similar range of airway geometry, breathing patterns and tidal volumes as adults. Moreover the development of co-ordination and skill in using devices in adolescents is considered to be similar to that in adults.

IV.3 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 Salflumix Easyhaler.

Safety specification
Summary of safety specification:

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	-
Missing information	• Patients with hepatic impairment • Breastfeeding women

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 approvable.

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 benefit/risk ratio is considered positive and Fusacomb Easyhaler, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose, inhalation powder is 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 Fusacomb Easyhaler, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose, inhalation powder was positively finalised on 2018-03-15.

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MEDICAL PRODUCTS AGENCY

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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