CBG MEB

Public Assessment Report

Scientific discussion

Salmeterol/Fluticasonpropionaat Sandoz micrograms pressurised inhalation, suspension

(salmeterol xinafoate/fluticasone propionate)

NL/H/3707/001-002/DC

Date: 15 November 2017

This module reflects the scientific discussion for the approval of Salmeterol/ Fluticasonpropionaat Sandoz 25/125 and 25/250 micrograms pressurised inhalation, suspension. The procedure was finalised on 16 March 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
COPD	Chronic Obstructive Pulmonary Disease
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
Log_{kow}	Logarithm of octanol/water partition coefficient
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board of the Netherlands
OIP	Orally Inhaled Products
$PEC_{SURFACEWATER}$	Predicted Environmental Concentration in surface water
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Salmeterol/Fluticasonpropionaat Sandoz 25/125 and 25/250 micrograms, pressurised inhalation, suspension from Sandoz B.V.

The product is indicated in the regular treatment of asthma where use of a combination product (long-acting β2 agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist

This medicine is not recommended for use in children.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming similarity with the innovator product Seretide Evohaler 25/125 and 25/250 micrograms per metered dose pressurised inhalation, suspension, containing the active substances salmeterol and fluticasone. Seretide Evohaler has been registered by Glaxo Wellcome UK Ltd. Trading as GSK, UK since 16 June 2000.
The Dutch reference product is Seretide Inhalator CFK-vrij, pressurised inhalation, suspension (NL License RVG 25866-25867), registered by GlaxoSmithKline BV since 30 January 2001 through MRP UK/H/0392/002-003.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Romania, Slovakia, Slovenia and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Salmeterol/Fluticasonpropionaat Sandoz is a white homogeneous suspension.
Salmeterol/Fluticasonpropionaat Sandoz 25/125 micrograms - each metered dose (ex valve) contains 25 micrograms of salmeterol (as salmeterol xinafoate) and 125 micrograms of fluticasone propionate. This is equivalent to a delivered dose (ex actuator) of 21 micrograms of salmeterol and 110 micrograms of fluticasone propionate.

Salmeterol/Fluticasonpropionaat Sandoz 25/250 micrograms - each metered dose (ex valve) contains 25 micrograms of salmeterol (as salmeterol xinafoate) and 250 micrograms of fluticasone propionate. This is equivalent to a delivered dose (ex actuator) of 21 micrograms of salmeterol and 220 micrograms of fluticasone propionate.

The suspension is packed in an aluminium container with a suitable metering valve and a polypropylene actuator with dose indicator and fitted with dust cap in a sealed pouch with a silica gel bag. Each container is filled to deliver 120 metered doses.

The only excipient used is norflurane (the propellant).

II.2 Drug Substances

Salmeterol xinafoate
The active substance salmeterol xinafoate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water, soluble in methanol, slightly soluble in anhydrous alcohol. Polymorphic form I is used. This form is maintained throughout the manufacturing process of the drug product and upon storage. Since the drug product is a pressurized metered dose inhaler, in which the drug substance is present as a suspension, the particle size of the drug substance is critical for the performance of the drug product. The particle size limit was demonstrated to be suitable for the drug product.

The CEP procedure is used for this active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with or tighter than the Ph. Eur. requirements with the additional parameters as mentioned on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The substance should be stored protected from light according to the storage condition described in the Ph. Eur. monograph.
The packaging effectively protects the drug substance against light.

Fluticasone propionate
The active substance fluticasone propionate is an established active substance described in the Ph.Eur. The active substance is practically insoluble in water, sparingly soluble in methylene chloride, and slightly soluble in alcohol. Polymorphic form I is used. This form is maintained throughout the manufacturing process of the drug product and upon storage. Since the drug product is a pressurized metered dose inhaler, in which the drug substance is present as a suspension, the particle size of the drug substance is critical for the performance of the drug product. The particle size limit was demonstrated to be suitable for the drug product.

The CEP procedure is used for this active substance.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with or tighter than the Ph. Eur. requirements with the additional parameters as mentioned on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Quality control of drug substance
The active substance specification is in line with the Ph. Eur., the additional parameters as mentioned on the CEP and additional in-house requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of the excipient is justified and its function is explained. All aspects of the *Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products* and of the *Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products For Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents* regarding the pharmaceutical equivalence between the test the and reference product have been discussed.
Test and reference product were compared for description, identification, number of actuations per container, average weight, moisture content, assay, net weight, mean delivered dose, retention in container, X-ray diffraction, impurities, delivered dose uniformity data and fine particle mass. The data shows that the physicochemical parameters of the reference product and test product are comparable.
The dose proportionality was evaluated between both strengths of test product and the reference product strengths by means of the cascade data generated using the Anderson Cascade Impactor. For Salmeterol, the fine particle mass was comparable for both the strengths of the test and reference product. For Fluticasone, the pharmaceutical data demonstrates dose proportionality across the two strengths (250 mcg/actuation and 125 mcg/actuation) of fluticasone propionate. As per the OIP guidelines, based on in vitro dose proportionality, in vivo results with the highest strength can therefore be extrapolated to the lower strength and vice versa.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consist of mixing the drug substances with the propellant under stirring and pressure and filling the mixture into the containers. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches of both strengths. The data adequately demonstrated that the drug product can be manufactured in a reproducible way.

Control of excipients
Although a Ph. Eur. monograph is available for norflurane, in-house specifications have been set. The specification for norflurane is acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, average weight, number of actuations per container, moisture, fine particle mass, microbiological contamination, total can assay, mean delivered dose, delivered dose uniformity, leak test, related substances and particulate matter.
The specifications for fine particle mass have been adequately justified based on the results of the batches used in the pharmacokinetic studies, range observed in the tested reference product batches and the variation in batches of the proposed products. The proposed limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches of both strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full scale batches of both strengths. The batches were stored for 24 months at 25°C/60%RH and 30°/65%RH and 6 months at 40°/65%RH. The batches were stored in the commercial packaging, including an aluminium overpouch. Only an increase in moisture was observed, yet all results complied. The stability results support the accepted shelf-life and storage condition of 2 years, in the outer packing, stored not above 25°C.
An in-use stability study was conducted, covering 3 months. It was performed on two batches of both strengths of the product by removing the actuator from the protective aluminium pouch three months

prior to the end of-shelf-life. It was adequately demonstrated that the product is stable for 3 months after opening the pouch at the end of the shelf-life.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Salmeterol/Fluticasonpropionaat Sandoz 25/125 and 25/250 micrograms, pressurised inhalation, suspension has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The MAH has performed a Phase I environmental risk assessment (ERA) of salmeterol xinafoate and fluticasone propionate, which is considered acceptable. The $PEC_{SURFACEWATER}$ for both substances is below the action limit of 0.01 mcg/L. The log_{KOW} values for both substances are below the threshold value (4.5). Since the product is a hybrid and is intended to replace already marketed fixed-dose combination products containing the same active substances, no increased exposure to the environment is expected. No further action is necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Seretide Evohaler 25/125 and 25/250 micrograms which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, it is agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Salmeterol and fluticasone are well-known active substances with established efficacy and tolerability.

To support this hybrid application, the MAH submitted 8 pharmacokinetic bioequivalence studies and one pharmacodynamic study for the safety of salmeterol. In the 8 pharmacokinetic studies Salmeterol/Fluticasonpropionaat Sandoz was compared to Seretide Evohaler for both the 25/250 mcg and 25/125 mcg strength.

IV.2 Pharmacokinetics

IV.2.1 Design and populations studied

Pharmacokinetic studies with and without charcoal blockage have been submitted as well as a pharmacokinetic study using a spacing device.

The study design of comparative bioavailability studies without charcoal is considered adequate to demonstrate equivalence with respect to safety and efficacy of fluticasone because the oral bioavailability of fluticasone is negligible. Because orally ingested salmeterol contributes significantly

to the systemic exposure of salmeterol, bioequivalence studies with charcoal (lung deposition) and without administration of charcoal (total systemic exposure for safety) for both strengths are provided, which is in accordance with the CHMP guideline on orally inhaled products (CPMP/EWP/4151/00 Rev. 1, dated January 2009).

Pharmacokinetics of salmeterol is dose proportional, and to improve the accuracy of analysis of salmeterol in plasma, in each study the subjects inhaled two puffs. This corresponds to salmeterol 50 mcg (2*25 mcg) and fluticasone 250 mcg (2*125 mcg) or 500 mcg (2*250 mcg) .
The analytical methods for the determination of fluticasone and salmeterol were adequately validated. Statistics was described adequately, and methods were acceptable.

In all studies the washout period was long enough, i.e. at least 10 times the elimination half-life for both salmeterol and fluticasone ($t_{1/2}$ of 5.5 hours for salmeterol and 8 hours for fluticasone).

In the SmPC of Seretide Evohaler, two specific spacers are indicated for use. Bioequivalence between the test and the reference product of the 25/250 mcg strength has also been demonstrated using the indicated spacers for fluticasone and salmeterol in Study PRC/CRD/13/11. It is acceptable to demonstrate bioequivalence using spacers for the higher strength alone, as bioequivalence using spacing device can be expected for the lower 25/125 mcg strength by considering the demonstration of bioequivalence for the lower strength without a spacer and also considering the similarity in dose proportionality of *in vitro* fine particles.

1) Study E-RES/15/13-Q13

A randomised, single-dose, open-label, two-period crossover bioequivalence study comparing the test product Salmeterol/Fluticasonpropionaat Sandoz pressurised metered dose inhaler (pMDI) 25/250 mcg per actuation with the reference product Seretide Evohaler 25/250 mcg per actuation, administered as 2 puffs in healthy adult male subjects under fasting conditions.
A total of 74 healthy male adults, aged 19-41 years were dosed. Venous blood samples were drawn for fluticasone at pre-dose (0 h) and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 3.50, 4, 6, 8, 10, 12, 18, 24 and 36 hours following drug administration in each period. The venous blood samples were drawn for salmeterol at pre-dose (0 h) and at 0.05, 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours following drug administration in each period.

The statistical analysis for demonstration of bioequivalence for salmeterol was performed based on all the 66 subjects who completed both treatment periods. For fluticasone the analysis was based on 65 subjects, because one subject had pre-dose value >5% of C_{max}.

2) Study PRC/CRD/03/12

A randomised, single-dose, open-label, four-period crossover replicate bioequivalence study comparing only salmeterol component from the test product of Salmeterol/Fluticasonpropionaat Sandoz pPMDI 25/250 mcg per actuation with the reference product Seretide Evohaler, administered as 2 puffs in healthy adult male subjects under fasting conditions using a charcoal blockade method.

A total of 42 healthy male adults, aged 18-38 years were dosed. Venous blood samples were drawn for salmeterol at pre-dose (0 h) and at 0.05, 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 6, 8, 10, 12, 14, 16 and 18 hours following drug administration in each period.

Three subjects completed only the first 3 treatment periods. All 42 subjects were included in the analysis. As stated in the protocol this study was designed as a replicate study to reduce the intra-subject variability. The use of replicate design is acceptable as a high variability in pharmacokinetics of salmeterol can be expected.

3) Study PRC/CRD/13/11

A randomised, single-dose, open-label, four-way crossover bioequivalence study comparing the test product Salmeterol/Fluticasonpropionaat Sandoz pMDI 25/250 mcg per actuation with the reference product Seretide Evohaler, both administered as 2 puffs. The Volumatic spacer was used for the administrations in period 1 and 2, the AeroChamber Plus VHC spacer was used in period 3 and 4.

A total of 24 healthy male adults, aged 22-43 years were dosed. Venous blood samples were drawn for fluticasone at pre-dose (0 h) and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3, 4, 6, 8, 10, 12, 18, 24 and 36 hours following drug administration in each period. The venous blood samples were drawn for salmeterol at pre-dose (0 h) and at 0.05, 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 6, 10, 12, 14, 18 and 24 hours following drug administration in each period.

One subject did not complete any treatment period, and was therefore excluded from the statistical analysis.

4) Pilot study PRC/CRD/07/10

A randomised, single-dose, open-label, two-period crossover bioequivalence study comparing the test product Salmeterol/Fluticasonpropionaat Sandoz pMDI 25/250 mcg per actuation with the reference product Seretide Evohaler 25/250 mcg per actuation, administered as 2 puffs in healthy adult male subjects under fasting conditions.

Bioequivalence for fluticasone and salmeterol without charcoal was investigated in 24 healthy subjects. Venous blood samples were drawn for fluticasone at pre-dose (0 h) and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 3.50, 4, 6, 8, 10, 12, 18, 24 and 36 hours following drug administration in each period. The venous blood samples were drawn for salmeterol at pre-dose (0 h) and at 0.05, 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours following drug administration in each period.

Overall, statistical analysis for fluticasone was performed based on the data of 19 subjects (exclusion of 5 subjects due to pre-dose level > 5% of C_{max}), and for salmeterol the analysis was performed for all 24 subjects.

5) Study E-RES/24/13-Q13

A randomised, single dose, open label, four period crossover bioequivalence study comparing the test product Salmeterol/Fluticasonpropionaat Sandoz pMDI 25/125 mcg per actuation with the reference product Seretide Evohaler 25/125 mcg, administered as 2 puffs in healthy adult male subjects under fasting conditions both with and without charcoal blockade.

A total of 80 healthy male adults, aged 18-42 years were dosed. Blood samples were drawn pre-dose and at 0.05, 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours post dose. 20 of these samples were used for fluticasone analysis without charcoal at time points of pre-dose and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3, 4, 6, 8, 10, 12, 18, 24 and 36 hours post dose.
For the with charcoal arms (for which samples for salmeterol only were obtained), blood samples were withdrawn as follows: pre-dose and at 0.05, 0.08, 0.17, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours post dose.

The statistical analysis for demonstration of bioequivalence for fluticasone and salmeterol without charcoal was performed based on all the 72 subjects who completed both test and reference treatment without charcoal.
For salmeterol with charcoal the analysis was based on the 73 subjects who completed both test and reference treatment with charcoal.

6) Study E-RES/14/12-Q13

A randomised, single dose, open label, four period crossover bioequivalence study comparing the test product Salmeterol/Fluticasonpropionaat Sandoz pMDI 25/125 mcg per actuation with the reference product Seretide Evohaler 25/125 mcg per actuation, administered as 2 puffs in healthy adult male subjects under fasting conditions both with and without charcoal blockade.

74 subjects were dosed. Blood samples were drawn pre-dose and at 0.05, 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours post dose. 20 of these samples

were used for fluticasone analysis without charcoal at time points of pre-dose and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3, 4, 6, 8, 10, 12, 18, 24 and 36 hours post dose.
For the with charcoal arms (for which samples for salmeterol only were obtained), blood samples were withdrawn as follows: pre-dose and at 0.05, 0.08, 0.17, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours post dose.

Statistical analyses for fluticasone and salmeterol without charcoal were performed based on the data of 68 subjects (exclusion of 4 subjects who only completed the first period due to personal reasons and 2 subjects who were discontinued due to improper dosing), and for salmeterol with charcoal the analysis was performed for 62 subjects (additional exclusion of 5 subjects who did not arrive for period 3 and 4, and 1 subject who did not arrive for period 4 due to personal reasons).

7) Study EU-FS-MU-HV103

A randomised, single-dose, open-label, four-period crossover replicate bioequivalence study comparing the salmeterol component alone from Salmeterol/Fluticasonpropionaat Sandoz pMDI 25/125 mcg per actuation (test product) with Seretide Evohaler 25/125 mcg per actuation (reference product), administered as 2 puffs in healthy adult male subjects under fasting conditions with charcoal blockade.

The study was conducted in 72 healthy adult male subjects, aged 18 to 45 years. Venous blood samples were drawn for salmeterol at pre-dose (0 h) and at 0.05, 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours following drug administration in each period.

Out of the 72 subjects, 63 subjects completed all four periods. Five subjects were excluded from the statistical analysis: four subjects did not arrive for period 2, 3 and 4 due to personal reasons, and one subject discontinued in period 1 due to adverse event. The statistical analysis was conduct for the 67 subjects who completed at least one treatment of test and one treatment of reference product.

8) Study EU-FS-MU-HV104

A randomised, single-dose, open-label, four-period crossover replicate bioequivalence study comparing the salmeterol component alone from Salmeterol/Fluticasonpropionaat Sandoz pMDI 25/125 mcg per actuation (test product) with Seretide Evohaler 25/125 mcg per actuation (reference product), administered as 2 puffs in healthy adult male subjects under fasting conditions with charcoal blockade.

The study was conducted in 72 healthy adult male subjects, aged 19 to 38 years. Venous blood samples were drawn for salmeterol at pre-dose (0 h) and at 0.05, 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 and 36 hours following drug administration in each period.

Out of the 72 subjects, 69 subjects completed all four periods. Two subjects were excluded from the statistical analysis: one was discontinued in period 1 due to adverse events, and another subject did not arrive for period 2 and the rest of periods due to personal reasons. The statistical analysis was conducted for the 70 subjects who completed at least one treatment of test and one treatment of reference product.

IV.2.2 Results

Across study comparisons of pharmacokinetic statistical analyses for salmeterol and fluticasone are summarised in Table 1 below, and the 90% CIs and the ratios for both AUC_t and C_{max} are presented in the table for fluticasone without charcoal, and salmeterol with and without charcoal.

Table 1. Summary of results from all pharmacokinetic studies.

Studies	Design	Fluticasone without charcoal, ratios (90% CIs)		Salmeterol without charcoal, ratios (90% CIs)		Salmeterol with charcoal, ratios (90% CIs)	
		AUCt	Cmax	AUCt	Cmax	AUCt	Cmax
25/250 mcg strength							

1) E-RES/15/13-Q13	N=65 (fluticasone) N=66 (salmeterol)	1.06 (0.99 – 1.14)	0.97 (0.90 – 1.04)	1.10 (1.03 – 1.19)	0.91 (0.82 – 1.00)	-	-
2) PRC/CRD/03/12	N=42 (replicate)	-	-	-	-	1.08 (0.99 – 1.18)	1.05 (0.96 – 1.14)
3) PRC/CRD/13/11	N=23 (Volumatic spacer)	1.10 (1.03 – 1.17)	1.09 (1.02 – 1.17)	1.08 (0.97 – 1.20)	1.08 (0.98 – 1.18)	-	-
	N=23 (AeroChamber)	1.04 (0.96 – 1.13)	1.03 (0.94 – 1.13)	1.11 (1.03 – 1.20)	1.10 (0.99 – 1.23)	-	-
4) PRC/CRD/07/10#	N=19 (fluticasone) N=24 (salmeterol)	0.95 (0.85-1.06)	0.96 (0.84-1.10)	1.11 (1.02-1.20)	1.17 (1.01-1.36)	-	-
25/125 mcg strength							
5) E-RES/24/13-Q13	N=72; N=73 (with charcoal)	0.91 (0.82–0.99)	0.92 (0.84 - 1.00)	1.05 (0.98–1.12)	0.94 (0.86 – 1.03)	0.83 (0.72–0.96)	0.90 (0.80 – 0.99)
6) E-RES/14/12-Q13	N=68; n=62 (with charcoal)	1.10 (1.03 – 1.19)	1.06 (0.99 – 1.14)	1.28 (1.21–1.36)	1.29 (1.17 – 1.43)	1.15 (1.03 – 1.29)	1.21 (1.10 – 1.35)
7) EU-FS-MU-HV 103	N=67 (replicate)					0.92 (0.85-0.99)	0.84 (0.78-0.90)
8) EU-FS-MU-HV 104	N=70 (replicate)	-	-	-	-	1.14 (1.05 – 1.23)	1.09 (1.02 – 1.16)

#This study is considered as a pilot study.

Salmeterol/Fluticasonpropionaat Sandoz 25/250 mcg

For investigation of therapeutic equivalence for the 25/250 mcg strength, the MAH started with Study PRC/CRD/07/10, where bioequivalence could not be demonstrated for salmeterol without charcoal due to relatively high variability for C_{max} of salmeterol (31%). A higher systemic exposure of salmeterol with the test product was identified than with the reference product. For this reason the MAH conducted a pharmacodynamic safety study (PRC/CRD/02/11) to establish comparable safety for salmeterol (see below under IV.3 'Pharmacodynamics').

Although equivalence for fluticasone was shown in Study PRC/CRD/07/10, there were 5 subjects with a pre-dose level of fluticasone >5% of C_{max}. Therefore, the MAH conducted bioequivalence study E-RES/15/13-Q13 (Pivotal study) in a larger population based on the same study design as PRC/CRD/07/10 for both salmeterol and fluticasone without charcoal blockade. The 90% CIs for AUC and C_{max} are within the acceptance range of 0.80-1.25 for both salmeterol and fluticasone

Study PRC/CRD/03/12 (25/250 mcg strength) using charcoal was conducted for comparing lung deposition of salmeterol of test and reference product. The use of replicate design is acceptable as a high variability in pharmacokinetics of salmeterol can be expected. The 90% CIs for AUC and C_{max} are within the acceptance range of 0.80-1.25 for salmeterol with charcoal.

Salmeterol/Fluticasonpropionaat Sandoz 25/125 mcg

For the 25/125 mcg strength, Study E-RES/14/13-Q13 was conducted in 74 subjects initially for investigating fluticasone and salmeterol without charcoal and salmeterol alone with charcoal. The study failed to demonstrate bioequivalence for salmeterol with and without charcoal. Therefore the study was repeated using the same study design: Study E-RES/24/13-Q13 in 80 subjects. In this study equivalence could not be demonstrated for salmeterol with charcoal blockade, therefore the MAH performed two replicate design bioequivalence studies: EU-FS-M-HV103 and EU-FS-M-HV104. The latter study was conducted for confirmation, because there was an outlier in Study HV103 who was critical for demonstration of bioequivalence for salmeterol with charcoal. Study EU-FS-M-HV104

showed that the 90% CIs for AUC and C_{max} were within the acceptance range of 80-125% for salmeterol with charcoal.

IV.2.3 Conclusion on the pharmacokinetic studies

The results of the studies for the 25/250 mcg strength showed that the test product was bioequivalent to reference product for fluticasone without charcoal, and for salmeterol with and without charcoal.
The study using a spacer was only conducted for the higher strength, which is considered acceptable because similar *in vitro* differences for the 25/125 and 25/250 mcg test/reference comparisons were observed. For the low 25/125 mcg strength, there is no indication of a relevant difference in lung deposition or systemic exposure to salmeterol following inhalation of Salmeterol/Fluticasonpropionaat Sandoz 25/125 mcg as compared to Seretide Evohaler 25/125 mcg. In conclusion, bioequivalence between Salmeterol/Fluticasonpropionaat Sandoz and Seretide Evohaler has been demonstrated for both strengths under the required conditions.

IV.3 Pharmacodynamics

Study PRC/CRD/02/11
Design
Regarding pharmacodynamic safety of AirFluSal, the MAH submitted one study investigating the safety of salmeterol. The study was designed as a randomised, double blind, placebo controlled, five way crossover study in healthy adult male subjects to compare the systemic pharmacodynamic effects of the salmeterol component from AirFluSal and Seretide Evohaler. In the study, the subjects were randomised to receive a single dose of 150/1500 mcg and 300/3000 mcg of the test and reference products as well as placebo on 5 treatment days in a crossover manner as per the randomisation scheme. Each study day was separated by a 7-day washout period. On each treatment day, a 12 lead ECG was taken at 30 minute intervals starting from 90 minutes prior to dosing. The baseline heart rate was considered to be stable when two consecutive readings of heart rate were within ±10 beats/min prior to dosing. The QTc baseline was obtained from the last two consecutive ECG recordings obtained for heart rate. The average of the last two stable and consecutive baseline values was used for the pre-dose values for heart rate and QTc interval.

Results
A dose-related increase in heart rate, QTc and plasma glucose and a dose-related decrease in serum potassium was observed. Both the supra-therapeutic doses (150 mcg and 300 mcg) showed a significant difference for the primary endpoint (average heart rate) compared with placebo for both the test and reference product. There was also a significant difference between the doses tested.
The average increase in heart rate was equivalent for the test product and the reference product when the dose was increased for salmeterol. For the other safety endpoints such as average serum potassium, average plasma glucose and maximum QTc interval, no significant or appreciable differences were observed between the treatments at any dose level whilst there were clear differences between doses for each product. The two active products were comparable at each dose level with respect to the effects on systolic and diastolic blood pressure. Overall, the study demonstrated that the safety profile of the salmeterol component of the test product (6 puffs/12 puffs) is well tolerated in healthy subjects. The test product is comparable with the reference product in the aspects of pharmacodynamic safety.

IV.4 Risk Management Plan

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 AirFluSal.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Respiratory-related events or deaths - Pneumonia

	- 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	- Off-label use in children below 12 years old
Missing information	- Patients with hepatic impairment - Pregnant and breastfeeding women

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Seretide Evohaler. No new clinical studies were conducted. Bioequivalence has been demonstrated for both strengths under requested conditions (including with charcoal and specific spacers). A comparable safety profile for salmeterol following inhalation (6 puffs/12 puffs) of Airflusal with the reference product has been demonstrated. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The PL is identical in content to the currently approved and successfully user tested package leaflet of the reference product of Seretide Evohaler, approved via procedure UK/H/0392/MR. The bridging report is acceptable based upon similarities in the textual content, format, design, layout and wording of the PL of Seretide Evohaler.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Salmeterol/Fluticasonpropionaat Sandoz 25/125 and 25/250 micrograms, pressurised inhalation, suspension have a proven chemical-pharmaceutical quality and are hybrid forms of Seretide Evohaler 25/125 and 25/250 micrograms per metered dose pressurised inhalation, suspension. Seretide Evohaler is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence between Salmeterol/Fluticasonpropionaat Sandoz and Seretide Evohale has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that similarity has been demonstrated for Salmeterol/Fluticasonpropionaat Sandoz with the reference product, and has therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 March 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached