



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/486136/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aerivio Spiromax

International non-proprietary name: salmeterol / fluticasone propionate

Procedure No. EMEA/H/C/002752/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

AE	adverse event
ABS	Acrylonitrile Butadiene Styrene
ANOVA	analysis of variance
APSD	Aerodynamic Particle Size Distribution
AUC _{0-t}	area under the plasma concentration time curve from time zero (pre-dose) to the time of the last quantifiable concentration
BE	bioequivalence
CDA	Critical Device Attributes
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CMA	Critical Material Attributes
COPD	chronic obstructive pulmonary disease
CPP	Critical process parameter
CQA	Critical Quality Attribute
CSR	clinical study report
C _{max}	maximum plasma concentration
CI	confidence interval
DD	Delivered Dose
DoE	Design of experiments
DPI	dry powder inhaler/inhalation-driven, multi-dose dry powder inhaler
EC	European Commission
ECG	electrocardiogram
EDQM	European Directorate for the Quality of Medicines and Healthcare
FDC	fixed-dose combination
FP	fluticasone propionate
FPD	fine particle dose
FS Spiromax	salmeterol xinafoate / fluticasone propionate Spiromax inhalation powder
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICS	inhaled corticosteroid
IR	Infrared
ITT	intent-to-treat population
LSM	least squares means
LABA	long-acting β_2 adrenergic agonist
MMAD	Mass Median Aerodynamic Diameter
MAH	Marketing Authorisation holder
MOC	Micro-orifice Collector
MO	Major Objection
NGI	next generation impactor
NLT	Not less than
NMT	Not more than
OIP	orally inhaled product
PD	pharmacodynamics
PE	Polyethylene
Ph Eur	European Pharmacopoeia
PIF	peak inspiratory flow
PIFR	peak inspiratory flow rate
PIL/PL	patient information leaflet/package leaflet
PK	pharmacokinetics
PP	Polypropylene
PP	per protocol population
PSD	particle size distribution
QbD	Quality by design

QP	Qualified person
QTPP	Quality target product profile
RH	Relative Humidity
RMP	risk management plan
SAE	serious adverse event
SmPC	summary of product characteristics
SX	salmeterol xinafoate
T _{1/2}	terminal phase half-life
T _{max}	time to maximum observed plasma concentration
TD	total dose
TEAR	treatment-emergent adverse events
TLC	Thin layer chromatography
TSE	Transmissible Spongiform Encephalopathy
UDD	Uniformity of Delivered Dose
UHPLC	ultra-high performance liquid chromatography
µg	microgram
XRD	X-Ray Diffraction

Medicinal product no longer authorised

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 5 June 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Aerivio Spiromax, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2012. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 10b of Directive 2001/83/EC.

The applicant applied for the following indication:

Aerivio Spiromax is indicated in adults aged 18 years and older.

Asthma

Aerivio Spiromax is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 -agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β_2 -agonist
- or
- patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 -agonist.

Chronic Obstructive Pulmonary Disease (COPD)

Aerivio Spiromax is indicated for the symptomatic treatment of patients with COPD, with a FEV1 < 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Seretide Accuhaler 50 microgram/500 microgram/dose inhalation powder, pre-dispensed and appropriate non-clinical and clinical data.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Seretide Diskus forte 50 mikrogram/500 mikrogram/dos inhalationspulver, avdelad dos; Inhalation powder, pre-dispensed
- Marketing authorisation holder: GlaxoSmithKline AB
- Date of authorisation: 07-09-1998
- Marketing authorisation granted by:
 - Member State (EEA) : Sweden
 - National procedure
- Marketing authorisation number: 14593

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Seretide Diskus forte 50 mikrogram/500 mikrogram/dos inhalationspulver, avdelad dos; Inhalation powder, pre-dispensed
- Marketing authorisation holder: GlaxoSmithKline AB
- Date of authorisation: 07-09-1998
- Marketing authorisation granted by:
 - Member State (EEA): Sweden
 - National procedure
- Marketing authorisation number: 14593

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Seretide Accuhaler 50 microgram/500 microgram/dose inhalation powder, pre-dispensed; Inhalation powder, pre-dispensed
- Marketing authorisation holder: Glaxo Wellcome UK Ltd trading as GlaxoSmithKline UK
- Date of authorisation: 01-02-1999
- Marketing authorisation granted by:
 - Member State (EEA): United Kingdom
 - MRP
 - Marketing authorisation number: PL 10949/0316
- Bioavailability study number(s): FSS-AS-104/2009-015412-18 and FSS-BE-107/2012-003441-15

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 July 2010, with clarification advice provided on 14 September 2010 and follow-up advice on 18 November 2010 and with final advice given on 19 April 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: John Joseph Borg

- The application was received by the EMA on 5 June 2015.
- The procedure started on 25 June 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015.
- During the meeting on 22 October 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 October 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 29 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 March 2016.
- The PRAC RMP Advice and assessment overview was adopted on 17 March 2016.
- During the CHMP meeting on 1 April 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 8 June 2016.
- During the meeting on 23 June 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Aerivio Spiromax.

2. Scientific discussion

2.1. Introduction

Aerivio Spiromax (FS Spiromax) is an orally inhaled fixed-dose combination product containing the active substances fluticasone propionate, an inhaled glucocorticosteroid (ICS) with anti-inflammatory activity in the lungs and salmeterol xinafoate, a selective long-acting inhaled β_2 adrenoceptor agonist (LABA). This combination of active substances is already approved at national level in several EU countries for use in the regular treatment of adults, adolescents and children with asthma where the use of the combination of an inhaled corticosteroid and an inhaled long-acting β_2 adrenoceptor agonist is deemed appropriate and in the symptomatic treatment of adults with severe chronic obstructive pulmonary disease (COPD).

Fluticasone propionate is an orally inhaled glucocorticosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Fluticasone propionate has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyper reactive airways. Fluticasone propionate is a well-established active substance and is recommended for use in the management of asthma in both adults and children.

Salmeterol xinafoate is a selective long-acting β_2 adrenergic agonist and exerts a preferential effect on β_2 adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Salmeterol is used via the orally inhaled route in the management of patients with reversible airway obstruction. Inhalation of salmeterol produces bronchodilatation, which lasts for 12 hours following a single dose. Salmeterol is particularly useful in patients with reversible airway obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airway obstruction and particularly asthma recommend the addition of a long-acting β_2 agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting β_2 agonist provides better control of asthma than increasing the dose of inhaled corticosteroid.

The mechanisms of action of the two drugs, fluticasone propionate and salmeterol xinafoate, are different but complementary. Fluticasone propionate and salmeterol xinafoate demonstrate additive effects.

Asthma

The goal of pharmacologic therapy in asthma is to control chronic and nocturnal symptoms, maintain normal activity levels (including exercise), maintain near-normal pulmonary function, prevent acute episodes of asthma, minimize emergency room visits and hospitalizations, and avoid adverse effects of asthma medications (GINA 2015, NAEPP 2007).

Quick-relief medications, such as short-acting beta2-adrenergic agonists and anticholinergics are used to treat acute symptoms by rapidly reversing airflow limitation and bronchoconstriction. Long-term control medications such as ICS, immunomodulators, and LABAs are used to help achieve daily control of persistent asthma symptoms.

The ICS are the most effective anti-inflammatory treatment for persistent asthma; they reduce asthma symptoms and airway hyper-responsiveness, improve lung function and reduce exacerbations (Hodgson et al 2010). When symptoms persist despite low-dose ICS (Step 2 Global Initiative for Asthma [GINA]), the addition of a LABA is the most effective next step (GINA 2015). Combination

therapy involving the use of an ICS and a LABA provides a therapeutic benefit to patients with inadequate asthma control on ICS alone and is the recommended therapeutic option for patients over 4 years of age who have inadequate asthma control on low to medium-dose ICS in addition to as-needed use of short-acting beta2-agonist bronchodilators (GINA 2015).

The fixed combination of salmeterol xinafoate / fluticasone propionate has been shown to provide greater improvement in pulmonary function and overall asthma control than either individual compound alone. In addition, its use does not result in any untoward interaction that affects the pharmacodynamic (PD) or pharmacokinetic (PK) profiles of the individual drugs or their safety profiles (Spencer and Jarvis 1999). The use of such a combination is in accordance with current guidelines for the management of asthma.

Chronic Obstructive Pulmonary Disease (COPD)

Fixed-dose combinations of ICS and LABA licensed for use in COPD in the EU include twice-daily salmeterol xinafoate / fluticasone propionate and budesonide/formoterol. Once-daily fluticasone furoate/vilanterol has recently been approved for the treatment of COPD.

ICS/LABA combinations, which have been available for many years, have been shown to provide improvements in lung function and health status and to reduce symptoms and COPD exacerbations (Bateman et al 2014). These are recommended in the Global initiative for Chronic Obstructive Lung Disease (GOLD) strategy document, and the selection of treatments is based on the assessment of symptoms and risk.

FS Spiromax is an orally inhaled fixed-dose combination containing the active substances fluticasone propionate, an inhaled glucocorticosteroid with anti-inflammatory activity in the lungs, and salmeterol xinafoate, a selective long-acting inhaled β^2 adrenoceptor agonist. This combination of salmeterol / fluticasone is a well-known combination of two known active substances and is formulated as inhalation powder.

The applicant applied for the following indication:

Aerivio Spiromax is indicated in adults aged 18 years and older.

Asthma

Aerivio Spiromax is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β^2 -agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled shortacting β^2 -agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β^2 -agonist.

Chronic Obstructive Pulmonary Disease (COPD)

Aerivio Spiromax is indicated for the symptomatic treatment of patients with COPD, with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

The proposed therapeutic indication is identical to the therapeutic indications of the reference fixed-dose combination product.

The proposed route of administration is for inhalation use.

The drug is delivered by an inhalation-driven, multi-dose dry powder inhaler device (the Spiromax inhaler).

This application has been submitted in accordance with Directive 2001/83/EC Article 10(3) – hybrid application – application for a medicinal product referring to a so-called reference medicinal product with a Marketing Authorisation in a Member State or in the Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC and which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA.

The reference product was first authorised in Sweden under the brand name Seretide Diskus on 7 September 1998 and as such has been authorised in the Community for a period exceeding 10 years. The marketing authorizations for Seretide Diskus (also known as Seretide Accuhaler in the UK and some other markets) have been extended to 29 member states via mutual recognition procedure SE/H/0169/001-003/MR and national applications.

As an orally inhaled product, salmeterol / fluticasone inhalation powder (FS Spiromax) is locally applied and locally acting, so conventional bioavailability studies based on systemic measurements may not be appropriate to establish bioequivalence for this type of product (CPMP/EWP/QWP/1401/98 Rev.1 and CPMP/EWP/239/95 Final). Requirements for demonstrating therapeutic equivalence between two inhalation products are described in the 'OIP Guideline' (CHMP/EWP/4151/00 Rev.1, 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)).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as inhalation powder. Each delivered dose (the dose that leaves the mouthpiece) contains 45 micrograms of salmeterol (as salmeterol xinafoate) and 465 micrograms of fluticasone propionate. This is equivalent to a metered dose of 50 micrograms of salmeterol (as salmeterol xinafoate) and 500 micrograms fluticasone propionate.

The other ingredient is lactose monohydrate.

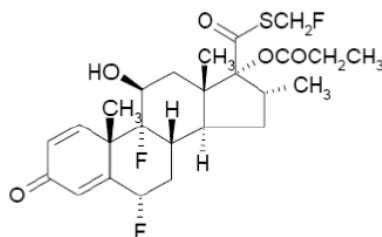
The product is available in a plastic inhaler as described in section 6.5 of the SmPC. The inhaler is white with a semi-transparent yellow mouthpiece cover. The drug/mucosal contact parts of the inhaler are made of acrylonitrile butadiene styrene (ABS), polyethylene (PE) and polypropylene (PP). Each inhaler contains 60 doses and is foil-wrapped. The device is an adapted version of the device used in a marketed product (DuoResp Spiromax 160 micrograms/4.5 micrograms dry powder inhaler) authorised under the centralised procedure.

2.2.2. Active substance

Fluticasone propionate

General information

The chemical name of fluticasone propionate is 6 α ,9-difluoro-17-[[[(fluoromethyl)sulfonyl]carbonyl]-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-dien-17 α -yl] propanoate corresponding to the molecular formula C₂₅H₃₁F₃O₅S. It has a relative molecular mass 500.57 g/mol and the following structure:



The active substance is a white to almost white powder, insoluble in water, sparingly soluble in acetone and dichloromethane, and slightly soluble in alcohol (96%).

Polymorphism has been observed for the active substance. Only one polymorphic form may be encountered in fluticasone propionate when crystallised in conventional conditions. Literature describes another polymorphic form (called form II) obtained by crystallisation from supercritical fluids. The absence of a higher melting point of form II and the presence of an exothermic event before melting of both forms strongly suggest a monotropic system meaning form II can convert into form I but not the other way around. It is therefore highly unlikely that fluticasone propionate form I converts into form II based on fundamental thermodynamic principles supported by data evidence. In addition, the applicant and the active substance manufacturer have committed to provide additional data for the crystallisation experiments to confirm the polymorphic form of fluticasone propionate manufactured.

As there is a monograph of fluticasone propionate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for fluticasone propionate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all covered by the CEP. The active substance is manufactured at one manufacturing site.

In addition the active substance is micronised. The CEP does not cover the micronisation step. The active substance manufacturer is responsible for micronisation of the active substance and only limited information on micronisation process has been included in the dossier. The Applicant has confirmed that the micronisation step is subject to audits by the QP as mentioned in the relevant declaration. The information provided was considered acceptable.

Specification

The control tests comply with the specifications and test methods of the Ph. Eur. monograph, as confirmed by the CEP. The CEP includes additional controls for one residual solvent used in the manufacturer's synthetic route and for one related substance. In addition active substance particle size distribution test was included in the active substance specification. Active substance amorphous content test is included in the active substance manufacturer specifications.

The active substance specification includes tests for: identity (IR, HPLC), specific optical rotation (Ph. Eur.), water content (Ph. Eur.), assay (Ph. Eur.), related substances (Ph. Eur.), residual solvents (Ph. Eur., GC), microbiological quality (Ph. Eur.), particle size distribution (laser diffraction), amorphous content test* (solution calorimetry).

*performed only by the active substance manufacturer

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification, assay and impurity testing has been presented.

Batch analysis data are provided for three production scale batches of the micronised active substance. The results are within the specifications and consistent from batch to batch.

Stability

A retest period is specified on the CEP for the non micronised fluticasone propionate.

Additional stability data were also provided to substantiate the re-test period of the micronised active substance.

Stability data were provided on 12 pilot and production scale batches of micronised active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions at 25 °C / 60% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines.

The parameters tested are the same as for release. Particle size results have been provided only on 4 pilot scale batches and not for all time points. No particle size distribution (PSD) results are presented at accelerated conditions. The analytical methods used were the same as for release (except for the PSD testing parameters).

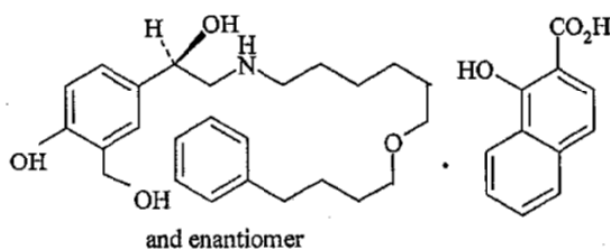
All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container for the non-micronised fluticasone propionate and the proposed retest period in the proposed container for the micronized fluticasone propionate.

Salmeterol xinafoate

General information

The chemical name of salmeterol xinafoate is (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol 1-hydroxynaphthalene-2-carboxylate corresponding to the molecular formula $C_{36}H_{45}NO_7$. It has a relative molecular mass 603.74g/mol and the following structure:



The active substance is a white to almost white powder, insoluble in water, soluble in methanol and slightly soluble in ethanol.

Salmeterol xinafoate exhibits stereoisomerism due to the presence of one chiral centre. Salmeterol xinafoate manufactured by the proposed supplier is a racemic mixture.

Polymorphism has been observed for the active substance. Two polymorphs of salmeterol xinafoate are described in the literature. The proposed supplier synthesises the polymorph I which is the most thermodynamically stable form at room temperature.

As there is a monograph of salmeterol xinafoate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for salmeterol xinafoate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all covered by the CEP. The active substance is manufactured at one manufacturing site.

In addition the active substance is micronised. The CEP does not cover the micronization step. The active substance manufacturer is responsible for micronization of the drug substances and only limited information on micronization process has been included in the dossier. The Applicant has confirmed that the micronization step is subject to audits of QP declarations. The information provided is considered acceptable.

Specification

The control tests comply with the specifications and test methods of the Ph. Eur. monograph, as confirmed by the CEP. The CEP includes additional controls for one residual solvent used in the

manufacturer's synthetic route and for heavy metals. In addition active substance particle size distribution and microbiological quality tests were included in the active substance specification.

The active substance specification includes tests for: identity (IR), assay (Ph. Eur.), related substances (Ph. Eur.), residual solvents (GC), water content (Ph.Eur.), heavy metals (ICP-MS), and sulfated ashes (Ph. Eur.), microbiological quality (Ph. Eur.), particle size distribution (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three batches of the micronized active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

A retest period is specified on the CEP for the non micronised salmeterol xinafoate.

Additional stability data are also provided to substantiate the re-test period of the micronised active substance.

Stability data were provided on 4 production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions at 25 °C / 60% RH.

Stability data were provided on 3 primary scale up scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for 48 months under long term conditions at 25 °C / 60% RH and for 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines.

In addition, supportive stability data were provided on 3 pilot scale batches.

In addition to the Ph. Eur. tests, the particle size distribution (PSD) of micronised salmeterol xinafoate was tested. Long term stability data for PSD have been provided on 2 production scale batches and on the 3 pilot scale batches. No data have been produced under accelerated conditions, which is considered acceptable taking into account that the stability of the finished drug product does not substantiate any concerns. Further, the micronised active substance raw material is subjected to retesting by the finished product manufacturer on a yearly basis.

All results submitted, are well within the specification, and do not show any trend in any parameter tested.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when stored protected from light in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The objective was to develop a dry powder for inhalation containing a fixed dose combination of fluticasone propionate and salmeterol xinafoate. The product is to be delivered in the Spiromax inhaler,

an inhalation driven multi-dose dry powder delivery device. The product is designed to have an equivalent performance to the reference product Seretide Accuhaler 50/500 µg (salmeterol xinafoate 50 µg/ fluticasone propionate 500 µg inhalation powder) also named Seretide Diskus. As such, the finished product has been developed following the EMA "Guideline on the requirements for clinical documentation for orally inhaled products including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease in adults and for the use in the treatment of asthma in children and adolescents" (CPMP/EWP/4151/00 Rev. 1). Akin the reference product, the formulation is a simple combination of the two active substances and lactose.

Lactose is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Solid state characteristics of micronised drug substances are known to affect pharmaceutical performance characteristics of the finished products. Therefore, physical characterisation of both active substances was conducted in relation to its effect on the functionality of the final product as per EMA Guideline "Guideline on the Pharmaceutical Quality of Inhalation and Nasal products" CHMP/QWP/49313/2005 Corr. Particle size, particle shape, rugosity, and crystallinity were studied, as these are recognised as the critical material attributes that determine the performance and quality of inhalation products. The effect of pre-processing the material (e.g. micronisation) on the physical characteristics was also evaluated. Results support the active substance specifications.

The principles of Quality by Design were applied to the pharmaceutical development, although no design space was applied for. The applicant defined key parameters of the reference product (flow resistance and dependence, uniformity of delivered dose (UDD) and aerodynamic particle size distribution (APSD). Pharmacokinetic studies were carried out to establish relationships between these parameters and the in vivo performance (bioequivalence) of each active substance. A quality target product profile (QTPP) was then defined as follows: the product should closely match the quality profile of Seretide Diskus; it should produce equivalent lung deposition and total systemic exposure to Seretide Diskus as demonstrated by equivalent in vivo PK performance; it should meet the quality requirements as per EMA Guidance "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" (CHMP/QWP/49313/2005 Corr), as well as other relevant quality guidelines.

Flow resistance and dependence, UDD, and APSD were defined as critical quality attributes (CQAs). Critical material attributes (CMAs) are particle size distribution (PSD) of both active substances and lactose and critical process parameters (CPPs) are mixing time and speed during blending. The relationship between APSD and lung deposition was determined and used to guide development. Limits for the various CQAs and CPPs required to ensure the desired APSD were established using Design of Experiments methodology (DoE). In addition, critical device attributes (CDAs) were compared with those of the reference product to ensure equivalent performance of the inhaler.

During the development of the finished product, the delivered dose (DD) for Seretide in the EU was not available. Therefore, it was agreed with the EMA during Scientific Advice, that the DD of the Advair product (the US equivalent of Seretide) could be used as the target for the DD of the finished product, provided that the DD of Seretide and Advair were demonstrated as being similar. The DD found for the Seretide product was in agreement with the DD of the Advair product. The applicant has therefore targeted the Advair DD for the finished product development, which correspondingly resulted in pharmaceutical *in vitro* and pharmacokinetic equivalence to Seretide product.

A series of trial formulations using micronised active substances and lactose of varying PSD were manufactured and their performance evaluated, first in vitro, and then by PK studies in vivo. Once the final formulation had been decided, a further pivotal in vivo PK study was carried out to demonstrate bioequivalence to Seretide Diskus.

The primary packaging is a white inhaler with a semi-transparent yellow mouthpiece cover. The active substance/mucosal contact parts of the inhaler are made of acrylonitrile butadiene styrene (ABS), polyethylene (PE), and polypropylene (PP). The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: blending of micronised salmeterol xinafoate and micronised fluticasone propionate with lactose monohydrate, filling of the homogeneous powder blend into the device sub-assembly followed by assembly of the entire device, equilibration of the filled device, packaging and labelling of the filled device. The process is considered to be a non-standard manufacturing process. Controls are applied to critical steps of the manufacturing process (blending, filling, device assembly, packaging) as follow: blend homogeneity testing, measurement of net powder weight in each device to ensure correct fill weight, check to ensure each device is assembled correctly, actuation check on each device to ensure correct functionality, dose counter check, and leak testing to ensure foil pouch seal integrity.

Major steps of the manufacturing process have been validated by a number of studies. Validation data were provided for three production scale batches packaged on a semi-automated line. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The applicant committed to validate the first three commercial batches packed on the automated packaging line. In addition, as the current production scale batch size is small, the Applicant committed that any future changes in the proposed batch size will be submitted as a Type II variation, supported by appropriate process validation data.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (TLC, UPLC), uniformity of delivered dose (Ph. Eur./In-house), aerodynamic assessment of fine particles (NGI) (Ph. Eur./ In-house), number of actuations per inhaler, assay of inhaler content (UPLC), related substances (UPLC), moisture content (Ph. Eur), microbial contamination (Ph. Eur.).

The specifications are supported by the clinical and stability batches except for the limits of aerodynamic assessment of fine particles for both active substances. The applicant committed to review the limits for both active substances 12 months after launch of the product and tighten them if appropriate.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay has been presented.

Batch analysis results are provided for 6 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for 3 production scale batches of finished product stored under long term conditions for 24 months at 25 °C / 60% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines. Samples were stored inverted or upright. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition supportive stability data from other two strengths initially developed were also provided.

No photostability studies have been performed. Due to the nature of the container closure system which protects the formulation from light, this is considered acceptable.

In-use studies were included in the stability study to simulate removal of the aluminium-foil pouch on the first day of use by the patient. Samples stored wrapped at long-term conditions for various periods of times were un-wrapped and stored at the same conditions and orientation for an additional 3 months before testing in order to evaluate the possible effect of a 3 month in-use period.

Samples were tested according to the release specifications. The analytical procedures used are stability indicating.

Stability results showed no significant difference when the inhalers were stored under different orientations.

The mean delivered dose results for fluticasone were centered slightly above the target, while salmeterol mean delivered dose results were slightly below target. All mean results were well within the acceptance limits of 85-115% label claim with the exception of one data point, which was significantly below the lower acceptance limit. This data point also represented OOS results for the uniformity of delivered dose. All subsequent time points reported results within specification.

Following investigations, it was concluded that the OOS might be caused by moisture or triboelectrification effects. Nevertheless, this is unlikely to be a stability trend.

The trend of the mean delivered doses was also studied. A decrease in mean delivered dose was observed for both active substances when stored under accelerated conditions and for the first 12 months under long term conditions. The mean delivered dose stabilized at 12-24 months under long term storage conditions.

A decrease in FPD was observed under long term condition, this decreasing trend sharpens when stored as unwrapped. Correspondingly, the MMAD increases upon storage. For both FDP and MMAD, all data were within the proposed specification limits.

All inhalers tested on stability delivered NLT 60 actuations. No significant changes were observed in the moisture content.

For the assay of inhaler content, all data were within the proposed specification limits even if a slight decrease in the assay content was observed for the inhaler during storage.

Fluticasone was stable over the shelf-life and no significant differences were observed in the related substances. In comparison, the related substances for salmeterol have increased during storage. However all results are within the proposed specification.

No microbial growth was observed in stability samples

No significant differences was observed in all parameters tested when the finished product was stored unwrapped for up to 3 months.

Based on available stability data, the proposed shelf-life of 2 years, the in-use shelf-life of 3 months and the following storage conditions "Do not store above 25°C. Keep the mouthpiece cover closed after removal of the foil wrap" as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and its manufacturing processes. However, design spaces were not claimed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- the applicant and the active substance manufacturer should generate and provide additional data for the crystallisation experiments to confirm the polymorphic form of fluticasone propionate
- the applicant should review the limits of aerodynamic assessment of fine particles for both active substances 12 months after launch of the product and tighten them if appropriate .
- the applicant should validate the first three commercial batches packed on the automated packaging line

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant has not conducted or sponsored any non-clinical studies using salmeterol xinafoate and fluticasone propionate to support this Marketing Authorisation Application as the pharmacological and toxicological effects of both salmeterol xinafoate / fluticasone propionate are documented in the published literature. The Applicant submitted literature data for the non-clinical characterisation of salmeterol xinafoate / fluticasone propionate and their combination.

Extractables and leachables testing has not been conducted as this is not required for dry powder inhalers, which is in accordance with CHMP Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMA/CHMP/QWP/49313/2005 Corr) and therefore acceptable.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Salmeterol

Salmeterol xinafoate is a selective long-acting β_2 -adrenoceptor agonist (LABA) with a long side chain which binds to the exo-site of the receptor used in patients with asthma and COPD.

Salmeterol belongs to a group of structurally related catecholamine derivatives. It produces a longer duration of bronchodilatation (lasting for at least 12 hours) than recommended doses of conventional short-acting β_2 -agonists. β_2 -adrenoceptor agonists are effective in the management of both asthma and COPD. These drugs induce bronchodilatation by causing direct relaxation of airway smooth muscle through activation of adenylate cyclase, which in turn increases intracellular 3,5-cyclic adenosine monophosphate levels. The long duration of salmeterol is considered to be due to its lipophilicity and persistence at the receptor site, which allows a twice daily dosing regimen, while the high potency and selectivity means that small doses (50 μg bid) are effective, limiting the potential for systemic exposure and site effects (Owen et al., 2010).

In vitro studies showed salmeterol to be at least 50 times more selective for β_2 adrenoceptors than salbutamol. Although β_2 adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle, there are also β_2 adrenoceptors in the human heart comprising 10 –50% of the total β adrenoceptors of the body. The pharmacologic effects of β_2 adrenoceptors agonistic drugs, including salmeterol are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of ATP to cyclic-3,5-adenosine monophosphate. Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Three types of β receptors are known; designated β_1 , β_2 and β_3 . β_1 -adrenergic receptors are located mainly in the heart and in the kidney; β_2 -adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth and skeletal muscle, and heart while β_3 -adrenergic receptors are located in fat cells.

Although β_2 -adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1 -adrenoceptors are the predominant receptors in the heart, there are also β_2 -adrenoceptors in the human heart comprising 10-50% of the total β -adrenoceptors. The precise function of these is not yet

established, but they raise the possibility that even highly selective β_2 -adrenoceptors may have cardiac effects. The selectivity of salmeterol in comparison with other β_2 -adrenoceptors is summarised in Table 1 (Dollery, 1999).

Table 1: Receptor potency

β_2 -agonist	Airways Smooth Muscle (β_2)	Cardiac Tissue (β_1)	Selectivity Ratio
Isoprenaline	1.0	1.0	1
Salbutamol	0.25	0.0004	650
Fenoterol	1.0	0.005	200
Salmeterol	5.0	0.0001	50.000

Salmeterol has demonstrated anti-inflammatory activity in vitro and in vivo in animals as shown by its inhibitory effect on the cellular release of inflammatory mediators, inflammatory cell infiltration and plasma protein extravasations.

Fluticasone propionate

Non-clinical studies have demonstrated that fluticasone is a highly lipophilic molecule, a characteristic which results in rapid penetration into the cells and retention in lung tissue. In vitro fluticasone has been demonstrated to inhibit anti-CD3-induced proliferation of T cells, Phytohaemagglutinin stimulated proliferation of lymphocytes from volunteers and interleukin (IL)-4, IL-6, IL-8 and tumour necrosis factor (TNF) in mast cells. It also inhibited platelet derived growth factor stimulated production of IL-1 β and IL-6 in human alveolar macrophage and fibroblast cells. Fluticasone has been demonstrated to possess the highest levels of both lung tissue binding (approximately 4.89 ng/mg) and lipophilicity when compared with beclomethasone dipropionate and beclomethasone 17-monopropionate; this translates into a sustained duration of action of fluticasone in the respiratory system, and a rapid and greater activity with respect to more hydrophilic compounds such as budesonide, flunisolide and hydrocortisone.

Studies in rodents were conducted to quantify and compare anti-inflammatory activity after topical administration of fluticasone and the ability to produce specific systemic steroid-related effects after topical, oral or parenteral administration. Topical anti-inflammatory activity was measured in rats and mice using the inflammatory response to croton oil applied topically to the ear. Results showed that fluticasone was essentially equipotent with fluocinolone acetonide in both rats and mice. Systemic responses to repeated topical applications of fluticasone were assessed by measurement of thymus involution and reduction in stress-induced plasma corticosterone (HPA axis suppression) in rats and mice, and adrenal atrophy in the rat. In these tests fluticasone was 50-100 fold less potent than fluocinolone acetonide in the rat (56-fold greater therapeutic index) and 100 times less potent than fluocinolone acetonide in mice (relative therapeutic index 91). Therefore, in both species, the separation between topical antiinflammatory and systemic activity after topical application was highly favourable to fluticasone. Comparison of systemic activity after topical and subcutaneous dosing of fluticasone shows that, in both rats and particularly in mice, fluticasone is more potent when given subcutaneously. After oral dosing in rats, fluticasone caused some thymus involution, adrenal atrophy and HPA axis suppression but was 6 to 38 times less potent than betamethasone alcohol. In the mouse, oral fluticasone is 60 to 200 times less potent than betamethasone alcohol.

Animal studies of the relative anti-inflammatory and hypothalamic-pituitary-adrenal (HPA) axis inhibitory potencies of topically applied drug demonstrated that fluticasone has an advantageous therapeutic index (>200 times that of beclomethasone dipropionate).

Fluticasone has also been found to have high glucocorticoid-receptor selectivity with highly desirable "fast-on, slow-off" receptor kinetics. The net effect is a Fp-receptor half-life of 10 hours, markedly greater than the half-life of beclomethasone and its active metabolite.

Combination

There is a strong scientific rationale for combination of these two drug classes. Although the primary effect of LABAs is on β_2 receptors, but in addition to their bronchodilatory action, LABAs complement the effects of corticosteroids via interaction with glucocorticoid signal transduction. LABAs can activate glucocorticoid receptors and enhance the transcription of anti-inflammatory mediators.

Secondary pharmacodynamic studies

Both formoterol and salmeterol have been shown to inhibit LPS (lipopolysaccharide)-stimulated release of tumor necrosis factor (TNF), and granulocyte/monocyte colony-stimulating factor (GM-CSF) but not CXCL-8 from monocyte-derived macrophages in culture.

Salmeterol also exhibits a concentration-dependent inhibition of thrombin-stimulated albumin transport with an EC of 2.6 nM, via activation of β_2 -adrenoceptors on these cells. Salmeterol, by a functional antagonist effect mediated by increased intracellular cyclic AMP may maintain the integrity of the vascular endothelium, there-by limiting plasma protein extravasation.

Salmeterol has also been demonstrated to inhibit acute leukocyte influx following endotoxin (neutrophils), platelet-activating factor (PAF), and antigen (eosinophils) challenge of guinea pig airways in vivo.

Pharmacodynamic drug interactions

Parallel treatment with salmeterol and gestagens can be more than twice as effective as salmeterol therapy alone. Preterm birth was induced with a combination of mifepristone and prostaglandin E2 on day 19 of pregnancy. Rats were treated with salmeterol or gestagens (progesterone or 17-hydroxyprogesterone) or their combination. The treatments were launched on different days (15-18) of pregnancy. The efficacy of treatment was determined in terms of the delivery time counted from the mifepristone injection. Salmeterol treatment delayed premature labour by 2.4 hours, whereas the delay due to gestagen-salmeterol combinations was more than 5 hours. Parallel treatment with salmeterol and gestagens can be more than twice as effective as salmeterol therapy alone (Galik et al., 2008).

2.3.3. Pharmacokinetics

Absorption

Salmeterol is extensively absorbed across the gastrointestinal tract in both rat and dog following oral administration. In repeat-dose, combined oral/inhalation toxicity studies showed that the maximum

concentrations of salmeterol detected in plasma exceeds by several hundred-fold the maximum concentrations (200 pg/ml) determined after the standard therapeutic dose in humans.

Salmeterol acts locally in the lung; plasma levels therefore do not predict therapeutic effect.

No firm results of salmeterol P-gp inhibition capability and in vitro studies demonstrating bidirectional and induction capabilities of salmeterol could be found in the public domain. Given that salmeterol is structurally similar to salbutamol, a known P-gp inhibitor in the same therapeutic class, the Applicant suggests that salmeterol can be classified as a class 2 drug and therefore potentially showing clinical evidence of P-gp-mediated drug-drug interactions. This hypothesis is supported.

Fluticasone has low oral bioavailability due to poor absorption and extensive first pass metabolism. Evidence in support of fluticasone low bioavailability when compared to the other corticosteroids, has been obtained by measuring plasma cortisol, as an index of adrenal suppression. Animal pharmacokinetic studies have shown that only small percentage of intratracheally orally administered compound reaches the systemic circulation, resulting in very low systemic effects typical for glucocorticoids.

On CHMP's request, the Applicant has submitted information regarding the P-gp bidirectional transport and induction capabilities of both fluticasone and salmeterol. Fluticasone has been seen to increase P-gp expression by 80% in peripheral blood cell lines but this effect was lost in the equilibrium study, suggesting that fluticasone was a poor P-gp substrate. Furthermore, lack of inhibitory action on the movement of other substrates was demonstrated, conversely to budesonide and beclometasone which are classified as P-gp inhibitors.

Plasma levels of fluticasone were not affected by salmeterol administration, as shown in studies in rats and dogs.

Distribution

Only traces of fluticasone radioactivity pass into the systemic circulation. When administered orally to pregnant rats or rabbits, a very small fraction of the dose (<0.005%) passes across the placenta.

The distribution of salmeterol xinafoate in body tissues is consistent with that expected of a highly lipophilic base. At least 93% of the salmeterol distributed between erythrocytes and plasma is reversibly bound to the plasma proteins, β 1-acid glycoprotein and albumin, in the mouse, rat, rabbit, dog and man. Salmeterol showed high plasma clearance, indicating that changes in the degree of protein binding are unlikely to influence the rate of elimination.

Following oral and intravenous administration of ¹⁴C-salmeterol xinafoate in rats, the highest concentrations were observed in bile ducts, kidney medulla and liver, by intestinal content, heart, pituitary, bone marrow, lung and stomach/small intestine wall. Lower concentrations of radioactivity were retrieved in blood, whereas only trace amounts were detected in the central nervous system. The extent of binding of salmeterol to mouse, rat, rabbit, dog and human plasma proteins in vitro was ~95% and was independent of drug concentration.

On CHMP's request, the Applicant has provided information regarding the distribution sites of fluticasone and salmeterol. In a single oral dose study in rats using radioactive fluticasone, radioactivity was detected in the stomach and its contents, the jejunum and large intestine. Other organs showing significant levels of radioactivity were the liver and brown fat and to a lesser degree the adrenals, pancreas and skin. Following intravenous administration, the kidneys also showed significant levels of radioactivity. Following oral or intravenous administration at its peak levels,

radioactivity in the plasma was <1% of that found in the liver. In 6-hour disposition studies in rats and dogs following inhalation with radioactive fluticasone, the lungs showed the highest levels of radioactivity. Distribution studies of aerosolized fluticasone in rats and dogs indicate that the highest levels were found in the lungs of both species. Fluticasone binds to the same high degree (94.6 – 96.5%) to plasma proteins of rats, dogs and humans.

Pharmacokinetic drug interactions

Both salmeterol and fluticasone are substrates of CYP3A4. Since the compounds are lipophilic and act locally in the lung, the resulting low plasma concentrations following inhalation are not predictive of therapeutic effect. Therefore, although both substances are substrates of cytochrome CYP3A4, the risk of a DDI is negligible at the low inhalation doses intended for clinical use.

Hepatic clearance is predominantly responsible for the clearance of salmeterol and fluticasone, meaning that patients with hepatic disease who receive salmeterol and fluticasone should be closely monitored and caution is recommended when salmeterol and fluticasone are co-administered with potent CYP3A4 inhibitors, as stated into the SmPC.

Following repeat dosing of salmeterol / fluticasone combination by inhalation in rat and dog toxicity studies, plasma levels were not affected by each other.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies conducted individually or in combination demonstrated no specific target organ toxicity.

Repeat dose toxicity

Repeat inhalation studies were performed in rats and dogs. Focal coronary arthritis occurred transiently and sporadically in Wistar rats but not in dogs or Sprague Dawley rats exposed daily to salmeterol xinafoate and fluticasone propionate. In 2-week inhalation studies in dogs, salmeterol-related pulse rate increases were slightly more marked in groups given the combination compared with those given salmeterol alone. However, there were no significant effects of the combination on ECG or on cardiac histopathology in these species.

Genotoxicity

None of the compounds revealed genotoxic potential.

Carcinogenicity

None of the compounds revealed carcinogenic potential.

Reproduction Toxicity

The results coming from the reprotoxicity studies indicate that no major safety issue occurred following administration of each compound or the combination.

Glucocorticosteroids have, however, been shown to induce malformations (cleft palate, skeletal malformations) in animal experimental studies, but these findings may not be relevant for man given the recommended doses. Animal studies with salmeterol have shown embryofetal toxicity only at high exposure levels. Co-administration of salmeterol and fluticasone to rats, led to increased incidences of transposed umbilical artery and incomplete ossification of occipital bone, effects seen at doses associated with known glucocorticoid- induced abnormalities.

Toxicokinetic data

There was no drug interaction in the pharmacological and toxicity studies between salmeterol and fluticasone.

Local Tolerance

With regards to the local tolerance potential of salmeterol xinafoate and fluticasone propionate, these were found not to be irritating to the eye or the respiratory tract of the species examined.

Other toxicity studies

Studies in Juvenile Animals

Two studies were performed using juvenile rats. Animals were dosed daily using the subcutaneous route to increase bioavailability relative to the inhaled route. Doses ranged from 0.4 to 10 µg/kg/day administered from day 3 of life until day 44. Animals receiving the higher doses of fluticasone manifested the standard effects associated with drugs of the glucocorticoid class. No effects on growth or indices of sexual maturation were seen at the lower doses.

However, some animals dosed at the higher levels of 5 or 10 µg/kg/day did show a reduction in the rate of weight gain. There was no reported effect on sexual maturation.

A 52-week study was performed using 24 juvenile beagle dogs. Fluticasone was administered twice daily with doses started at 1500 µg for the first 8 weeks, then were reduced to 750 µg for the remainder of the study. Delivered doses were calculated to be as high as 140 µg/kg/day for the first week, to as low as approximately 25 µg/kg/day by the end of the study. The results of this study confirm the typical clinical and laboratory changes associated with prolonged administration of a potent glucocorticoid. The animals were "stunted" in overall growth and showed a reduction in long bone length. A decrease in the expected length of the trachea was also reported. The lowest dose of 25 µg/kg/day that produced developmental effects observed in this study was greater than five times the highest expected dose delivered to an average 4 year old pediatric patient weighing 15 kg and receiving the maximum recommended daily dose of 200 µg. However, FS Spiromax is not indicated for children below 18 years of age.

Studies on Excipients

The only excipient used in the final drug product, lactose monohydrate (lactose) is well characterised and corresponds with the Pharm Eur. Each dose contains approximately 10 mg of lactose (as monohydrate). In the non-clinical overview the Applicant explains that the excipient used in the final

drug product, lactose monohydrate, may contain trace amounts of milk protein which may cause reactions in patients with hypersensitivity or allergy to milk protein. In addition, lactose is contraindicated in patients with galactose intolerance, Lapp lactase deficiency or with glucose-galactose malabsorption and patients with these rare hereditary problems should not take this medicine. This has been adequately addressed in the product information.

Studies on Impurities

Limits for related substances, impurities and degradation products are in accordance with current ICH Guideline ICH Q3B (CPMP/ICH/2738/99) and are based on the maximum daily doses of salmeterol xinafoate / fluticasone propionate.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the Applicant as the introduction of FS Spiromax 500 microgram/50 microgram inhalation powder containing fluticasone propionate and salmeterol xinafoate is considered unlikely to result in any significant increase in the combined sales volumes for all salmeterol xinafoate / fluticasone propionate containing products and the exposure of the environment to the active substance. Moreover, the patient population for FS Spiromax will be even smaller, as it is indicated only in adults aged 18 years and older, whereas the reference product is also indicated in a younger population. The Applicant has provided additional evidence using IMS Market Data from June 2015 to demonstrate that the market for DPI combination products containing fluticasone in both the EU and Germany has not increased over the past 6 and 10 years, respectively. Since the introduction of FS Spiromax 500 microgram/50 microgram inhalation powder is intended for generic substitution, it is considered that this will not lead to an increase in environmental exposure to fluticasone. Thus, the ERA is expected to be similar and not increased and therefore salmeterol xinafoate / fluticasone propionate is considered unlikely to present a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology, pharmacokinetics and toxicology studies in vitro, ex vivo and in vivo were described in the literature with salmeterol xinafoate / fluticasone propionate alone and in combination. The Applicant has not conducted or sponsored any non-clinical studies using budesonide and formoterol to support this Marketing Authorisation Application as the pharmacological and toxicological effects of both salmeterol xinafoate and fluticasone propionate are documented in the published literature. The Applicant relied on the literature on the non-clinical characterisation of salmeterol xinafoate and fluticasone propionate and their combination. This is acceptable to the CHMP.

Hepatic clearance is predominantly responsible for the clearance of salmeterol xinafoate and fluticasone propionate, meaning that patients with hepatic disease who receive salmeterol and fluticasone should be closely monitored and caution is recommended when salmeterol and fluticasone is co-administered with potent CYP3A4 inhibitors, as stated into the product information.

The only excipient used in the final drug product, lactose monohydrate (lactose) is well characterised and corresponds with the Pharm Eur. This excipient may contain trace amounts of milk protein which may cause reactions in patients with hypersensitivity or allergy to milk protein. In addition, lactose is contraindicated in patients with galactose intolerance, Lapp lactase deficiency or with glucose-galactose malabsorption and patients with these rare hereditary problems should not take this medicine. This has been adequately addressed in the product information.

The justification for the absence of an environmental risk assessment ERA is acceptable and an ERA is not deemed necessary. FS Spiromax is considered unlikely to present a risk to the environment when use as prescribed.

2.3.7. Conclusion on the non-clinical aspects

On the basis of the considerable amount of published scientific evidences on salmeterol xinafoate / fluticasone propionate combination, the CHMP concluded that salmeterol xinafoate / fluticasone propionate inhalation powder produces the claimed pharmacological activity and can be safely administered within therapeutic indication.

2.4. Clinical aspects

2.4.1. Introduction

The development of this new fixed-dose combination orally inhaled product (OIP) follows the CHMP Guideline on OIPs (CPMP/EWP/4151/00 Rev. 1) and aims to demonstrate therapeutic equivalence of this new product to the reference product authorised in a Member State or in the Community on the basis of a complete dossier. The development is based on the demonstration of pharmacokinetic equivalence between this new fixed-dose combination in one high strength and the corresponding strength of the reference product. The applicant received Scientific Advice from the CHMP on several occasions pertaining to quality and clinical aspects of the dossier.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Clinical studies

To support the application, the applicant has submitted four clinical pharmacokinetic (PK) studies, two pilot studies, (Studies FSC-AS-101 and FSS-AS-104) comparing different batches and devices and two pivotal studies, (Studies FSS-BE-107 and FSS-BE-10020), which were identical studies bar the administration of activated charcoal in Study FSS-BE-10020. No pharmacodynamic (PD) studies or Phase 3 clinical efficacy or safety studies have been conducted comparing the test and reference products in any population.

The modified Spiromax device used in pilot study, Study FSS-AS-104, was used in both pivotal pharmacokinetic studies and is the device proposed for the market.

- Tabular overview of clinical studies

Study/ treatment	Design	Key results
Study FSC-AS-101 FS Spiromax 500/50 µg Batch A RD124 and Batch B RD130 versus Seretide Accuhaler 50/500µg	Single-center, open-label, randomized, 3-period crossover, single-dose study without charcoal block. (N=18)	<u>Fluticasone propionate</u> Batch A was not similar to Seretide Accuhaler Batch B was not similar to Seretide Accuhaler <u>Salmeterol</u> Batch A was not similar to Seretide Accuhaler Batch B was not similar to Seretide Accuhaler
Study FSS-AS-104 FS Spiromax 500/50 µg Batch AEH45A versus Seretide Accuhaler 50/500µg	Single-center, open-label, randomized, 2-period crossover, single-dose study without charcoal block. (N=18)	<u>Fluticasone propionate</u> Similar to Seretide Accuhaler. <u>Salmeterol</u> Not similar to Seretide Accuhaler
Study FSS-BE-107 FS Spiromax 500/50 µg Batch RD1204 versus Seretide Accuhaler 50/500µg	Single-center, open-label, randomized, 2-period crossover, single-dose study without charcoal block. (N=79)	<u>Fluticasone propionate</u> Bioequivalent to Seretide Accuhaler <u>Salmeterol</u> Bioequivalent to Seretide Accuhaler
Study FSS-BE-10020 FS Spiromax 500/50 µg Batch RD1204 versus Seretide Accuhaler 50/500µg	Single-center, open-label, randomized, 2-period crossover, single-dose study with charcoal block. (N=75)	<u>Fluticasone propionate</u> Bioequivalent to Seretide Accuhaler <u>Salmeterol</u> Bioequivalent to Seretide Accuhaler

2.4.2. Pharmacokinetics

Methods

The studies were single center, open label, single dose, crossover studies to compare the salmeterol xinafoate and fluticasone propionate following FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg, administered to healthy volunteers. Two inhalations of each product were administered in order to optimize the ability to quantify salmeterol xinafoate and fluticasone propionate over their entire PK profile. Apart from the administration of charcoal in Study FSS-BE-10020, the 2 pivotal studies were identical in design and were conducted at the same study site within the same year using the same batch of FS Spiromax.

Pilot Studies

FSC-AS-101 primary objective:

The primary objective of this study was to assess the pharmacokinetic (PK) profiles of fluticasone propionate (FP) and salmeterol xinafoate (SAL) in 18 healthy volunteers following 2 inhalations from 2 batches of FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg.

The purpose of this study was to compare the PK of 2 batches of FS Spiromax that have different fine particle doses (FPD) with a single batch of Seretide Accuhaler.

FSS-AS-104 primary objective:

The primary objective of this study was to assess the pharmacokinetic (PK) profiles of a single batch of FS Spiromax in the modified Spiromax device relative to Seretide Accuhaler following 2 inhalations from each of the 2 treatments administered in 18 healthy volunteers.

Pivotal Studies

Study FSS-BE-107 Primary Objective:

The primary objective of the study was to assess the pharmacokinetic (PK) profile of single doses of the fixed-dose combination of fluticasone propionate (FP) and salmeterol (SAL) inhalation powder administered as 2 inhalations from salmeterol/ fluticasone propionate 50/500µg inhalation powder (FS Spiromax) and Seretide Accuhaler 50/500µg in healthy volunteers aged 18-45 years.

FSS-BE-10020 Primary Objective:

The primary objective of the study was to assess the pharmacokinetic (PK) profiles of the fixed-dose combination of fluticasone propionate (FP) and salmeterol (SAL) inhalation powder administered as 2 inhalations from salmeterol / fluticasone 50/500µg inhalation powder (FS Spiromax) and 2 inhalations from Seretide Accuhaler 50/500µg, with charcoal block in healthy volunteers aged 18-45 years.

Test and reference products

Table 2 Test and reference products

Study	salmeterol/ fluticasone Spiromax 50/500µg	Seretide Accuhaler 500/50 mcg
FSC-AS-101	Treatment A Manufactured by TEVA Pharmaceuticals Ireland Lot No.: RD124 Expiration date: 13 April 2009	Manufactured by: A&H Lot No.: R376267 Expiration date: January 2010
	Treatment B Manufactured by TEVA Pharmaceuticals Ireland Lot No.: RD130 Expiration date: 15 May 2009	
FSS-AS-104	Manufactured by: Norton Waterford/ IVAX Pharmaceuticals, Ireland Lot No.: AEH45A Expiration Date: September 2010 Manufacture Date: May 2010	Manufactured by: Allen & Hanburys Lot No.: R466086 Expiration Date: August 2011 Manufacture Date: Unknown
FSS-BE-107	Manufacturer: Teva Pharmaceuticals Batch No.: RD1204 Expiry date: Nov 2013	Manufacturer: GlaxoWellcome UK Ltd T/A Allen & Hanburys Batch No.: 4460 Expiry date: Dec 2013
FSS-BE-10020	Manufacturer: Teva Pharmaceuticals Batch No.: RD1204 Expiry date: 06-Jan-2014; 09-Feb-2014	Manufacturer: GlaxoSmithKline Batch No.: 4527A Expiry date: 31-Mar-2014

Population(s) studied

Healthy volunteers.

Analytical methods

Blood samples for determining the plasma concentrations of fluticasone propionate and salmeterol were collected. Plasma concentrations of fluticasone propionate and salmeterol were determined using validated liquid chromatography/tandem/mass spectrometry (LC-MS/MS) methods for each of these drugs in human plasma. All reported concentration data were obtained from analytical runs that met the acceptance criteria of the Standard Operating Procedures and which were performed in accordance with Good Laboratory Practice (GLP) regulations in compliance with FDA regulations. The analysis period was 29 April 2013-28 June 2013 for Study FSS-BE-107 and 03 December 2103-28 January 2014 for Study FSS-BE-10020. The analytical reports were provided together with a statement of GLP compliance.

Certificates of Analysis for each reference standard (fluticasone propionate, fluticasone propionate-d3 and salmeterol, salmeterol-d3) were provided and purity was adequate.

Analyte stability was evaluated under various conditions; the long term stability demonstrated that the spiking solution was stable for 85 and 93 days at -20°C for fluticasone propionate and salmeterol respectively.

On CHMP's request, the Applicant has clarified the maximum sample storage time and conditions were within the validated storage duration and conditions.

The Applicant has also stated that samples with fluticasone propionate and salmeterol concentrations above the upper limit of quantification (ULOQ) were diluted to fall within the standard curve range. The dilution integrity was demonstrated in the validation report.

Pharmacokinetic variables

The primary endpoints in the pivotal pharmacokinetic bioequivalence studies (Studies FSS-BE-107 and FSS-BE-10020) were:

- area under the plasma concentration-time curve from time zero to the last quantifiable concentration as measured up to 24 hours post-dose (AUC_{0-t}) and,
- maximum observed plasma concentration (C_{max})

for both fluticasone propionate and salmeterol xinafoate.

The primary endpoint in the pilot pharmacokinetic bioequivalence studies (Studies FSC-AS-101 and FSS-AS-104) was AUC_{0-t} with C_{max} as a secondary endpoint.

Statistical methods

All pharmacokinetic parameters for fluticasone propionate and salmeterol xinafoate were calculated using non-compartmental analysis methods from the plasma concentration-time data.

The AUC and C_{max} data were natural log-transformed prior to the statistical analysis. Comparisons of AUC and C_{max} between treatments were carried out using a parametric analysis of variance (ANOVA) model with sequence, period and treatment as fixed effects and a random effect of subject within sequence. The least squares means (LSMs) and the difference between LSMs were obtained from the ANOVA. Ratios of LSM were calculated using the exponentiation of the LSM from the analysis of the log transformed AUC and C_{max} values. These ratios were expressed for the test relative to the reference formulation. The 90% CIs for the treatment ratios were derived.

In the pivotal studies (Studies FSS-BE-107 and FSS-BE-10020), the two products were considered equivalent for AUC_{0-t} and C_{max} if the 90% confidence intervals (CIs) of the ratios of geometric means for both fluticasone and salmeterol were contained within the 0.8 to 1.25 range.

The non-parametric analysis of the time to maximum observed plasma concentration (t_{max}) and terminal phase half-life ($t_{1/2}$) was performed based on the Wilcoxon signed rank test. The Hodges-Lehman estimator and estimated CI were used to examine the location shift in t_{max} in the pivotal studies (FSS-BE-107 and FSS-BE-10020).

The pharmacokinetic analysis set was the pre-specified primary population for analyses of the pharmacokinetic data in the pivotal studies (FSS-BE-107 and FSS-BE-10020). It included all randomized subjects who received at least one dose of study medication with sufficient data to calculate the pharmacokinetic parameters, AUC_{0-t} and C_{max} from any treatment period prior to experiencing a major protocol violation.

Major protocol violations were determined prior to database lock which could have resulted in the exclusion of one subject from the pharmacokinetic analysis set for one or more than one treatment period. Subjects were analyzed under the treatment they actually received, as opposed to the treatment sequence in which they were randomized.

In the pilot studies FSC-AS-101 and FSS-AS-104, the primary analysis set for the pharmacokinetic analysis was planned to be the intent-to-treat (ITT) analysis set. However pharmacokinetic data were to be excluded from the pharmacokinetic analysis if they met the criteria of non-zero baseline concentrations >5% of the corresponding C_{max} or lack of any measurable concentrations or very low plasma concentrations for the reference medicinal product as per the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr* 20 January 2010), which led to the removal of one subject in one period in the pharmacokinetic analysis in Study FSS-AS-104 (per protocol [PP] analysis set).

Results

Study FSS-BE-107

Bioequivalence of FS Spiromax 50/500 μ g and Seretide Accuhaler 50/500 μ g was demonstrated with respect to AUC_{0-t} and C_{max} for fluticasone propionate; the pharmacokinetic ratios were close to 1 with 90% CIs within the accepted bioequivalence range of 0.8, 1.25.

Table 3 Statistical Comparison of fluticasone propionate Pharmacokinetic Parameters in Study FSS-BE-107

Parameter	FS Spiromax 50/500 μ g (n=78)	Seretide Accuhaler 50/500 μ g (n=78)	Treatment comparison	90% Confidence interval	Root mean square error
AUC_{0-t} (pg-hr/mL)	1568.88	1452.98	1.080	1.029, 1.133 ^a	0.182
C_{max} (pg/mL)	146.00	134.40	1.086	1.036, 1.139 ^a	0.177
AUC_{0-inf} (pg-hr/mL)	1674.02	1549.92	1.080	1.029, 1.133 ^a	0.179

a – denotes within the range (0.80, 1.25)

Abbreviation: FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler

Note: AUC and C_{max} are geometric means

Note: Treatment comparison is geometric mean ratio for FS Spiromax versus Seretide Accuhaler for AUC and C_{max}

Bioequivalence of FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg was demonstrated with respect to AUC_{0-t} and C_{max} for salmeterol; the pharmacokinetic ratios were close to 1 with the 90% CIs within the accepted bioequivalence range of 0.8, 1.25.

Table 4 Statistical Comparison of salmeterol xinafoate Pharmacokinetic Parameters in Study FSS-BE-107

Parameter	FS Spiromax 500/50 µg (n=78)	Seretide Accuhaler 50/500 µg (n=78)	Treatment comparison	90% Confidence interval	Root mean square error
AUC _{0-t} (pg·hr/mL)	384.38	384.78	0.998	0.950, 1.049 ^a	0.186
C _{max} (pg/mL)	251.52	252.67	0.995	0.929, 1.064 ^a	0.253
AUC _{0-inf} (pg·hr/mL)	415.82	413.18	1.006	0.959, 1.056 ^a	0.177

a – denotes within the range (0.80, 1.25)

Abbreviation: FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler

Note: AUC and C_{max} are geometric means

Note: Treatment comparison is geometric mean ratio for FS Spiromax versus Seretide Accuhaler for AUC and C_{max}

Study FSS-BE-10020

Bioequivalence of FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg was demonstrated in the presence of charcoal blockade with respect to AUC_{0-t} and C_{max} for fluticasone propionate; the pharmacokinetic comparisons were all above 1 but with the 90% CIs within the accepted bioequivalence range of 0.8, 1.25 – see the Table below.

Table 5 Statistical Comparison of fluticasone propionate Pharmacokinetic Parameters in Study FSS-BE-10020

Parameter	FS Spiromax 500/50 µg + charcoal (n=73)	Seretide Accuhaler 50/500 µg + charcoal (n=73)	Treatment comparison	90% Confidence interval	Root mean square error
AUC _{0-t} (pg·hr/mL)	1640.38	1411.01	1.162	1.097, 1.232 ^a	0.210
C _{max} (pg/mL)	157.40	136.78	1.148	1.180, 1.221 ^a	0.223
AUC _{0-inf} (pg·hr/mL)	1763.74	1498.25	1.178	1.111, 1.248 ^a	0.208

a – denotes within the range (0.80, 1.25)

Abbreviation: FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler

Note: AUC and C_{max} are geometric means

Note: Treatment comparison is geometric mean ratio for FS Spiromax versus Seretide Accuhaler for AUC and C_{max}

Bioequivalence of FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg was demonstrated in the presence of charcoal blockade with respect to AUC_{0-t} and C_{max} for salmeterol; the pharmacokinetic comparisons were all slightly above 1 but with the 90% CIs well within the accepted bioequivalence range of 0.8 - 1.25; see Table 6.

Table 6 Statistical Comparison of salmeterol xinafoate Pharmacokinetic Parameters in Study FSS-BE-10020

Parameter	FS Spiromax 500/50 µg + charcoal (n=73)	Seretide Accuhaler 50/500 µg + charcoal (n=73)	Treatment comparison	90% Confidence interval	Root mean square error
AUC _{0-t} (pg·hr/mL)	353.45	328.89	1.074	1.024, 1.126 ^a	0.172
C _{max} (pg/mL)	247.81	226.04	1.093	1.017, 1.175 ^a	0.261
AUC _{0-inf} (pg·hr/mL)	395.07	365.67	1.080	1.029, 1.132 ^a	0.172

a – denotes within the range (0.80, 1.25)

Abbreviation: FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler

Note: AUC and C_{max} are geometric means

Note: Treatment comparison is geometric mean ratio for FS Spiromax versus Seretide Accuhaler for AUC and C_{max}

Pilot and Pivotal Studies

**Table 7 Summary of Pharmacokinetic Findings across the Pilot and Pivotal Studies
Pharmacokinetic Comparison Summary for FS Spiromax 50/500µg versus Seretide
Accuhaler 50/500µg**

Study	AUC _{0-t}	C _{max}
FSC-AS-101		
Batch A		
Fluticasone propionate	Not similar	Not similar
Salmeterol	Similar	Not similar
Batch B		
Fluticasone propionate	Not similar	Not similar
Salmeterol	Not similar	Not similar
FSS-AS-104		
Fluticasone propionate	Similar	Similar
Salmeterol	Similar	Not similar
FSS-BE-107		
Fluticasone propionate	Bioequivalent	Bioequivalent
Salmeterol	Bioequivalent	Bioequivalent
FSS-BE-10020		
Fluticasone propionate + charcoal	Bioequivalent	Bioequivalent
Salmeterol + charcoal	Bioequivalent	Bioequivalent

Abbreviation: FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler

Pivotal studies (FSS-BE-107 and FSS-BE-10020)

The following table reports the PK values of the two pivotal studies (FSS-BE-107 and FSS-BE-10020).

Table 8 PK values of the two pivotal studies (FSS-BE-107 and FSS-BE-10020)

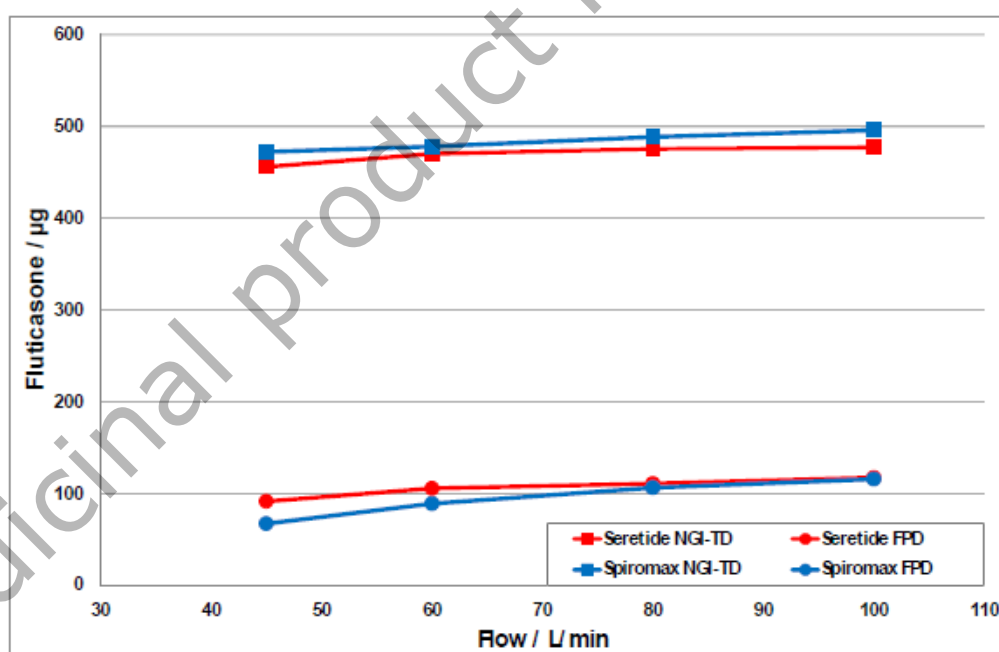
PK Parameter	FSS-BE-107 (without charcoal block)		FSS-BE-10020 (with charcoal block)	
	Fluticasone			
	FS Spiromax	Seretide	FS Spiromax	Seretide
C_{max} (pg/mL)	151.36 (40.369)	137.57 (33.641)	166.13(55.235)	142.55(39.981)
Mean (SD)	146.00	133.85	157.39	136.78
Geometric Mean				
AUC 0-t (pg xh/mL)	1622.64 (419.440)	1487.52(341.251)	1711.05(515.314)	1521.27(520.918)
Mean (SD)	1568.88	1443.79	1633.91	1411.01

Geometric Mean				
AUC 0-inf (pg xh/mL)	1730.39 (444.815)	1586.51(363.826)	1844.43(570.517)	1619.21(568.859)
Mean (SD)	1674.02	1539.80	1757.06	1498.25
Geometric Mean				
Salmeterol				
	FS Spiromax	Seretide	FS Spiromax	Seretide
Cmax (pg/mL)	269.48 (105.735)	265.66(87.275)	266.62(106.513)	246.45(94.222)
Mean (SD)	251.58	250.89	246.90	226.04
Geometric Mean				
AUC 0-t (pg xh/mL)	408.42(155.403)	401.79(125.317)	367.55(108.939)	338.36(80.743)
Mean (SD)	384.05	383.45	351.47	328.89
Geometric Mean				
AUC 0-inf (pg xh/mL)	439.09(156.030)	433.77(132.349)	410.76(122.641)	376.59(91.598)
Mean (SD)	415.78	414.96	392.55	365.67
Geometric Mean				

Flow Rate – Drug Delivery Relationships for the Spiromax and Accuhaler Devices

In vitro comparison of the test product (FS Spiromax) and the reference product (Seretide Accuhaler) has been conducted according to the CHMP guideline for orally inhaled products (CPMP/EWP/4151/00 Rev.1). Data have been generated for the complete particle size distribution profile of individual stages of a validated multistage impactor (next generation impactor (NGI)). Seretide Accuhaler data were generated in accordance with the Patient Information Leaflet for the reference product. The full results of the aerodynamic particle size distribution characteristics of FS Spiromax and Seretide Accuhaler were provided.

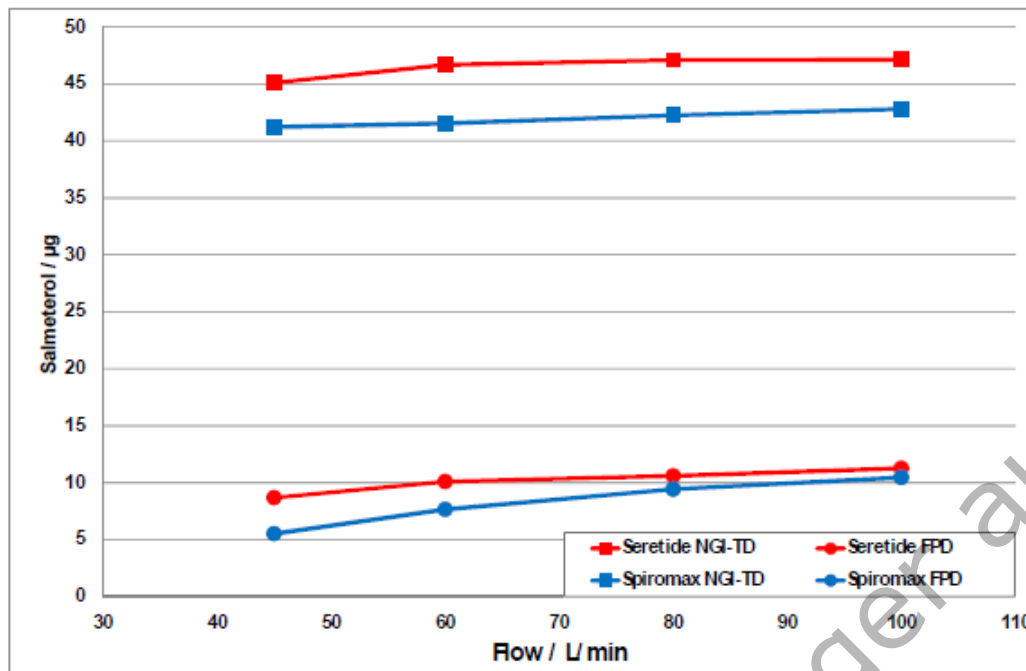
The results of the *in vitro* flow rate comparison conducted to investigate whether the flow rate dependence of the FS Spiromax device matched that of Seretide Accuhaler are presented below.



Source: Section 3.2.P.2.2

Abbreviations: FPD = fine particle dose; FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler; NGI TD = NGI total dose

Figure 1: Fluticasone propionate Fine Particle Dose and NGI Total Dose Versus Flow Rate for FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg



Source: Section 3.2.P.2.2

Abbreviations: FPD = fine particle dose; FS Spiromax = salmeterol / fluticasone propionate xinafoate dry powder inhaler; NGI TD = N GI total dose

Figure 2: Salmeterol Fine Particle Dose and NGI Total Dose Versus Flow Rate for FS Spiromax 50/500µg and Seretide Accuhaler 50/500µg

In vitro flow rate comparison was conducted to investigate whether the flow rate dependence of the FS Spiromax device matched that of Seretide Accuhaler; a lower FPD is seen at the lower flow rates of 45 and 60L/min and lower total delivered dose is seen at all four flow rates studied, 45, 60, 80 and 100L/min, for the salmeterol xinafoate component of FS Spiromax compared with the salmeterol xinafoate component of Seretide Accuhaler, as measured with the Next Generation Impactor.

Therefore the Applicant has been asked to discuss these findings in the light of the pharmacokinetic data presented in healthy volunteers inhaling with flow rates in excess of 60L/min and discuss the clinical relevance of these findings in patients with either asthma or COPD and inhaling with flow rates less than 60L/min.

Inhalation Characteristics of Patients with Asthma, Patients with COPD and Healthy Adult Volunteers

In order to demonstrate that the flow rates through FS Spiromax and Seretide Accuhaler did not differ between patients with asthma/COPD, with potentially lower flow rates, compared with healthy volunteers and to assess the impact of enhanced training in DPI technique on inhalation speed and volume, the Applicant submitted a clinical study.

The mean peak inspiratory flow rate (PIFR) was measured pre- and post-training of the inhalation technique. The training was conducted using the IN-Check Dial, a device comparable with that used in the FS Spiromax studies, to ensure all subjects were able to achieve an adequate inspiratory flow rate from each device.

Information from healthy volunteers was included in order to directly compare a group of patients with asthma with a group of healthy volunteers who were similar to the healthy volunteers who participated in the pharmacokinetic studies presented above in the development programme in support of this new fixed-dose combination, Studies FSC-AS-101 and FSS-AS-104 (pilot studies) and Studies FSS-BE-107 and FSS-BE-10020 (pivotal studies).

Five different age groups were studied, as follows:

- children with stable asthma, aged 4-11 years
- adolescents with stable asthma, aged 12-17 years
- adults with stable asthma, aged 18-45 years
- adults with stable COPD, aged over 55 years
- healthy volunteers, aged 18-45 years.

The findings were as follows:

Table 9 Peak Inspiratory Flow Rate per Device and Subject Group

Subject group	FS Spiromax device		Seretide Accuhaler device	
	Pre-training	Post training	Pre-training	Post training
Pediatric asthma, age 4-11 years (N=50)				
Mean (SD)	68.79 (16.95)	84.92 (14.76)	67.81 (18.01)	86.47 (15.10)
Min to Max	(34.47 to 108.98)	(45.27 to 117.07)	(33.61 to 113.68)	(48.53 to 123.98)
Adolescent asthma, age 12-17 years (N=50)				
Mean (SD)	81.01 (18.74)	106.72 (12.56)	81.89 (18.45)	109.44 (14.15)
Min to Max	(40.60 to 108.82)	(73.64 to 125.51)	(44.92 to 114.98)	(68.15 to 127.50)
Adult asthma, age 18-45 years (N=50)				
Mean (SD)	90.59 (15.08)	108.28 (12.25)	89.73 (17.41)	111.22 (12.52)
Min to Max	(60.98 to 123.59)	(70.37 to 129.24)	(47.37 to 125.94)	(68.90 to 130.66)
COPD, age 55 years (N=50)				
Mean (SD)	74.49 (15.73)	88.34 (14.41)	75.11 (16.80)	91.40 (15.62)
Min to Max	(44.78 to 116.01)	(60.80 to 120.64)	(41.42 to 123.71)	(63.21 to 127.11)
Healthy subjects, age 18-45 years (N=50)				
Mean (SD)	94.51 (12.22)	116.03 (11.53)	95.16 (12.38)	118.78 (11.49)
Min to Max	(71.14 to 125.42)	(87.80 to 140.26)	(68.71 to 121.44)	(100.32 to 148.80)

Source: Section 3.2.P.2.4, Appendix B, Table 3a

Abbreviations: COPD = chronic obstructive pulmonary disease; FS Spiromax = salmeterol / fluticasone propionate/xinafoate dry powder inhaler; Min to Max = range, minimum to maximum; SD= standard deviation

Regardless of age and underlying disease, children, adolescents and adults with asthma and patients with COPD can achieve inspiratory flow rates through both the Spiromax device and Accuhaler device.

Following training, adolescents and adults with asthma and patients with COPD are able to achieve inspiratory flow rates through both the Spiromax device and the Accuhaler device greater than 60L/min and similar to the range of flow rates observed in the pharmacokinetic equivalence studies carried out in healthy volunteers. While flow through both devices was somewhat lower in patients

with asthma and patients with COPD compared with healthy volunteers, the mean PIFR achieved by patients with asthma and patients with COPD pre-training was greater than 60L/min with a minimum PIFR greater than 40L/min, whereas post-training the minimum PIFR achieved in these subject groups was greater than 60L/min. Such flow rates (greater than 60L/min) are flow rates at which both the FS Spiromax device and the Seretide Accuhaler device are known/have been shown to deliver comparable amounts of drug to the lungs (pivotal pharmacokinetic studies, Study FSS-BE-107 and Study FSS-BE-10020).

Conclusions

The development of this new fixed-dose combination orally inhaled product aims to demonstrate therapeutic equivalence of these new products to an appropriate reference product and the development is based on the demonstration of *in vitro* equivalence or pharmacokinetic equivalence between a single high strength of this fixed-dose combination of salmeterol xinafoate / fluticasone propionate and the corresponding strength of the reference product.

Four pharmacokinetic studies are presented, two pilot studies, Studies FSC-AS-101 and FSS-AS-104 and two studies described as pivotal, Studies FSS-BE-107 and FSS-BE-10020.

The two pivotal studies were well designed, had appropriate objectives and were adequately powered to demonstrate therapeutic equivalence between the test and reference product. The statistical analysis is acceptable.

Full bioanalytical reports for the pivotal studies have been provided. These reports are in general acceptable. The Applicant has also stated that samples with salmeterol xinafoate / fluticasone propionate concentrations above the ULOQ were diluted to fall within the standard curve range. The dilution integrity was demonstrated in the validation report.

The clinical development of FS Spiromax was based on showing pharmacokinetic bioequivalence between FS Spiromax (salmeterol xinafoate / fluticasone propionate 50/500µg) and Seretide Accuhaler or Seretide Diskus (salmeterol xinafoate 50µg and fluticasone propionate 500µg) in the absence (Study FSS-BE-107) and in the presence (Study FSS-BE-10020) of a charcoal blockade. Indeed, in accordance with the CHMP Guideline for orally inhaled products (CPMP/EWP/4151/00 Rev.1). "A pharmacokinetic study designed to assess pulmonary deposition, has to be able to exclude absorption of the active moiety from the gastrointestinal tract (for example by using charcoal blockade). A pharmacokinetic study may be used for determination of pulmonary deposition but may also investigate systemic safety. In the investigation of systemic safety total systemic exposure has to be measured in the intended patient population and therefore the study must include the measurement of that amount of the active moiety absorbed through the lung and the gastrointestinal tract.

.... it may be possible for substances with negligible gastrointestinal absorption that the pharmacokinetic study designed to assess pulmonary deposition may be sufficient in the assessment of therapeutic equivalence.

In accordance with the standard accepted methods of assessment of bioequivalence the maximum concentration (C_{max}), the area under the curve (AUC) and the time to C_{max} (T_{max}) should be compared.

Equivalent pulmonary deposition and equivalent systemic safety of two inhaled products may be concluded if the 90 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25."

It is established that following oral inhalation of salmeterol xinafoate some 28-36% of the total

systemic availability comes from that part of the dose that is swallowed and not inhaled into the lungs therefore in order to characterise that portion of the long-acting β_2 agonist absorbed only through the lungs, as a surrogate for clinical efficacy, the pharmacokinetic parameters was measured following the oral ingestion of activated charcoal to block gastrointestinal absorption. The measurement of the total systemic exposure (systemic safety) of salmeterol xinafoate was measured in the absence of charcoal blockade as the active drug absorbed through both the lungs and the gastrointestinal tract.

In respect of fluticasone propionate and due to extensive ($\geq 99\%$) first pass hepatic metabolism, oral bioavailability is negligible and therefore the systemic bioavailability of fluticasone propionate was described as entirely derived from pulmonary absorption.

Equivalence of FS Spiromax 50/500 μg and Seretide Accuhaler 50/500 μg was demonstrated both without charcoal blockade (Study FSS-BE-107) and in the presence of charcoal blockade (Study FSS-BE-10020) with respect to AUC_{0-t} and C_{max} (primary variables) for both fluticasone propionate and salmeterol xinafoate.

In Study FSS-BE-107 the pharmacokinetic ratios were all close to unity with 90% CIs well within the accepted bioequivalence range of 0.8, 1.25 for both actives; however, both the lower and upper bounds of the CIs for the inhaled corticosteroid were above unity. This finding with fluticasone propionate recurs but is more exaggerated in the second pivotal study, Study FSS-BE-10020, the study with charcoal blockade, where it is to note that although both the lower and upper bounds of the CIs were above unity, the upper bound is very close to the upper limit of the accepted bioequivalence range. In Study FSS-BE-10020 the pharmacokinetic comparisons for salmeterol xinafoate were also all above unity but with the 90% CIs well within the accepted bioequivalence range of 0.8-1.25.

The findings in these two pivotal pharmacokinetic studies support therapeutic equivalence between the test product, FS Spiromax 50/500 μg and the reference product in respect of efficacy (pulmonary deposition and absorption as a surrogate for efficacy in both Study FSS-BE-107 and Study FSS-BE-10020 for fluticasone propionate and in Study FSS-BE-10020 for salmeterol xinafoate) and safety (total systemic absorption, pulmonary and gastrointestinal, in Study FSS-BE-107 and Study FSS-BE-10020 for fluticasone propionate and in Study FSS-BE-107 for salmeterol xinafoate).

The findings in the two pivotal studies demonstrate that the final formulation, the final device and the manufacturing process for this new fixed-dose orally inhaled fixed dose combination product containing the actives fluticasone propionate and salmeterol xinafoate formulated as an inhalation powder in one high strength, as FS Spiromax 50/500 μg , are robust and can provide an equivalent in vivo performance to that of the same dose of the reference product.

In the *in vitro* flow rate comparison conducted to investigate whether the flow rate dependence of the FS Spiromax device matched that of Seretide Accuhaler, lower fine particle dose is seen at the lower flow rates of 45 and 60L/min and lower total dose is seen at all four flow rates studied, 45, 60, 80 and 100L/min for salmeterol xinafoate as measured with the Next Generation Impactor. At the CHMP's request, the Applicant has discussed these findings in the light of the pharmacokinetic data presented in healthy volunteers inhaling with flow rates in excess of 60L/min and has discussed the clinical relevance and impact of these findings in patients with severe COPD and severe asthma or other causes of severely impaired inspiratory capacity and inhaling with flow rates less than 60L/min.

The CHMP concluded that this difference is unlikely to contribute to differences in systemic exposure particularly when patients with asthma and patients with COPD are trained in the use of the Spiromax device in order to achieve inspiratory flow rates through the device of greater than 60L/min. As a consequence, additional advice was added to the product information relating to training in optimal use of the device, to minimise any risk of underdosing as a consequence of low inspiratory flow rates.

Based on the presented bioequivalence studies FS Spiromax is considered bioequivalent to Seretide Accuhaler 50 microgram/500 microgram/dose inhalation powder, pre-dispensed.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Clinical efficacy

The efficacy of the individual components has been investigated extensively and is well known. The efficacy of these two active substances when formulated as a fixed-dose combination product as in the reference product has also been investigated extensively.

No specific clinical studies are presented.

Indications:

In the initial submission, the Applicant proposed a similar indication to the reference product for the regular treatment of asthma in adults aged 18 years and older, in whom the use of a fixed-dose combination of an inhaled corticosteroid and a long-acting β_2 agonist is appropriate and an indication for the symptomatic treatment of adults with COPD (FEV1 <60% predicted normal, pre-bronchodilator) with a history of repeated exacerbations and who have significant symptoms despite regular bronchodilator therapy.

The reference product is indicated for the treatment of asthma (low, mid and high – 50/500 μ g - strengths) and for the treatment of COPD (high strength: 50/500 μ g). FS Spiromax has been developed in the 50/500 μ g strength corresponding to the high strength of the reference product.

Asthma

The highest strength of this fixed-dose combination should not be used for treatment initiation or for maintenance therapy for moderate asthma.

Furthermore, this single high strength will have no role in the initial treatment of patients with mild to moderate persistent asthma and the absence of the low and mid dose strengths of FS Spiromax does not allow for downward titration of the dose of the inhaled corticosteroid component to attain the minimally effective dose to control asthma, which is an essential part of asthma management. Hence, there is a risk that when using FS Spiromax in the management of asthma, the dose of inhaled corticosteroid prescribed may not be titrated downwards as asthma is brought under control. Therefore, patients may be maintained on too high a dose of inhaled corticosteroid for too long a period of time.

Considering the above, the CHMP requested that the Applicant restrict the asthma indication to patients with severe asthma only. The Applicant agreed to this proposal.

Chronic obstructive pulmonary disease

The CHMP is of the view that the proposed indication for use in the management of chronic obstructive pulmonary disease is acceptable.

Special populations

Elderly patients

No specific clinical studies have been submitted. This is acceptable. Further to the pharmacokinetic studies in healthy volunteers the Applicant has submitted a study of the inhalation characteristics of healthy adult volunteers (aged 18 to 45 years), adults (18 to 45 years), adolescents (12 to 17 years) and children (4 to 11 years) with stable asthma and adults over 55 years of age with stable COPD in order to bridge the findings in the pharmacokinetic studies in healthy volunteers to the target patient populations in whom these fixed-dose combination products will be used (Chrystyn et al, 2014). Although the elderly were not studied per se, the inhalation characteristics in patients with COPD and over 55 years of age were and such is acceptable in the stead of a specific study of the elderly over 65 years of age.

Children and adolescents

The Applicant did not seek an indication for use in children (12 years of age and younger) or adolescents (aged 13 to 17 years).

2.4.5. Clinical safety

Patient exposure

Safety data are available from 4 FS Spiromax 50/500 µg studies conducted in healthy volunteers.

The main objective of this safety evaluation is to assess whether, from a clinical safety perspective, FS Spiromax 50/500 µg has a similar safety profile compared with Seretide Accuhaler.

No formal integration of the safety data from the clinical studies was performed due to the study designs employed (4 single-dose crossover PK studies) in healthy volunteers.

In all studies, adverse events were collected from the time of informed consent to the end of study visit. A treatment-emergent adverse event was defined as an adverse event that began or that worsened in severity after at least 1 dose of the study medication had been administered. The adverse events were reviewed for intensity, relationship to treatment and seriousness. The adverse events are coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding dictionary, Version 11.1 or higher. The following were also assessed at screening and at the end of study: vital signs, clinical laboratory tests, ECG results and changes in physical examination findings. Vital signs were also measured each day during the treatment periods.

Adverse events

The PK studies were all single-dose crossover studies and therefore provide limited safety information. The nature and intensity of adverse events for FS Spiromax 50/500 µg was very similar to that for Seretide Accuhaler. Headache was the most common adverse event in each of the PK studies.

Serious adverse event/deaths/other significant events

No deaths have been reported in this clinical development programme. One serious adverse event was reported after randomization but prior to treatment in the treatment period in Study FSS-BE-10020, where a subject experienced severe syncope in combination with muscle spasms, nausea, and vomiting, which required hospitalization. The observed events were assessed to have no causal relationship to the study drug. The subject was withdrawn and the serious adverse event resolved without sequelae.

Laboratory findings

Clinical laboratory tests were assessed at screening and at the end of study in each study. Across all studies, no treatment-related trends were observed in mean absolute values or changes from baseline of any of the clinical chemistry, haematology or urinalysis parameters following dosing with either FS Spiromax 50/500 µg or Seretide Accuhaler. There were few clinically significant laboratory abnormalities reported in any study and examination of out of range values at screening and end of study did not indicate any clinically relevant findings with regard to administration of FS Spiromax 50/500 µg.

Vital Signs, Electrocardiogram and Physical Examinations

Assessments of vital signs, ECGs and physical examinations were conducted at screening and at the end of study in each study. Across all studies, no treatment-related trends were observed for any vital sign parameter, and individual vital sign changes in each study were minimal following dosing with either FS Spiromax 50/500 µg or Seretide Accuhaler. No clinically significant abnormalities were reported that were considered relevant with regard to FS Spiromax 50/500 µg administration.

Likewise, ECG values (PR, QT, QRS, QTc and heart rate) remained within the reference range and no significant trends were noted from the screening visit to the end of study visit. No clinically significant ECG findings were reported in any of the PK studies following dosing with FS Spiromax 50/500 µg or Seretide Accuhaler that were considered relevant with regard to FS Spiromax 50/500 µg administration.

Finally, there were no clinically relevant changes in physical examination findings from screening to the end of study visit that were considered related to treatment with FS Spiromax 50/500 µg.

2.4.6. Post marketing experience

Seretide Diskus has been marketed in the EU for over 10 years for the treatment of asthma (3 strengths) and for the treatment of COPD (50/500 µg (high) strength). Salmeterol/fluticasone was first approved in the US in 2000.

Asthma

Salmeterol/fluticasone propionate is generally well tolerated in adults, adolescents and children with asthma (McKeage and Keam 2009). Overall, the most frequent treatment-related adverse effects include upper respiratory tract infection, pharyngitis, headaches and throat irritation/cough. In clinical trials, the incidence of treatment-related effects was generally similar to that of comparators, including fluticasone propionate alone, montelukast or formoterol/budesonide. The Cochrane review by

Lasserson et al 2011 reported that odds of experiencing any adverse event were similar between salmeterol xinafoate / fluticasone propionate and budesonide/formoterol (3 studies, N = 3547; OR 1.00, 95% CI 0.88 to 1.15). Differences between treatments in the odds of headache (OR 1.08, 95% CI 0.82 to 1.43), candidiasis (OR 1.64, 95% CI 0.68 to 4.00), upper respiratory tract infection (OR 1.09, 95% CI 0.81 to 1.47), dysphonia (OR 1.45, 95% CI 0.87 to 2.43) and throat irritation did not differ significantly between treatments. Study withdrawals were not significantly more frequent with either treatment in terms of overall discontinuations or discontinuations because of adverse events.

Chronic Obstructive Pulmonary Disease

In the Cochrane review by Nannini et al 2013, no significant difference was noted between salmeterol xinafoate / fluticasone and placebo in the occurrence of overall reported adverse events (OR 1.09, 95% CI 0.95 to 1.25) or serious adverse events (OR 1.08, 95% CI 0.95 to 1.23).

A significant increase in adverse events of pneumonia was recorded with salmeterol xinafoate / fluticasone propionate in comparison with placebo (OR 1.80, 95% CI 1.49 to 2.18). Candidiasis, nasopharyngitis, hoarseness and upper-respiratory tract infection also occurred more frequently among salmeterol xinafoate / fluticasone propionate 50/500µg -treated subjects than with placebo. Withdrawals because of adverse events occurred less frequently on treatment with salmeterol xinafoate / fluticasone propionate than with placebo.

2.4.7. Discussion on clinical aspects

The Applicant sought an indication for the regular treatment of asthma in adults aged 18 years and older, in whom the use of a fixed-dose combination of an inhaled corticosteroid and a long-acting β_2 agonist is appropriate. The Applicant also sought an indication for the symptomatic treatment of adults with COPD (FEV1 < 60% predicted normal, pre-bronchodilator) with a history of repeated exacerbations and who have significant symptoms despite regular bronchodilator therapy.

The efficacy and safety of salmeterol xinafoate and fluticasone propionate 50/500µg have been investigated extensively, are well known.

The efficacy and safety of these two active substances when formulated as a fixed-dose combination product as in the reference product have also been investigated extensively and this fixed-dose combination is well established.

The clinical dossier comprises four pharmacokinetic studies (two pilot studies and two pivotal studies) all carried out in male and female healthy volunteers, aged between 18 and 45 years and one study to determine whether flow rates through the Spiromax and Accuhaler devices differ between patients with stable asthma, including adults aged 18 to 45 years, adolescents aged 12 to 17 years and children aged 4 to 11 years and patients with COPD aged over 55 years, compared with healthy volunteers aged 18 to 45 years.

The lack of the submission of a full clinical efficacy programme is acceptable in this type of application and is in line with the CHMP Guideline for orally inhaled products (CHMP/EWP/4151/00 Rev. 1) providing that either in vitro equivalence and/or pharmacokinetic equivalence and/or pharmacodynamic therapeutic equivalence has been demonstrated. In this application pharmacokinetic equivalence between FS Spiromax and the reference product both administered in one high strength, has been demonstrated.

Hence, no new pharmacodynamic or efficacy studies were presented and no such studies are required for this application.

The findings in the two pivotal pharmacokinetic studies submitted support therapeutic equivalence between the test product, FS Spiromax 50/500µg and the reference product in respect of efficacy (pulmonary deposition and absorption as a surrogate for efficacy in both Study FSS-BE-107 and Study FSS-BE-10020 for fluticasone propionate and in Study FSS-BE-10020 for salmeterol xinafoate) and safety (total systemic absorption, pulmonary and gastrointestinal, in Study FSS-BE-107 and Study FSS-BE-10020 for fluticasone propionate and in Study FSS-BE-107 for salmeterol xinafoate).

Compared with Seretide Accuhaler, currently available on the market in low, mid and high strengths, FS Spiromax is proposed for marketing, based on bioequivalence studies carried out in only one high strength. This single high strength will have no role in the initial treatment of or maintenance of patients with mild to moderate persistent asthma and will not allow down-titration of the inhaled corticosteroid component of the fixed-dose combination in patients in whom asthma is controlled on this single high strength, to a lower dose of corticosteroid at which control of symptoms would be maintained. Therefore, the CHMP requested the Applicant to restrict the indication to patients with severe asthma only. The Applicant agreed to this proposal and revised information in the adult population, aged 18 years and older is as follows:

- for the regular treatment of patients with severe asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 agonist) is appropriate: patients not adequately controlled on a lower strength corticosteroid combination product, or patients already controlled on a high dose inhaled corticosteroid and long-acting β_2 agonist,
- for the symptomatic treatment of patients with COPD, with a FEV1 < 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy

In addition, the CHMP recommends the Applicant to complete the development of both the low and mid strengths of FS Spiromax as soon as possible. Due to the lack of the low and mid strengths of this orally inhaled fixed-dose combination product when prescribed for use in asthma there is a risk that the dose of inhaled corticosteroid prescribed in the management of asthma may be too high, it may not be titrated downwards as asthma is brought under control and the patient may end up on a dose of the inhaled corticosteroid which may be too high for too long a period of time.

The Applicant has discussed the possible clinical impact that the fall in fine particle dose at lower flow rates (flow rates less than 60L/min) might have in patients with severe COPD (and severe asthma or other causes of severely impaired inspiratory capacity). The Applicant has included additional advice in the product information relating to training in optimal use of the device, to minimise any risk of underdosing as a consequence of low inspiratory flow rates.

This product should not be used in the management of asthma in children and adolescents. This information is adequately reflected in the product information. In addition, it is included as missing information in the RMP.

Based on the safety parameters measured in the pharmacokinetic studies carried out with FS Spiromax and presented in this submission, no safety concerns are observed.

The adverse event profile is in line with the current knowledge on the safety pharmacology profiles of these two actives and is comparable with that of the reference product.

No clinically significant findings and no medically relevant events were observed with FS Spiromax. The safety profile is adequately reflected in the product information.

2.4.8. Conclusions on the clinical aspects

Pharmacokinetic equivalence between FS Spiromax and the reference product has been demonstrated.

The lack of the submission of a full clinical efficacy programme is acceptable in this type of application and is in line with the CHMP Guideline for orally inhaled products (CHMP/EWP/4151/00 Rev. 1) providing that either in vitro equivalence and/or pharmacokinetic equivalence and/or pharmacodynamic therapeutic equivalence has been demonstrated. In this application pharmacokinetic equivalence between FS Spiromax and the reference product both administered in one high strength, has been demonstrated. Hence, the absence of new pharmacodynamic and clinical studies is acceptable.

In the light of the availability of only the high strength of FS Spiromax, the CHMP requested that the Applicant restrict the asthma indication to patients with severe asthma only. The Applicant agreed to this proposal.

2.5. Pharmacovigilance

Risk Management Plan

Safety concerns

Table 10 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Pneumonia in COPD patient populations
	Exacerbation of asthma which may be life-threatening
	Paradoxical bronchospasm
	Systemic effects of inhaled corticosteroids, including Cushing's syndrome, adrenal suppression and acute adrenal crisis
	Hypersensitivity reactions including anaphylactic reactions
	Cardiac arrhythmias, especially in patients with severe cardiovascular disorders, heart rhythm abnormalities and those with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium
	Angina pectoris
	Interaction with CYP450 3A4 inhibitors leading to increased salmeterol and fluticasone exposure

Important potential risks	Use in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway
	Pneumonia in asthma patient population
	Risk of overdose in patients that need a lower dose than the authorized dose
Missing information	Patients with hepatic impairment
	Breastfeeding women
	Use in children and adolescent aged less than 18 years

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 11 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Pneumonia in COPD patient populations	<p>Special warnings and precautions for use listed in section 4.4 of the SmPC.</p> <p>Pneumonia is listed in section 4.8 of the SmPC (Undesirable effects).</p> <p>Clinical trials described in section 5.1 of the SmPC (Pharmacodynamic properties).</p> <p>Instructions in PIL.</p> <p>Prescription only medicine.</p>	Not applicable.
Exacerbation of asthma which may be life-threatening	<p>Information on appropriate use described in section 4.2 of the SmPC (Posology and method of administration).</p> <p>Special warnings and precautions for use described in section 4.4 of the SmPC.</p> <p>Key findings from the SMART study described in section 5.1 of</p>	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>the SmPC (Pharmacodynamic properties).</p> <p>Instructions in PIL.</p> <p>Prescription only medicine.</p>	
Paradoxical bronchospasm	<p>Special warnings and precautions for use described in section 4.4 of the SmPC.</p> <p>Paradoxical bronchospasm is listed in section 4.8 of the SmPC (Undesirable effects).</p> <p>Instructions in PIL.</p> <p>Prescription only medicine.</p>	Not applicable.
Systemic effects of inhaled corticosteroids, including Cushing's syndrome, adrenal suppression and acute adrenal crisis	<p>Systemic effects of inhaled corticosteroid described in section 4.4 of the SmPC (Special warnings and precautions for use).</p> <p>Interactions of fluticasone propionate described in section 4.5 of the SmPC (Interactions with other medicinal products and other forms of interaction)</p> <p>Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density, Anxiety, Sleep disorders, Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children), Depression, aggression (predominantly in children), Cataract and Glaucoma listed in section 4.8 of the SmPC (Undesirable effects).</p> <p>Instructions in PIL.</p> <p>Prescription only medicine.</p>	Not applicable.
Hypersensitivity reactions	Contraindications listed in	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
including anaphylactic reactions	section 4.3 of the SmPC. Hypersensitivity reactions listed in section 4.8 of the SmPC (Undesirable effects). Instructions in PIL. Prescription only medicine.	
Cardiac arrhythmias, especially in patients with severe cardiovascular disorders, heart rhythm abnormalities and those with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium	Cardiac arrhythmias described in section 4.4 of the SmPC (Special warnings and precautions for use). Cardiac arrhythmias listed in section 4.8 of the SmPC (Undesirable effects). Instructions in PIL. Prescription only medicine.	Not applicable.
Angina pectoris	Angina pectoris listed in section 4.8 of the SmPC (Undesirable effects). Instructions in PIL. Prescription only medicine.	Not applicable.
Interaction with CYP450 3A4 inhibitors leading to increased salmeterol and fluticasone exposure	Concomitant use of other medication with salmeterol and fluticasone described in section 4.4 of the SmPC (Special warnings and precautions for use). Interactions of salmeterol/fluticasone described in section 4.5 of the SmPC (Interaction with other medicinal products and other forms of interaction). Metabolism pathway of fluticasone described in section 5.2 of the SmPC (Pharmacokinetic properties). Instructions in PIL. Prescription only medicine.	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT POTENTIAL RISKS		
Use in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway	Warning in section 4.4 of the SmPC (Special warnings and precautions for use). Instructions in PIL. <i>Prescription only medicine.</i>	Not applicable.
Pneumonia in Asthma patient population	Prescription only medicine.	Not applicable.
Risk of overdose in patients that need a lower dose than the authorized dose	Warning in section 4.4 of the SmPC (Special warnings and precautions for use). Instructions in PIL. Prescription only medicine.	Not applicable.
MISSING INFORMATION		
Patients with hepatic impairment	Special populations information in section 4.2 of the SmPC (Posology and method of administration). Instructions in PIL. Prescription only medicine.	Not applicable.
Breastfeeding women	Information on breast-feeding in section 4.6 of the SmPC (Fertility, pregnancy and lactation). Instructions in PIL. Prescription only medicine.	Not applicable.
Use in children and adolescents aged less than 18 years	Not indicated for use in the paediatric population information in section 4.2 of the SmPC (Posology and method of administration). Instructions in PIL. Warning on outer packaging Prescription only medicine.	Not applicable.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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*.

3. Benefit-Risk Balance

This application concerns a hybrid version of a fixed-dose combination of salmeterol xinafoate and fluticasone propionate inhalation powder. The reference product Seretide Diskus forte, containing the same two active, is indicated for the treatment of asthma and COPD.

Nonclinical studies have not been provided for this application and the review of the literature references is considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacodynamics or the efficacy and safety of the active substance. The lack of the submission of a full clinical efficacy programme is acceptable in this type of application and is in line with the CHMP Guideline for orally inhaled products (CHMP/EWP/4151/00 Rev. 1) providing that either in vitro equivalence and/or pharmacokinetic equivalence and/or pharmacodynamic therapeutic equivalence has been demonstrated. In this application pharmacokinetic equivalence between FS Spiromax and the reference product both administered in one high strength, has been demonstrated. Hence, the absence of new pharmacodynamic or clinical studies is acceptable.

The design of the bioequivalence studies was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of FS Spiromax met the protocol-defined criteria for bioequivalence when compared with the Seretide Diskus. The point estimates and their 90% confidence intervals for the

parameters AUC_{0-t} , and C_{max} were all contained within the protocol-defined acceptance range of 0.8 to 1.25. Bioequivalence of the two formulations was demonstrated.

In the in vitro flow rate comparison conducted to investigate whether the flow rate dependence of the FS Spiromax device matched that of Seretide Accuhaler, lower fine particle dose is seen at the lower flow rates of 45 and 60L/min and lower total dose is seen at all four flow rates studied, 45, 60, 80 and 100L/min for salmeterol xinafoate as measured with the Next Generation Impactor. These findings were discussed in the light of the pharmacokinetic data presented in healthy volunteers inhaling with flow rates in excess of 60L/min and in respect of the clinical relevance and impact of these findings in patients with severe COPD and severe asthma or other causes of severely impaired inspiratory capacity and inhaling with flow rates less than 60L/min.

This difference is unlikely to contribute to differences in systemic exposure particularly when patients with asthma and patients with COPD are trained in the use of the Spiromax device in order to achieve inspiratory flow rates through the device of greater than 60L/min. As a consequence, additional advice was added to the product information relating to training in optimal use of the device, to minimise any risk of under dosing as a consequence of low inspiratory flow rates.

FS Spiromax will be available in only one high strength. This single high strength will have no role in the initial treatment of patients with severe asthma unless the requirement for such a high dose of the corticosteroid together with a long-acting β_2 agonist has been established previously and will have no role in the initial treatment of and maintenance of patients with mild to moderate persistent asthma. This single high strength of FS Spiromax will not allow down-titration of the inhaled corticosteroid component of the fixed-dose combination in patients in whom asthma is controlled on this single high strength, to a lower dose of corticosteroid at which control of symptoms would be maintained. Therefore, a restricted indication to patients with severe asthma only was granted.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Aerivio Spiromax:

- for the regular treatment of patients with severe asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 agonist) is appropriate: patients not adequately controlled on a lower strength corticosteroid combination product, or patients already controlled on a high dose inhaled corticosteroid and long-acting β_2 agonist,
- for the symptomatic treatment of patients with COPD, with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy

in adults aged 18 years and older only is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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 European Medicines Agency;
- 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.