Public Assessment Report

Decentralised Procedure

Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension

Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension

Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension

(Salmeterol xinafoate and fluticasone propionate)

Procedure Number(s): UK/H/6076/001-003/DC

UK Licence No(s): PL 36532/0001-0003

Genetic S.p.A.
LAY SUMMARY

Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension
Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension
Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension

(Salmeterol (as xinafoate) 25 microgram/fluticasone propionate 50, 125 or 250 microgram per metered dose pressurised inhalation, suspension)

This is a summary of the Public Assessment Report (PAR) for Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension (PL 36532/0001; UK/H/6076/001/DC), Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension (PL 36532/0002; UK/H/6076/002/DC) and Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 36532/003; UK/H/6076/0003/DC). It explains how the applications Combisal 25 microgram/50 microgram, 25 microgram/125 microgram and 25 microgram/250 microgram per metered dose pressurised inhaler, suspension were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these medicines.

The products may be collectively referred to as ‘Combisal’ or ‘Combisal 25 microgram/50 microgram, Combisal 25 microgram/125 microgram and Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension’ throughout the remainder of this Public Assessment Report (PAR), for ease of reading. At initial approval, the product name for the products in the UK was ‘Combiflu’; this was later changed to ‘Combisal’ (Please see pages 28-29 for further information).

For practical information about using Combisal, the patient should read the package leaflet or contact their doctor or pharmacist.

What is Combisal and what is it used for?
Combisal 25 microgram/50 microgram, 25 microgram/125 microgram and 25 microgram/250 microgram per metered dose pressurised inhalation, suspension are ‘hybrid applications’. This means that they are similar to the ‘reference medicines’ containing the same active substances, already authorised in the European Union (EU), called Seretide Evohaler 25 microgram/50 microgram per metered dose pressurised inhalation, suspension (PL 10949/0337; Glaxo Wellcome UK Limited), Seretide Evohaler 25 microgram/125 microgram per metered dose pressurised inhalation, suspension (PL 10949/0338; Glaxo Wellcome UK Limited) and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 10949/0339; Glaxo Wellcome UK Limited).

Combisal is used to help prevent breathing problems such as asthma. The patient must use this medicine every day as directed by their doctor. This will make sure it works properly in controlling the patient’s asthma.

This medicine helps to stop breathlessness and wheeziness coming on. However, this medicine should not be used to relieve a sudden attack of breathlessness or wheezing. If this happens, the patient needs to use a fast-acting ‘reliever’ (‘rescue’) inhaler, such as salbutamol. The patient should always have their fast-acting ‘rescue’ inhaler with them.
How does Combisal work?
Combisal contains two active substances, salmeterol (as salmeterol xinafoate) and fluticasone propionate:
- Salmeterol is a long-acting bronchodilator. Bronchodilators help the airways in the lungs to stay open. This makes it easier for air to get in and out. The effects last for at least 12 hours.
- Fluticasone propionate is a corticosteroid which reduces swelling and irritation in the lungs.

How is Combisal used?
The pharmaceutical form of this medicine is a pressurised inhalation, suspension and the route of administration is inhalation through the mouth.

The patient should always use this medicine exactly as their doctor or pharmacist has told them. They should check with their doctor or pharmacist if they are not sure.

The patient should use their Combisal every day, until their doctor advises them to stop. Do not take more than the recommended dose. The patient should check with their doctor or pharmacist if they are not sure.

The patient should not stop taking Combisal or reduce the dose of Combisal without talking to their doctor first.

Combisal should be inhaled through the mouth into the lungs.

Adults
Adults and adolescents aged 12 years and over
- Combisal 25 microgram/50 microgram - 2 puffs twice a day
- Combisal 25 microgram/125 microgram - 2 puffs twice a day
- Combisal 25 microgram /250 microgram - 2 puffs twice a day

Children 4 to 12 years of age
- Combisal 25 microgram/50 microgram - 2 puffs twice a day
- Combisal 25 microgram/125 microgram and Combisal 25 microgram/250 microgram are not recommended for use in children below 4 years of age.

The patient’s symptoms may become well controlled using Combisal twice a day. If so, your doctor may decide to reduce the patient’s dose to once a day. The dose may change to:

- once at night - if the patient has night-time symptoms.
- once in the morning - if the patient has daytime symptoms

However, if the patient’s asthma or breathing gets worse they should tell their doctor straight away. The patient may find that they feel more wheezy, their chest feels tight more often or they may need to use more of their fast-acting ‘reliever’ inhaler. If any of these happen, the patient should continue to take Combisal but not increase the number of puffs they take. The patient’s chest condition may be getting worse and they could become seriously ill. The patient should see their doctor straightaway as they may need additional treatment.

The patient’s doctor will assess their asthma symptoms regularly to make sure they are taking the correct dose of Combisal and will reduce their dose to the lowest dose required to control their symptoms.
It is very important that the patient follows their doctor’s instructions on how many puffs to take and how often to take their medicine.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, instructions for use and the duration of treatment.

This medicine can only be obtained with a prescription:

**What benefits of Combisal have been shown in studies?**
Combisal 25 microgram/50 microgram, 25 microgram/125 microgram and 25 microgram/250 microgram per metered dose pressurised inhalation, suspension are hybrid applications. Studies in patients have been limited to tests to determine that these medicines are therapeutically equivalent to the reference medicines, Seretide Evohaler 25 microgram /50 microgram per metered dose pressurised inhalation, Seretide Evohaler 25 microgram /125 microgram per metered dose pressurised inhalation, suspension and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 10949/0337-0339; Glaxo Wellcome UK Limited). Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

**What are the possible side effects of Combisal?**
Like all medicines, this medicine can cause side effects, although not everybody gets them. To reduce the chance of side effects, the patient’s doctor will prescribe the lowest dose of Combisal to control their asthma.

The most common side effects are:

**Very common (may affect more than 1 person in 10)**
- Headache - this usually gets better as treatment continues.
- An increased number of colds have been reported in patients with chronic obstructive pulmonary disease (COPD).

**Common (may affect up to 1 person in 10)**
- Thrush (sore, creamy-yellow, raised patches) in the mouth and throat. Also, sore tongue and hoarse voice and throat irritation. Rinsing the mouth out with water and spitting it out immediately and/or the patient brushing their teeth after taking each dose of their medicine may help. The patient’s doctor may prescribe an anti-fungal medicine to treat the thrush.
- Aching, swollen joints and muscle pain.
- Muscle cramps.

The following side effects have also been reported in patients with COPD:
- Pneumonia and bronchitis (lung infection). The patient should tell their doctor if they notice any of the following symptoms: increase in sputum production, change in sputum colour, fever, chills, increased cough, increased breathing problems.
- Throat irritation. Rinsing the patient’s mouth out with water and spitting it out immediately after taking each puff may help.
- Bruising and fractures.
- Inflammation of sinuses (a feeling of tension or fullness in the nose, cheeks and behind the eyes, sometimes with a throbbing ache)
- A reduction in the amount of potassium in the blood (the patient may get an uneven heartbeat, muscle weakness, cramp).
For the full list of all side effects reported with Combisal, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why is Combisal approved?**

It was concluded that, in accordance with EU requirements, Combisal 25 microgram/50 microgram, Combisal 25 microgram/125 microgram and Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension have been shown to have comparable quality and to be therapeutically equivalent to Seretide Evohaler 25 microgram/50 microgram per metered dose pressurised inhalation, suspension, Seretide Evohaler 25 microgram /125 microgram per metered dose pressurised inhalation, suspension and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 10949/0337-339; Glaxo Wellcome UK Limited). Therefore, the view was that, as for Seretide Evohaler 25 microgram /50 microgram per metered dose pressurised inhalation, Seretide Evohaler 25 microgram /125 microgram per metered dose pressurised inhalation, suspension and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 10949/0337-339; Glaxo Wellcome UK Limited), the benefits of Combisal 25 microgram/50 microgram, Combisal 25 microgram/125 microgram and Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension’ outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Combisal?**

A Risk Management Plan (RMP) has been developed to ensure that Combisal is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Combisal including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Combisal**

Greece, Italy, Poland and the UK agreed to grant Marketing Authorisations on 16 October 2017. Marketing Authorisations were granted in the UK to Genetic S.p.A on 10 November 2017.

The full PAR for Combisal follows this summary.

For more information about treatment with Combisal, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2018.
# SCIENTIFIC DISCUSSION

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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension (PL 36532/0001; UK/H/6076/001/DC), Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension (PL 36532/0002; UK/H/6076/002/DC) and Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 36532/0003; UK/H/6076/003/DC) could be approved. For ease of reading, the products may be collectively referred to as ‘COMBISAL’ in this scientific discussion. At initial approval, the product name for the products in the UK was ‘Combiflu’; this was later changed to ‘COMBISAL’ via variation (Please see Annex 1 - Table of content of the PAR update for MRP and DCP on pages 28 - 29 for further information).

The products are Prescription Only Medicines (POM) indicated in the regular treatment of asthma where use of a combination product (long-acting β2 agonist and inhaled corticosteroid) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and ‘as needed’ inhaled short-acting β2 agonist
or
- patients already adequately controlled on both an inhaled corticosteroid and a long-acting β2 agonist.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Greece, Italy and Poland as Concerned Member States (CMS). The applications for Combisal were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The applications refer to the reference products Seretide Evohaler 25 microgram /50 microgram per metered dose pressurised inhalation, suspension (PL 10949/0337; Glaxo Wellcome UK Limited), Seretide Evohaler 25 microgram /125 microgram per metered dose pressurised inhalation, suspension (PL 10949/0338; Glaxo Wellcome UK Limited) and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 10949/0339; Glaxo Wellcome UK Limited), which were first authorised in the UK on 16 June 2000.

COMBISAL contains the active substances salmeterol (as salmeterol xinafoate) and fluticasone propionate. Salmeterol xinafoate is a long acting β2-adrenoceptor agonist acting directly on bronchial smooth muscle to cause relaxation and bronchodilation. Fluticasone propionate is a potent and selective glucocorticoid receptor agonist. When administered by inhalation, fluticasone propionate has potent local anti-inflammatory activity by reducing inflammatory cell (mast, cell, eosinophil, basophil, macrophage and T-cell) activation, and airway hyper-responsiveness.

Three pharmacokinetic studies were submitted to support these applications, comparing the applicant’s test product Salmeterol xinafoate/fluticasone propionate HFA pressurised metered dose inhaler 25/250 microgram per actuation (Genetic S.p.A, Italy) versus the reference product Seretide Evohaler 25/250 microgram pressurised metered dose inhaler (containing salmeterol xinafoate/fluticasone propionate 25/250 microgram per actuation; Allen & Hanburys) under fasting conditions. It is stated that the pharmacokinetic studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA
has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 16 October 2017. After a subsequent national phase, licences were granted in the UK to Genetic S.p.A. on 10 November 2017.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The pharmaceutical form of the products is a pressurized inhalation, suspension.

Each metered dose (ex valve) contains:
25 micrograms of salmeterol (as salmeterol xinafoate) and 50 micrograms of fluticasone propionate.
This is equivalent to a delivered dose (ex actuator) of 21 micrograms of salmeterol and 44 micrograms of fluticasone propionate (25/50 microgram strength product).
Or
25 micrograms of salmeterol (as salmeterol xinafoate) and 125 micrograms of fluticasone propionate.
This is equivalent to a delivered dose (ex actuator) of 21 micrograms of salmeterol and 110 micrograms of fluticasone propionate (25/125 microgram strength product).
Or
25 micrograms of salmeterol (as salmeterol xinafoate) and 250 micrograms of fluticasone propionate.
This is equivalent to a delivered dose (ex actuator) of 21 micrograms of salmeterol and 220 micrograms of fluticasone propionate (25/250 microgram strength product).

The products also contain the propellant norflurane (HFA 134a).

All strengths of the finished product are packed into aluminium alloy pressurised canisters, each sealed with a suitable metering valve. The canister is fitted into plastic incorporating an atomising mouthpiece and fitted with a dustcap.

Each pressurised canister contains 120 actuations (metered doses). The products are available in a pack size of 1 canister containing 120 actuations.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances

Drug substance (1) Salmeterol xinafoate
INN: Salmeterol xinafoate
Chemical name: (1RS)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol 1-hydroxynaphthalene-2-carboxylate.
Structure:

Molecular formula: $\text{C}_{36}\text{H}_{45}\text{NO}_7$

$M_r$: 604

Appearance: White or almost white powder.

Solubility: Practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol

Polymorphism: Two polymorphs have been reported in the literature.

Chirality: Salmeterol xinafoate has one chiral centre

Salmeterol xinafoate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, salmeterol xinafoate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

**Drug Substance (2) Fluticasone propionate**

INN: Fluticasone propionate

Chemical name: 6α, 9-Difluoro-17-[(fluoromethyl)sulphonyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate; S-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate

Structure:

Molecular formula: $\text{C}_{25}\text{H}_{31}\text{F}_{3}\text{O}_{5}\text{S}$

$M_r$: 500.57

Appearance: White or almost white powder.

Solubility: Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol

Polymorphism: Two polymorphs have been reported in the literature.

Isomerism: There are nine chiral centres, the chirality position 6 and 16 are synthetically created and are exclusively $\alpha$-isomerism. Hence Fluticasone propionate has only one isomer

Fluticasone propionate is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, fluticasone propionate, are covered by a EDQM Certificate of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate products that are pharmaceutically and clinically equivalent to the reference products Seretide Evohaler 25 microgram/50 microgram per metered dose pressurised inhalation, suspension, Seretide Evohaler 25 microgram/125 microgram per metered dose pressurised inhalation, suspension and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 10949/0337-0339; Glaxo Wellcome UK Limited). Suitable pharmaceutical development data have been provided for these applications.

Comparative physicochemical data have been demonstrated between the proposed test products and reference products Seretide Evohaler 25 microgram /50 microgram per metered dose pressurised inhalation, suspension, Seretide Evohaler 25 microgram /125 microgram per metered dose pressurised inhalation, suspension and Seretide Evohaler 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (Glaxo Wellcome UK Limited). The comparative physicochemical data was satisfactory.

The propellant norflurane (HFA 134a) complies with a suitable in-house specification. A Certificate of Analysis have been provided, showing compliance with the proposed specification.

Norflurane (HFA 134a) does not contain materials of animal or human origin.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 24 months with the special storage conditions ‘Do not store above 25°C. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C, protect from direct sunlight. Do not pierce or burn the canister even when empty. As with most inhaled medicinal products in pressurised canisters, the therapeutic effect of this medicinal product may decrease when the canister is cold.’ has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product for the lowest strength.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of salmeterol xinafoate and fluticasone propionate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
There are no toxicological concerns relating to impurities and residual solvents in the drug substance or extractables/leachables in the drug product.

III.5 Ecotoxicity/environmental risk assessment (ERA)
No environmental risk assessment has been conducted and an acceptable justification for its absence has been provided. It is anticipated that sales of the proposed product will replace those of similar marketed products and it is unlikely that an increase in environmental exposure to the active substances will occur on marketing of the proposed product.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted or necessary for applications of this type.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of salmeterol xinafoate and fluticasone propionate has been investigated extensively, is well known and has been the subject of many publications.

The clinical development consists of three clinical studies;
1. GEN-SFM-001 - charcoal block study - comparing the pulmonary exposure (surrogate for efficacy) of salmeterol when administered as test/reference is an appropriate study to demonstrate the equivalent efficacy of salmeterol.
2. GEN-SFM-002 - without charcoal block study - comparing the total exposure (surrogate for safety) of salmeterol and fluticasone when administered as test/reference is an appropriate study to demonstrate the equivalent safety of salmeterol as well as equivalent efficacy and safety of fluticasone propionate as fluticasone has negligible absorption through the gut.
3. GEN-SFM-003 – study comparing the total exposure of salmeterol and fluticasone administered as test/reference, which is an appropriate study to support the use of the test products with a spacer in children.

In accordance with the Committee for Medicinal Products for Human Use (CHMP) Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP), the above studies should be
adequate to demonstrate equivalence convincingly by the above investigations of pulmonary deposition and systemic safety; further pharmacodynamic studies or therapeutic equivalence studies are only required if the results of the above studies are not positive.

As the clinical development only compared the highest dose-strength (25/250 microgram) of the test and reference products, the applicant has put forward a biowaiver justification for the two lower dose-strengths of the combination (25/50 microgram and 25/125 microgram) based on comparative quality attributes. The request for biowaiver is acceptable.

IV.2 Pharmacokinetics
In support of the applications, the Marketing Authorisation Holder submitted the following pharmacokinetic studies.

Study GEN-SFM-001
A double-blind, randomised, single-dose, replicate, four-way, crossover study to demonstrate the bioequivalence of the salmeterol component only from the test product Salmeterol xinafoate/fluticasone propionate HFA pressurised metered dose inhaler [pMDI] 25/250 microgram per actuation (Genetic S.p.A) with the reference product Seretide Evohaler pMDI (containing salmeterol xinafoate/fluticasone propionate 25/250 microgram per actuation; Allen & Hanburys), administered as 50/500 μg (2 actuations) in healthy adult male subjects under fasting conditions using a charcoal blockade method.

The primary objective of this study was to demonstrate that the rate and extent of pulmonary absorption of the salmeterol component from the test and reference product were equivalent when administered as a single dose of 50/500 microgram (two inhalations of 25/250 microgram).

The study consisted four study periods and in line with the replicate design, there were two treatments (T-Test and R- Reference). Eligible subjects were randomly assigned to one of two sequences, that is, TRTR or RTRT of active treatment. Each study period included a single dose drug administration of either the test (active) combined with the reference (placebo), or test (placebo) and reference (active) treatments on two separate dosing occasions. The use of test (placebo) and active (placebo) was to maintain the double blind. Each study drug administration in the four separate periods involved a total of 4 actuations two from the active and two from the placebo. The four actuations took approximately 90 seconds for each subject.

A non-investigational medicinal product (NIMP) of activated charcoal suspension (Carbomix) 5g in 50 ml was given to subjects 2 minutes before the first inhalation and 2 minutes after the first inhalation. Thereafter, approximately 10 g activated charcoal suspension in 100 ml of water was given at 1.0, 2.0 and 3.0 hours after dosing of the trial medication. The charcoal blockade was required to prevent gastrointestinal tract absorption and the charcoal blockade protocol is appropriate for the purpose.

After an overnight fast of at least 10 hours, subjects self-administered four actuations of study medications from two devices in accordance to randomization schedule. The washout period between the treatment arms was at least one week (7 days). Subjects were to fast for four hours after dosing. Blood sampling for determination of salmeterol were taken at 1.5 minutes and up to 12 hours after each administration.

Study GEN-SFM-002
A double-blind, randomised, single-dose, replicate, four-way, crossover bioequivalence study to demonstrate the bioequivalence of salmeterol and fluticasone from the test product Salmeterol xinafoate/fluticasone propionate HFA pressurised metered dose inhaler [pMDI] 25/250 μg per actuation (Genetic S.p.A) with that from the reference product Seretide Evohaler 25/250
microgram(containing salmeterol xinafoate/fluticasone propionate 25/250 microgram per actuation; Allen & Hanburys), administered as 50/500 microgram (2 actuations) in healthy adult male subjects under fasting conditions.

The primary objective of this study was to demonstrate that the rate and extent of systemic absorption of salmeterol and fluticasone administered as a single dose of 50/500 μg from test and reference products to healthy male subjects are bioequivalent.

This was a single-centre, two-sequence pivotal pharmacokinetic study. The study consisted four study periods and in line with the replicate design there were two treatments (T-test and R-Reference). Eligible subjects were randomly assigned to one of two sequences, that is, TRTR or RTRT of active treatment. Each study period included a single dose drug administration of either the Test (active) combined with the Reference (placebo), or Test (placebo) and Reference (active) treatments on two separate dosing occasions. The use of test (placebo) and active (placebo) was to maintain the double blind. Each study drug administration in the four separate periods involved a total of four actuations, two from the active (containing 25/250 salmeterol/fluticasone and delivering a total of 50/500 micrograms) and two from the placebo. The four actuations took approximately 90 seconds for each subject. Thereafter, water was given to subjects to rinse their mouth and swallow the remaining water (a total of 120ml).

After an overnight fast of at least 10 hours, subjects self-administered 4 actuations of study medications from two devices in accordance to randomisation schedule. Subjects were to fast for four hours after dosing. There was a wash-out of at least one week (7 days) between each treatment period. Blood sampling for determination of salmeterol were taken at 1.5 minutes and up to 24 hours post-dosing; blood sampling up to 72 hours post-dosing was taken for fluticasone only.

Study GEN-SFM-003

A double blind, randomised, single dose, four-way crossover bioequivalence study to demonstrate the bioequivalence of the salmeterol and fluticasone from the test product Salmeterol xinafoate/fluticasone propionate HFA pMDI 25/250 microgram per actuation (Genetic S.p.A) with the reference product Seretide Evohaler 25/250 microgram (containing salmeterol xinafoate/fluticasone propionate 25/250 microgram per actuation; Allen & Hanburys), administered as 50/500 μg (2 actuations) in healthy adult male subjects under fasting conditions using a Volumatic spacer (treatment period 1 and 2) and an AeroChamber Plus valved holding chamber (VHC) (treatment period 3 and 4).

The primary objective of GEN-SFM-003 was to demonstrate that the rate and extent of systemic absorption of salmeterol and fluticasone administered as a single dose of 50/500 μg from test (T) and reference (R) products to healthy male subjects were bioequivalent when administered with a Volumatic spacer (treatment period 1 and 2) and an AeroChamber Plus valved holding chamber (VHC) (treatment period 3 and 4).

This was a single-centre, two-sequence, pivotal pharmacokinetic study. Each eligible subject was scheduled to participate in four treatment periods. Subjects were required to demonstrate adequate inhalational technique. Subjects were required to refrain from drinking water from 1 hour pre-dose to 2 hours post-dose following which, water may have been consumed as required. Subjects were to fast for four hours after dosing.

After an overnight fast of at least 10 hours, subjects self-administered two actuations of the study medication and two actuations of placebo in accordance with the randomization schedule. There was a wash-out of at least one week (7 days) between each treatment period.
For treatment period 1 and treatment period 2, administration of medication was performed through the Volumatic spacer (with two possible sequences TR or RT). For treatment period 3 and treatment period 4, administration of medication was performed through the AeroChamber Plus VHC (again with two possible sequences TR or RT).

In each treatment period, two inhalations from test inhaler and two inhalations from reference inhaler (where one would be active and other placebo) were administered to ensure blinding. After each set of two inhalations, subjects rinsed their mouth with 60 ml of water and swallowed it. Overall 120 ml of water was taken with the four inhalations in each period.

Pharmacokinetic blood sampling for determination of salmeterol and fluticasone were taken at 1.5 minute and up to 24 h post-dosing. Additional pharmacokinetic blood samples were taken up to 72 hours for measuring fluticasone only.

**Results for Studies GEN-SFM-001, GEN-SFM-002 and GEN-SFM-003:**
The results of the pharmacokinetic data for salmeterol in the 3 pharmacokinetic studies (GEN-SFM-001, 002 and 003) are given in the table below:

**Table 1: Pharmacokinetic data for salmeterol in GEN-SFM-001, GEN-SFM-002 and GEN-SFM-003**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Arithmetic Means (±CV%)</th>
<th>Test product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN-SFM-001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCₙₐ₀ (pg h/mL)</td>
<td>86.505 (56.300)</td>
<td>87.498 (59.338)</td>
<td></td>
</tr>
<tr>
<td>AUCₜₘₐₓ (pg h/mL)</td>
<td>114.163 (69.608)</td>
<td>118.020 (76.735)</td>
<td></td>
</tr>
<tr>
<td>Cₘₐₓ (pg/mL)</td>
<td>107.413 (64.354)</td>
<td>105.692 (60.690)</td>
<td></td>
</tr>
<tr>
<td>Tₘₐₓ₁ (h)</td>
<td>0.05 (0.05, 0.11)</td>
<td>0.05 (0.03, 0.17)</td>
<td></td>
</tr>
<tr>
<td>GEN-SFM-002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCₙₐ₀ (pg h/mL)</td>
<td>183.337 (56.15)</td>
<td>183.822 (57.05)</td>
<td></td>
</tr>
<tr>
<td>AUCₜₘₐₓ (pg h/mL)</td>
<td>218.331 (51.58)</td>
<td>219.936 (54.28)</td>
<td></td>
</tr>
<tr>
<td>Cₘₐₓ (pg/mL)</td>
<td>123.883 (64.61)</td>
<td>122.999 (63.17)</td>
<td></td>
</tr>
<tr>
<td>Tₘₐₓ₁ (h)</td>
<td>0.05 (0.03, 1.50)</td>
<td>0.05 (0.03, 1.25)</td>
<td></td>
</tr>
<tr>
<td>GEN-SFM-003 AeroChamber Plus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCₙₐ₀ (pg h/mL)</td>
<td>79.473 (78.80)</td>
<td>73.386 (70.21)</td>
<td></td>
</tr>
<tr>
<td>AUCₜₘₐₓ (pg h/mL)</td>
<td>105.308 (73.26)</td>
<td>91.049 (65.26)</td>
<td></td>
</tr>
<tr>
<td>Cₘₐₓ (pg/mL)</td>
<td>108.777 (62.40)</td>
<td>103.887 (59.60)</td>
<td></td>
</tr>
<tr>
<td>Tₘₐₓ₁ (h)</td>
<td>0.05 (0.03-0.17)</td>
<td>0.05 (0.03-0.17)</td>
<td></td>
</tr>
<tr>
<td>GEN-SFM-003 Volumatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCₙₐ₀ (pg h/mL)</td>
<td>57.512 (56.58)</td>
<td>46.293 (65.00)</td>
<td></td>
</tr>
<tr>
<td>AUCₜₘₐₓ (pg h/mL)</td>
<td>76.465 (53.76)</td>
<td>82.346 (60.93)</td>
<td></td>
</tr>
<tr>
<td>Cₘₐₓ (pg/mL)</td>
<td>94.105 (42.85)</td>
<td>82.346 (49.54)</td>
<td></td>
</tr>
<tr>
<td>Tₘₐₓ₁ (h)</td>
<td>0.05 (0.05-0.11)</td>
<td>0.05 (0.05-0.17)</td>
<td></td>
</tr>
</tbody>
</table>

Tₘₐₓ₁ median (range)
The results of PK data for fluticasone in the 2 PK studies (GEN-SFM-002 and 003) are given in the table below:

Table 2: Pharmacokinetic data for fluticasone in GEM-SFM-002 and GEN-SFM-003

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Arithmetic Means (±CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GEN-SFM-002</strong></td>
<td></td>
</tr>
<tr>
<td>AUC (0-t) (pg h/mL)</td>
<td>808.779 (64.14)</td>
</tr>
<tr>
<td>AUC (0-∞) (pg h/mL)</td>
<td>872.685 (60.47)</td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>94.068 (56.97)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.00 (0.17-4.00)</td>
</tr>
<tr>
<td><strong>GEN-SFM-003 Aerochamber Plus</strong></td>
<td></td>
</tr>
<tr>
<td>AUC (0-t) (pg h/mL)</td>
<td>588.644 (62.65)</td>
</tr>
<tr>
<td>AUC (0-∞) (pg h/mL)</td>
<td>639.315 (59.96)</td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>72.047 (64.77)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.50 (0.33-4.00)</td>
</tr>
<tr>
<td><strong>GEN-SFM-003 Volumatic</strong></td>
<td></td>
</tr>
<tr>
<td>AUC (0-t) (pg h/mL)</td>
<td>492.076 (47.16)</td>
</tr>
<tr>
<td>AUC (0-∞) (pg h/mL)</td>
<td>538.735 (45.28)</td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>54.748 (44.58)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.50 (0.3-4.00)</td>
</tr>
</tbody>
</table>

Tmax median (range)

Bioequivalence criteria
The results of bioequivalence for salmeterol in the three pharmacokinetic studies (GEN-SFM-001, GEN-SFM-002 and GEN-SFM-003) are given in the table below:

Table 3: Bioequivalence evaluation of salmeterol in GEN-SFM-001, GEN-SFM-002 and GEN-SFM-003

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric Mean Ratio Test/Ref</th>
<th>90% Confidence Interval</th>
<th>Intra-Subject CV (%)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GEN-SFM-001</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>102.21</td>
<td>84.54 – 123.57</td>
<td>101.86</td>
<td>Equivalent</td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>100.43</td>
<td>85.66 – 117.76</td>
<td>75.12</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Cmax</td>
<td>101.69</td>
<td>89.26 – 115.85</td>
<td>63.17</td>
<td>Equivalent</td>
</tr>
<tr>
<td><strong>GEN-SFM-002</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>102.71</td>
<td>94.94 – 111.10</td>
<td>39.15</td>
<td>Equivalent</td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>102.91</td>
<td>94.89 – 111.61</td>
<td>38.56</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Cmax</td>
<td>102.63</td>
<td>94.24 – 111.77</td>
<td>42.78</td>
<td>Equivalent</td>
</tr>
<tr>
<td><strong>GEN-SFM-003 Aerochamber Plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>104.36</td>
<td>89.36 – 122.02</td>
<td>53.05</td>
<td>Equivalent</td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>103.25</td>
<td>89.19 – 124.20</td>
<td>33.13</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Cmax</td>
<td>104.20</td>
<td>92.59 – 117.26</td>
<td>39.00</td>
<td>Equivalent</td>
</tr>
<tr>
<td><strong>GEN-SFM-003 Volumatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>127.17</td>
<td>110.50 – 146.34</td>
<td>48.54</td>
<td>Not equivalent</td>
</tr>
<tr>
<td>AUC (0-∞)</td>
<td>126.88</td>
<td>111.27 – 144.63</td>
<td>42.79</td>
<td>Not equivalent</td>
</tr>
<tr>
<td>Cmax</td>
<td>116.04</td>
<td>104.49 – 128.88</td>
<td>35.39</td>
<td>Not equivalent</td>
</tr>
</tbody>
</table>
The results of bioequivalence for fluticasone in the two pharmacokinetic studies (GEN-SFM-002 and 003) are given in the table below:

Table 4: Bioequivalence evaluation of fluticasone in GEM-SFM-002 and GEN-SFM-003

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric Mean Ratio Test/Ref</th>
<th>90% Confidence Interval</th>
<th>Intra-Subject CV (%)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN-SFM-002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>100.42</td>
<td>93.03 – 108.40</td>
<td>38.00</td>
<td>Equivalent</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>101.66</td>
<td>94.46 – 109.40</td>
<td>36.21</td>
<td>Equivalent</td>
</tr>
<tr>
<td>C_{max}</td>
<td>103.21</td>
<td>95.86 – 111.12</td>
<td>36.64</td>
<td>Equivalent</td>
</tr>
<tr>
<td>GEN-SFM-003 Aerosol Plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>100.72</td>
<td>88.71 – 114.37</td>
<td>42.19</td>
<td>Equivalent</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>101.08</td>
<td>89.48 – 114.18</td>
<td>40.35</td>
<td>Equivalent</td>
</tr>
<tr>
<td>C_{max}</td>
<td>102.38</td>
<td>91.29 – 114.81</td>
<td>37.78</td>
<td>Equivalent</td>
</tr>
<tr>
<td>GEN-SFM-003 Volumatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>118.00</td>
<td>105.27 – 132.26</td>
<td>38.72</td>
<td>Not equivalent</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>115.47</td>
<td>103.86 – 128.38</td>
<td>35.46</td>
<td>Not equivalent</td>
</tr>
<tr>
<td>C_{max}</td>
<td>112.14</td>
<td>100.89 – 124.64</td>
<td>35.68</td>
<td>Not equivalent</td>
</tr>
</tbody>
</table>

Conclusions

**Study 001** – Therapeutic equivalence was shown appropriately with the 90% confidence intervals of the primary pharmacokinetic parameters of C_{max}, AUC_{0-t} and AUC_{0-inf} being within 80.00% -125.00%. However, more than 50% of the AUC_{0-t}/AUC_{0-inf} was less than 80%, which suggests that the elimination phase was not adequately characterized. To justify the acceptability of the conclusion of equivalent ‘pulmonary exposure’, the applicant provided AUC_{0-30} data from study 002 (without charcoal block) which is shown to meet the criteria for concluding therapeutic equivalence. This is acceptable evidence to conclude equivalence of pulmonary exposure for salmeterol as indicated in the CHMP positions on questions raised to the Pharmacokinetic Working Party (PKWP) The duration of sampling is further justified by the fact that the 12 hours period covers the ‘dosing interval’ and the measurement of drug at the 12-hour time points were generally low (<2% of C_{max}).

**Study 002** - Therapeutic equivalence was demonstrated with the 90% confidence limits of the primary pharmacokinetic parameters of C_{max}, AUC_{0-t} and AUC_{0-inf} for both salmeterol and fluticasone. Although based on the intra-subject CV of >30% seen for the C_{max} with the reference, a wider confidence interval could have been allowed for C_{max}, this was not needed.

Although this study had sampling for up to 24 hours to measure salmeterol, more than 25% of the determined AUCs values had an AUC_{0-t}/AUC_{0-inf} ratio of <0.8. The half-life of salmeterol in this study was 8.2 hours for the test product and 8.3 hours for reference product. The sampling duration of 24 hours is therefore slightly less than 3 half-lives which may be the reason for this occurrence. However, in response to the concerns raised, the applicant has included the salmeterol levels measured in the 48-hour and 72-hour samples for the statistical analysis which shows that the therapeutic equivalence criteria are still met when these time-points are included in the analysis. This supports equivalence of systemic exposure of the salmeterol component.

There were no major issues with the characterization of the AUC of fluticasone which in any case was measured up to 72 hours.

Based on this study it can be accepted that the fluticasone component of the test and reference have equivalent total exposure. Considering that fluticasone has negligible absorption from the gut, this can be considered reflective of a similar efficacy and safety profile between the test and reference. This study supports the equivalence of the fluticasone component of the combination.
**Study 003** - Both the salmeterol and fluticasone components, of the test and reference were not equivalent when administered through the Volumatic Spacer. The applicant has withdrawn the claim for use of the product with the Volumatic spacer, which is appropriate.

Equivalence between test and reference was demonstrated for the fluticasone component when administered through the AeroChamber Plus. For the salmeterol component through AeroChamber Plus, although bioequivalence criteria were met, the 24-hour sampling duration appears to have been insufficient to characterize the $AUC_{0\rightarrow inf}$ of salmeterol. In the response to the Day70/100 concerns, the applicant has stated that the measurement of salmeterol levels in the 48 and 72 hour samples were all below limit of quantification (BLQ). Therefore, these values are not expected to alter the conclusion of bioequivalence of the products when used with Aerochamber plus.

**General Comments** - A cross-study comparison of the exposures in study GEN-SFM-003 with the exposure in study GEN-SFM-002, shows that both salmeterol and fluticasone had lower exposures when administered through spacers as compared to without spacers for both the test and reference products. The applicant has attributed this to a different study population in this cross-study comparison.

**IV.3 Pharmacodynamics**
The clinical efficacy profiles of salmeterol xinafoate and fluticasone are well-known. No new efficacy data are presented or are required for applications of this type.

**IV.4 Clinical efficacy**
No new clinical efficacy data are required for these applications and none have been submitted. Pharmacokinetic studies, discussed above, have demonstrated therapeutic equivalence to the reference products.

**IV.5 Clinical safety**
With the exception of the data generated during the pharmacokinetic studies, no new safety data were submitted with these applications and none were required. No new or unexpected safety concerns arose during the pharmacokinetic studies.

**IV.6 Risk Management Plan (RMP)**
The Marketing Authorisation Holder (MAH) has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Combisal.

A summary of safety concerns, as approved in the RMP is listed in the table below:
Table 5: Summary of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inappropriate device use and non-compliance with approved usage of the product</td>
<td>• Use during pregnancy</td>
<td>• Safety and efficacy in children under 4 years of age</td>
</tr>
<tr>
<td>• Lower respiratory tract infections including pneumonia and bronchitis; use in patients</td>
<td>• Off label use in COPD; risk of pneumonia and bronchitis</td>
<td>• Use in hepatic impairment</td>
</tr>
<tr>
<td>with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of</td>
<td>• Safety in breastfeeding</td>
<td></td>
</tr>
<tr>
<td>the airway</td>
<td>• Drug interactions including CYP3A4 inhibitors, other β</td>
<td></td>
</tr>
<tr>
<td>• Cardiac arrhythmias and use in patients with severe cardiovascular disorders or hearth</td>
<td>adrenergic agonists and beta blockers</td>
<td></td>
</tr>
<tr>
<td>rhythm abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Asthma exacerbations including paradoxical bronchospasm, treatment of acute asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>attack and abrupt withdrawal of the treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Systemic corticosteroid effects in adults and children including Cushing’s syndrome,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushingoid features, adrenal suppression and growth retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hyperglycemia and Hypokalemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Psychiatric disorders including behavioural changes, depression and aggression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>predominantly in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious respiratory-related events or deaths in American-African or Afro-Caribbean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ancestry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Misuses for illegal purposes (doping)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation activities are proposed for all safety concerns. This is satisfactory.

**IV.7 Discussion on the clinical aspects**
The grant of Marketing Authorisations is recommended for these applications, from a clinical point of view.

**V USER CONSULTATION**
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

**VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**
The quality of the products is acceptable.

The equivalence of Combisal to the reference Seretide Evohaler has been conclusively demonstrated for the higher strength product (25/250 microgram), based on the submitted *in-vivo* PK studies, when used
with the Aerochamber Plus spacer or without spacer. A biowaiver has been claimed for the lower strengths 25/50 microgram and 25/125 microgram), which is supported by *in-vitro* data.

There are no outstanding clinical concerns and the favourable benefit-risk analysis of the proposed product is considered to be adequately demonstrated by the bridging to the reference product.

The grant of Marketing Authorisations is, therefore, recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labelling text are satisfactory and in line with current guidance.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The Marketing Authorisation Holder has submitted the text version only for Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension (PL 36532/0001; UK/H/6076/001/DC) and Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension (PL 36532/0002; UK/H/6076/002/DC) and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed. Mock ups for Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension (PL 36532/0003; UK/H/6076/003/DC) have been submitted and approved. The current labelling text/mock ups are provided below:
Combisal 25 microgram/50 microgram:

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| PACK/CARTON |

1. **NAME OF THE MEDICINAL PRODUCT**

Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension
Salmeterol (as xinafoate) / fluticasone propionate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

One metered dose contains 25 micrograms of salmeterol (as xinafoate) and 50 micrograms of fluticasone propionate

3. **LIST OF EXCIPIENTS**

Also contains: norfluorane (HFA 134a)

4. **PHARMACEUTICAL FORM AND CONTENTS**

Pressurised inhalation, suspension
120 metered actuations

5. **METHOD AND ROUTE OF ADMINISTRATION**

Inhalation use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Pressurised container.
Do not pierce, break or burn the canister even when apparently empty.

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C
Do not expose to temperatures higher than 50°C, protect from direct sunlight.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Genetic S.p.A.
Via G. Della Monica, 26
84083 Castel San Giorgio (SA)
Italy

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 36532/0001

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Read the package leaflet carefully before use.
Inhale through your mouth into your lungs as directed by your doctor

Shake well before use
Use regularly as directed by your doctor

16. **INFORMATION IN BRAILLE**

Combisal 25 mcg/50 mcg

17. **UNIQUE IDENTIFIER – 2D BARCODE**

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:
SN:
NN:
MINIMUM PARTICULARS TO APPEAR ON PRIMARY PACKAGING

ALUMINIUM/CANISTER

1. NAME OF THE MEDICINAL PRODUCT

Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension
Salmeterol (as xinafoate)/fluticasone propionate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Genetic S.p.A.

3. MARKETING AUTHORISATION NUMBER(S)

PL 36532/0001

4. EXPIRY DATE

EXP:

5. BATCH NUMBER

Lot:

6. OTHER

POM
120 metered actuations
Shake well before use
Read the package leaflet carefully before use
Inhalation use
Pressurised canister
Do not pierce, break or burn the canister even when apparently empty
Do not store above 25°C
Do not expose to temperatures higher than 50°C, protect from direct sunlight.
Combisal 25 microgram/125 microgram:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK/CARTON

1. NAME OF THE MEDICINAL PRODUCT

Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension
Salmeterol (as xinafoate) / fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One metered dose contains 25 micrograms of salmeterol (as xinafoate) and 125 micrograms of fluticasone propionate

3. LIST OF EXCIPIENTS

Also contains: norfluorane (HFA 134a)

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, suspension
120 metered actuations

5. METHOD AND ROUTE OF ADMINISTRATION

Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Pressurised container.
Do not pierce, break or burn the canister even when apparently empty.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Do not expose to temperatures higher than 50°C, protect from direct sunlight.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genetic S.p.A.
Via G. Della Monica, 26
84083 Castel San Giorgio (SA)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

PL 36532/0002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Read the package leaflet carefully before use.
Inhale through your mouth into your lungs as directed by your doctor

Shake well before use
Use regularly as directed by your doctor

16. INFORMATION IN BRAILLE

Combisol 25 mcg /125 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON PRIMARY PACKAGING</th>
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<tbody>
<tr>
<td>ALUMINIUM / CANISTER</td>
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<table>
<thead>
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension</td>
</tr>
<tr>
<td>Salmeterol (as xinafoate)/fluticasone propionate</td>
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<table>
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<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tbody>
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<td>Genetic S.p.A.</td>
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<table>
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<tr>
<th>3. MARKETING AUTHORISATION NUMBER(S)</th>
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<tbody>
<tr>
<td>PL 36532/0002</td>
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</table>

<table>
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<th>4. EXPIRY DATE</th>
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<td>EXP:</td>
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<tr>
<th>5. BATCH NUMBER</th>
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<tr>
<td>Lot:</td>
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<table>
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<tr>
<th>6. OTHER</th>
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<tbody>
<tr>
<td>POM</td>
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<tr>
<td>120 metered actuations</td>
</tr>
<tr>
<td>Shake well before use</td>
</tr>
<tr>
<td>Read the package leaflet carefully before use</td>
</tr>
<tr>
<td>Inhalation use</td>
</tr>
<tr>
<td>Pressurised canister</td>
</tr>
<tr>
<td>Do not pierce, break or burn the canister even when apparently empty</td>
</tr>
<tr>
<td>Do not store above 25°C</td>
</tr>
<tr>
<td>Do not expose to temperatures higher than 50°C, protect from direct sunlight.</td>
</tr>
</tbody>
</table>
Combisal 25 microgram/250 microgram:

Warnings
Keep out of the sight and reach of children.
Pressurised container.
Do not pierce, break or burn the canister even when apparently empty.
Do not store above 25°C.
Do not expose to temperatures higher than 50°C, protect from direct sunlight.

Composition
One metered dose contains 25 micrograms of salmeterol (as xinafoate) and 250 micrograms of fluticasone propionate.

Excipients:
Also contains: norfloxan (NFA 1344a)

Instructions on use
Read the package leaflet carefully before use.
Inhale through your mouth into your lungs as directed by your doctor.
Shake well before use.
Use regularly as directed by your doctor.
Annex 1

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To change the (invented) name of the medicinal product in the RMS (UK) only, from ‘Combiflu’ to Combisal. Additionally, to correct typo errors in both common and UK product information. Consequently, sections 1, 3, 4.1, 4.2, 4.3, 4.4, 4.6, 4.7, 4.8, 4.9, 5.1, 6.4, 6.5 and 7 of the SmPC, the labelling and Leaflet have been updated.</td>
<td>UK/H/6076/001/IB/001</td>
<td>SmPC Leaflet Labelling</td>
<td>01/02/2018</td>
<td>02/03/2018</td>
<td>Approval</td>
<td>Yes</td>
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Annex 1.1

Our Reference:
- PL 36532/0001, Application 3
- PL 36532/0002, Application 3
- PL 36532/0003, Application 3

Product:
- Combisal 25 microgram/50 microgram per metered dose pressurised inhalation, suspension
- Combisal 25 microgram/125 microgram per metered dose pressurised inhalation, suspension
- Combisal 25 microgram/250 microgram per metered dose pressurised inhalation, suspension

Marketing Authorisation Holder:
Genetic SpA

Active Ingredient(s):
Salmeterol xinafoate, Fluticasone propionate.

Type of Procedure:
Mutual Recognition

Submission Type:
Variation

Submission Category:
Type IB

Submission Complexity:
Standard

EU Procedure Number (if applicable):
UK/H/6076/001-003/IB/001

Reason:
To change the (invented) name of the medicinal product in the RMS (UK) only, from ‘Combiflu’ to ‘Combisal’. Additionally, to correct typo errors in both common and UK product information. Consequently, sections 1, 3, 4.1, 4.2, 4.3, 4.4, 4.6, 4.7, 4.8, 4.9, 5.1, 6.4, 6.5 and 7 of the SmPC, the labelling and leaflet have been updated. The change to the product name has been requested by the MHRA.

Supporting Evidence
- Revised SmPC fragments- sections 1, 3, 4.1, 4.2, 4.3, 4.4, 4.6, 4.7, 4.8, 4.9, 5.1, 6.4, 6.5 and 7
- Revised Patient Information leaflet
- Revise labelling

Evaluation
The proposed changes to the SmPC leaflet and labelling are acceptable.

In accordance with Directive 2010/84/EU, the SmPC and PIL for products granted Marketing Authorisations at a national level are available on the MHRA website. The currently approved labelling is provided on pages 21 to 27 of this report.

Conclusion
The variation is approvable.

Decision - Approved on 02 March 2018