CBG MEB

Public Assessment Report

Scientific discussion

Salmeterol/Fluticasonpropionaat 25 microgram/125 microgram/dose and 25 microgram/250 microgram/dose Vincion, pressurised inhalation, suspension

(salmeterol xinafoate/fluticasone propionate)

NL License RVG: 115995-115996

Date: 16 October 2017

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasonpropionaat 25 microgram/125 microgram/dose and 25 microgram/250 microgram/dose Vincion, pressurised inhalation, suspension. The marketing authorisation was granted on 4 September 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
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 (MEB) of the Netherlands has granted a marketing authorisation for Salmeterol/Fluticasonpropionaat 25 microgram/125 microgram/dose and 25 microgram/250 microgram/dose Vincion, pressurised inhalation, suspension from Vincion BV.

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

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled shortacting 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 national 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 marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Salmeterol/Fluticasonpropionaat Vincion is a white homogeneous suspension. Every Salmeterol/Fluticasonpropionaat Vincion pre-dispensed dose contains 25 microgram salmeterol (as salmeterol xinafoate) and 125 or 250 microgram fluticasone propionate (metered dose). This is equivalent to a delivered dose of 21 microgram salmeterol and 110 or 220 microgram fluticasone propionate.

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

The only excipient is norflurane (HFA 134a) as 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
Stability data on the active substance have been provided for three commercial scale batches stored for 24 months at 25°C/60%RH and for 6 months at 40°C/75%RH. Photostability data of the drug substance are not included but since the packaging will effectively protect the drug substance against light, and should be stored protected from light according to the storage condition, no objection will be made.

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 and the addition an additional in-house requirement for mesityl oxide.. 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 3 commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 7 commercial scale batches stored for up to 72 months at 25°C/60%RH (3 batches) and for 3 batches stored at 40°C/75%RH. Photostability data of the drug substance are not included but since the packaging will effectively protect the drug substance against light, and should be stored protected from light according to the storage condition, no objection will be made.

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
The excipient norflurane complies with an in-house specification. This is acceptable as testing according the Ph Eur monograph is currently impossible due to monograph restrictions. The in-house specification is the currently usual specification and 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 30°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 3 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 Vincion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

Since Salmeterol/Fluticasonpropionaat Vincion is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.1 Discussion on the non-clinical aspects

This product is a hybrid formulation of Seretide Evohaler 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, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1.1 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 Vincion 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 Vincion pMDI 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 Vincion 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 Vincion 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 Vincion 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 Vincion 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 Vincion 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 Vincion 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.1.2 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	N=67					0.92	0.84

103	(replicate)					(0.85-0.99)	(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 Vincion 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 Vincion 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 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 Salmeterol/Fluticasonpropionaat Vincion

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity reactions, including anaphylactic reactions - Angina pectoris - Serious respiratory-related events and death - Cardiac arrhythmias - Paradoxical bronchospasm - Systemic effects of inhaled corticosteroid (Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression) - Pneumonia in patients with COPD
Important potential risks	- Adrenal suppression - Off-label use in children below 12 years old

	- Off-label use in COPD
Missing information	- Patients with hepatic impairment - Safety in lactating mothers - Information on children aged 4 to 11 years.

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

IV.3 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 Salmeterol/Fluticasonpropionaat 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 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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Salmeterol/Fluticasonpropionaat 25 microgram/125 microgram/dose and 25 microgram/250 microgram/dose Vincion, 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 Vincion and Seretide Evohaler has been shown to be in compliance with the requirements of European guidance documents.

In the Board meeting of 27 November 2014, the biowaiver for the 25/125 microgram strength was discussed. After bioequivalence has been demonstrated between the two strengths, all pharmacokinetic issues were considered resolved. In addition, the use of this product in adolescents was discussed. After raising the age limit of the indicating, this issue was also resolved.

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

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites); the activities for which the manufacturer/importer is responsible include batch release	IA	10-09-2015	16-09-2015	Approved	N
Replacement or addition of a manufacturer responsible for importation and/or batch release; Including batch control/testing	IA	12-11-2015	26-11-2015	Approved	N
Replacement or addition of a site where batch control/testing takes place	IA	12-11-2015	11-01-2016	Approved	N
Change in test procedure for the finished product; minor changes to an approved test procedure	IA/G	14-07-2016	12-09-2016	Approved	N