SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Seffalair Spiromax 12.75 micrograms/100 micrograms inhalation powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose from the mouthpiece) contains 12.75 micrograms of salmeterol (as salmeterol xinafoate) and 100 micrograms of fluticasone propionate.

Each metered dose contains 14 micrograms of salmeterol (as salmeterol xinafoate) and 113 micrograms of fluticasone propionate.

Excipient(s) with known effect:

Each delivered dose contains approximately 5.4 milligrams of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder

White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Seffalair Spiromax is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.

4.2 Posology and method of administration

Posology

Patients should be advised to take Seffalair Spiromax every day, even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be used for immediate relief.

When choosing the starting dose strength of Seffalair Spiromax (12.75/100 micrograms medium inhaled corticosteroid [ICS] dose or 12.75/202 micrograms high ICS dose), the patients' disease severity, their previous asthma therapy including ICS dose as well as the patients' current control of asthma symptoms should be considered.

Patients should be regularly reassessed by a doctor, so that the strength of the salmeterol/fluticasone propionate they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Note that the delivered doses for Seffalair Spiromax are different from other salmeterol/fluticasone containing products on the market. The different dose strengths (medium/high doses of fluticasone) for different products do not necessarily correspond to each other, thus the products are not interchangeable based on the corresponding dose strengths.

Adults and adolescents 12 years and older.

One inhalation of 12.75 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily.

Once control of asthma is attained, treatment should be reviewed and consideration given as to whether patients should be stepped down to salmeterol/fluticasone propionate containing a lower dose of the inhaled corticosteroid, and then, ultimately, to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

If an individual patient should require dosages outside the recommended regimen, appropriate doses of β_2 agonist and/or inhaled corticosteroid should be prescribed.

Special populations

Elderly (>65 years)

There is no need to adjust the dose in elderly patients

Renal impairment

There is no need to adjust the dose in patients with renal impairment.

Hepatic impairment

There are no data available on the use of Seffalair Spiromax in patients with hepatic impairment.

Paediatric population

The posology in patients 12 years of age and older is the same posology as in adults. The safety and efficacy in paediatric patients below 12 years of age have not been established. No data are available.

Method of administration

Inhalation use.

The device is a breath actuated, inspiratory flow-driven inhaler, which means that the active substances are delivered into the airways when the patient inhales through the mouthpiece.

Required training

This medicinal product should be used correctly in order to achieve effective treatment. As such, the patients should be advised to read the patient information leaflet carefully and follow the instructions for use as detailed in the leaflet. All patients should be provided with training by the prescribing Health Care Professional on how to use this medicinal product. This is to ensure that they understand how to use the inhaler correctly, and so that they understand the need to breathe in forcefully when inhaling to obtain the required dose. It is important to inhale forcefully to ensure optimal dosing.

The use of this medicinal product follows 3 simple steps: open, breathe, and close, which are outlined below.

Open: Hold the device with the mouthpiece cover at the bottom and open the mouthpiece cover by folding it down until it is fully opened when 1 click is heard.

Breathe: Breathe out fully. Do not breathe out through your inhaler. Put the mouthpiece in your mouth and close your lips tightly around it. Breathe in forcefully and deeply through the mouthpiece. Remove the device from the mouth and hold the breath for 10 seconds or as long as comfortable for you.

Close: Breathe out gently and close the mouthpiece cover.

Patients should not block the air vents at any time, or breathe out through the device when they are preparing the “Breathe” step. Patients are not required to shake the inhaler prior to use.

Patients should also be advised to rinse their mouths with water and spit the water out, and/or brush their teeth after inhaling (see section 4.4).

Patients may notice a taste when using this medicinal product due to the lactose excipient.

Patients should be advised to keep their inhaler dry and clean at all times by gently wiping the mouthpiece with a dry cloth or tissue as needed.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

Salmeterol/fluticasone propionate should not be used to treat acute asthma symptoms for which a fast- and short-acting bronchodilator is required. Patients should be advised to have their rescue inhaler available to be used for relief in an acute asthma attack at all times.

Patients should not be initiated on salmeterol/fluticasone propionate during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with salmeterol/fluticasone propionate. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on salmeterol/fluticasone propionate.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of asthma control and patients should be reviewed by a physician.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing inhaled corticosteroid therapy.

Cessation of therapy

Treatment with salmeterol/fluticasone propionate should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under physician supervision.

Coexisting conditions

Salmeterol/fluticasone propionate should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral, or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.

Cardiovascular effects

Rarely, salmeterol/fluticasone propionate may cause cardiac arrhythmias e.g., supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Salmeterol/fluticasone propionate should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with thyrotoxicosis,.

Hypokalaemia and hyperglycaemia

Beta-adrenergic agonist medicines may produce significant hypokalaemia in some patients, possibly through intracellular shunting, which has the potential to product adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes serum potassium were seen infrequently during clinical trials with salmeterol/fluticasone propionate at recommended doses (see section 4.8). There have been infrequent reports of increases in blood glucose levels (see section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Salmeterol/fluticasone propionate should be used with caution in patients with diabetes mellitus, uncorrected hypokalaemia, or patients predisposed to low levels of serum potassium.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing and may be life-threatening (see section 4.8). This should be treated immediately with a short-acting inhaled bronchodilator. Salmeterol/fluticasone propionate should be discontinued immediately, the patient assessed, and alternative therapy instituted if necessary.

Beta 2 adrenoreceptor agonists

The pharmacological effects of β_2 agonist treatment, such as tremor, palpitations, and headache, have been reported, but tend to be transient and reduce with regular therapy.

Systemic effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression, or aggression (particularly in children) (see Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Adrenal function

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 micrograms and less than 1000 micrograms. Situations, which could potentially trigger acute adrenal crisis include trauma, surgery, infection, or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore, these patients should be treated with special care and adrenocortical function regularly monitored. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Interactions with other medicinal products

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. There is also an increased risk of systemic undesirable effects when combining fluticasone propionate with other potent CYP3A inhibitors (see section 4.5).

Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g., prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic undesirable effects of salmeterol treatment (see section 4.5).

Paediatric population

This medicinal product is indicated for use in adolescents 12 years and older (see section 4.2). However, it should be noted that children and adolescents less than 16 years taking high doses of fluticasone propionate (typically ≥1000 micrograms/day)

may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression, or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. The dose of inhaled corticosteroid should always be reduced to the lowest dose at which effective control of asthma is maintained.

Oral infections

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely of the oesophagus, can occur in some patients (see section 4.8). Both hoarseness and the incidence of candidiasis of the mouth and throat may be relieved by rinsing the mouth with water and spitting the water out and/or brushing the teeth after using the product. Symptomatic candidiasis of the mouth and throat can be treated with topical anti-fungal therapy whilst still continuing with salmeterol/fluticasone propionate.

Lactose contents

This medicinal product contains lactose (see section 4.3). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. The excipient lactose may contain small amounts of milk proteins which may cause allergic reactions in those with severe hypersensitivity or allergy to milk protein.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with beta blockers

Beta adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use. Potentially serious hypokalaemia may result from β_2 agonist therapy (see section 4.4). Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, and diuretics.

Salmeterol

Potent CYP3A4 inhibitors

Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose, and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g., itraconazole, telithromycin, ritonavir).

Moderate CYP3A4 inhibitors

Co-administration of erythromycin (500 mg orally 3 times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold C_{max} and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

Fluticasone propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) administered 100 mg twice daily increased the fluticasone propionate plasma concentrations several hundred-fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid undesirable effects (see section 4.4).

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic undesirable effects. Caution is recommended and long-term treatment with such drugs should, if possible, be avoided.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

Interaction with P-glycoprotein inhibitors

Fluticasone propionate and salmeterol are both poor substrates of P-glycoprotein (P-gp). Fluticasone did not show P-gp inhibition potential in in vitro studies. No information is available on salmeterol P-gp inhibition potential. No clinical pharmacology studies with a specific P-gp inhibitor and fluticasone propionate/salmeterol have been conducted.

Sympathomimetic medicinal products

Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) can have a potentially additive effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300 to 1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of β_2 adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

This medicianl product should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

Studies have shown that salmeterol and fluticasone propionate and their metabolites, are excreted into the milk of lactating rats.

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue salmeterol/fluticasone propionate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

As this medicinal product contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the active substance may be expected. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds.

The most frequently reported adverse reactions were nasopharyngitis (6.3%), headache (4.4%), cough (3.7%) and oral candidiasis (3.4%).

Tabulated list of adverse reactions

Adverse reactions which have been associated with fluticasone propionate and salmeterol are presented below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Frequencies were derived from clinical trial data.

Table 1: Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Oral candidiasis[a]	Common[1]
	Influenza	Common
	Nasopharyngitis	Common
	Rhinitis	Common
	Sinusitis	Common
	Pharyngitis	Uncommon
	Respiratory tract infection	Uncommon
	Oesophageal candidiasis	Rare
Endocrine disorders	Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents	Rare[1]
Metabolism and nutrition disorders	Hypokalaemia	Common[2]
	Hyperglycaemia	Uncommon
Psychiatric disorders	Anxiety	Uncommon
	Insomnia	Uncommon
	Behavioural changes, including hyperactivity and irritability, especially in children	Uncommon
Nervous system disorders	Headache	Common
	Dizziness	Common
	Tremor	Uncommon
Eye disorders	Cataract	Uncommon
	Glaucoma	Rare[1]
	Vision blurred	Not known[1]
Cardiac disorders	Palpitations	Uncommon[1]
	Tachycardia	Uncommon

System Organ Class	Adverse reaction	Frequency
	Atrial fibrillation	Uncommon
	Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles)	Rare
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Throat irritation	Common
	Hoarseness/dysphonia	Common
	Oropharyngeal pain	Common
	Rhinitis allergic	Uncommon
	Nasal congestion	Uncommon
	Paradoxical bronchospasm	Rare[1]
Gastrointestinal disorders	Abdominal pain upper	Uncommon
	Dyspepsia	Uncommon
Skin and subcutaneous tissue disorders	Dermatitis contact	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common
	Myalgia	Common
	Pain in extremity	Uncommon
Injury, poisoning and procedural complications	Laceration	Uncommon

a. Includes oral candidiasis, oral fungal infection, oropharyngeal candidiasis, and oropharyngitis fungal

1. See section 4.4
2. See section 4.5

Description of selected adverse reactions

Specific β_2 agonist treatment effects

The pharmacological effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing (see section 4.4).

Inhaled corticosteroid treatment effects

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely, of the oesophagus, can occur in some patients (see section 4.4).

Paediatric population

The safety and efficacy of Seffalair Spiromax in paediatric patients below the age of 12 years have not been established.

Inhaled corticosteroids, including fluticasone propionate, a component of Seffalair Spiromax, may cause a reduction in growth velocity in adolescents (see section **4.4 Special warnings and precautions for use).** The growth of paediatric patients receiving orally inhaled corticosteroids, including salmeterol/fluticasone propionate, should be monitored routinely. To minimize the systemic effects of orally inhaled corticosteroids, including salmeterol/fluticasone propionate titrate each patient's dosage to the lowest dosage that effectively controls his/her symptoms.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are no data available from clinical trials on overdose with Seffalair Spiromax, however data on overdose with both active substances are given below:

Salmeterol

The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia. If salmeterol/fluticasone propionate therapy has to be withdrawn due to overdose of the β_2 agonist component of the medicinal product, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Fluticasone propionate

Acute

Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

Chronic overdose

Adrenal reserve should be monitored and treatment with a systemic corticosteroid may be necessary. When stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose. (see section 4.4: "Adrenal function").

In cases of both acute and chronic fluticasone propionate overdose, salmeterol/fluticasone propionate therapy should be continued at a suitable dose for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics, ATC code: R03AK06

Mechanism of action and pharmacodynamic effects

Seffalair Spiromax contains salmeterol and fluticasone propionate, which have differing modes of action.

The respective mechanisms of action of both active substances are discussed below.

Salmeterol is a selective long-acting (12 hour) β_2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs.

Clinical efficacy and safety

Seffalair Spiromax Asthma clinical trials

The safety and efficacy of Seffalair Spiromax were evaluated in 3004 patients with asthma. The development program included 2 confirmatory trials of 12-weeks duration, a 26-week safety trial and 3 dose-ranging trials. The efficacy of Seffalair Spiromax is based primarily on the the confirmatory trials described below.

Six doses of fluticasone propionate ranging from 16 mcg to 434 mcg (expressed as metered doses) administered twice daily via multidose dry powder inhaler (MDPI) and an open-label fluticasone propionate dry powder comparator (100mcg or 250mcg) were evaluated in 2 randomised, double-blind, placebo-controlled 12-week trials. Trial 201 was conducted in patients who were uncontrolled at baseline and had been treated by short-acting β_2 agonist alone or in combination with non-corticosteroid asthma medication. Low dose inhaled corticosteroid (ICS) patients may have been included after a minimum of 2 weeks washout. Trial 202 was conducted in patients who were uncontrolled at baseline and had been treated with high dose ICS with or without a long-acting beta-agonist (LABA). The metered doses for fluticasone propionate Spiromax [Fp MDPI] (16, 28, 59, 118, 225, and 434 mcg) used in Trial 201 and Trial 202 are different from the metered doses for the comparator products (fluticasone inhalation powder) and the Phase 3 investigational products which are the basis of the label claim metered dose (, 113, and 232 mcg for fluticasone propionate). The changes in doses between Phase 2 and 3 resulted from optimisation of the manufacturing process.

The efficacy and safety of 4 doses of salmeterol xinafoate were evaluated in a double-blind, 6-period crossover study compared with single dose fluticasone propionate Spiromax and open-label fluticasone propionate/salmeterol 100/50 mcg dry powder

inhaler as a comparator in patients with persistent asthma. The salmeterol doses studied were 6.8 mcg, 13.2 mcg, 26.8 mcg, and 57.4 mcg in combination with fluticasone propionate 118 mcg delivered by MDPI (expressed as metered dose). The metered doses for salmeterol (6.8, 13.2, 26.8, and 57.4 mcg) used in this study are slightly different from the metered doses for the comparator products (fluticasone/salmeterol inhalation powder) and the Phase 3 investigational products which are the basis of the label claim metered dose (113, and 232 mcg for fluticasone propionate and 14 mcg for salmeterol).

As a consequence of optimisation of the manufacturing process, the Phase 3 and commercial products better match the strengths of the comparator products. Plasma for pharmacokinetic characterization was obtained at each dosing period.

Adult and Adolescent Patients Aged 12 Years and Older:

Two Phase 3 clinical trials were conducted; 2 trials comparing the fixed-dose combination with fluticasone propionate alone or placebo (Trial 1 and Trial 2).

Trials comparing Seffalair Spiromax (FS MDPI) with fluticasone propionate alone or placebo

Two double-blind, parallel-group clinical trials, Trial 1 and Trial 2, were conducted with FS MDPI in 1375 adult and adolescent patients (aged 12 years and older, with baseline FEV_1 40% to 85% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were given as 1 inhalation twice a day from the Spiromax inhaler, and other maintenance therapies were discontinued.

Trial 1: This randomised, double-blind, placebo-controlled, 12-week, efficacy and safety trial compared Fp MDPI 55 mcg and 113 mcg (1 inhalation twice a day) with FS MDPI (14/55 mcg and 14/113 mcg (1 inhalation twice a day) and placebo in adolescents (aged 12 years and older) and adult patients with persistent symptomatic asthma despite low-dose or mid-dose inhaled corticosteroid or inhaled corticosteroid/LABA therapy. Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to beclomethasone dipropionate inhalation aerosol 40 mcg twice daily during the run-in period. Patients were randomly assigned to receive placebo or mid-strength dose treatments as follows: 130 received placebo, 130 received Fp MDPI 113 mcgand 129 received FS MDPI 14/113 mcg. Baseline FEV_1 measurements were similar across treatments groups. The primary endpoints for this trial were the change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 analyzed for a subset of 312 patients who performed post-dose serial spirometry.

Table 2: Primary analysis of change from baseline in trough FEV_1 at week 12 by treatment group Trial 1 (FAS)

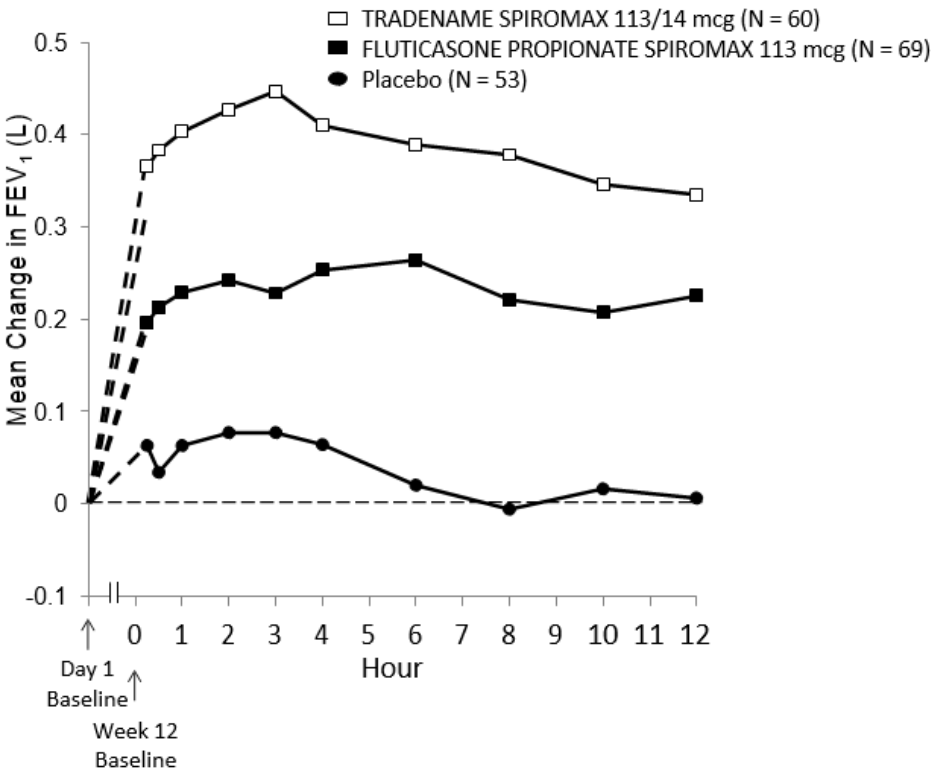
Variable Statistic		Fp MDPI	FS MDPI
	Placebo (N=129)	**113 mcg BID (N=129)**	**14/113 mcg BID (N=126)**
Change in trough FEV_1 (L) at week 12			
LS mean	0.053	0.204	0.315
Comparison to placebo			
Difference of LS mean		0.151	0.262
95% CI		(0.057, 0.244)	(0.168, 0.356)
p-value		0.0017	0.0000
Comparison to Fp MDPI			
			Compared with 113 mcg:
Difference of LS mean			0.111
95% CI			(0.017, 0.206)
p-value			0.0202

Comparisons of combination therapy with monotherapy were not controlled for multiplicity.

FEV1 = forced expiratory volume in 1 second; FAS = full analysis set; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; BID = twice daily; n = number; LS = least squares; CI = confidence interval

Improvements in lung function occurred within 15 minutes of the first dose (15 minutes post-dose, the difference in LS mean change from baseline in FEV_1 was 0.164 L for FS MDPI 14/113 mcg compared with placebo(unadjusted p-value <0.0001). Maximum improvement in FEV_1 generally occurred within 6 hours for FS MDPI 14/113 mcg, and improvements were sustained over the 12 hours of testing at weeks 1 and 12 (Figure 1). No diminution in the 12-hour bronchodilator effect was observed following 12 weeks of therapy.

Figure 1: Primary analysis serial spirometry: Mean change from baseline in FEV1 (L) at week 12 by time point and treatment group Trial 1 (FAS; Serial spirometry subset)



- FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

Trial 2: This randomised, double-blind, placebo-controlled, 12-week, efficacy and safety trial compared Fluticasone Propionate Multidose Dry Powder Inhaler (Fp MDPI) 113 mcg and 232 mcg (1 inhalation twice a day) with Salmeterol/Fluticasone Multidose Dry Powder Inhaler (FS MDPI) 14/113 mcg and 14/232 mcg (1 inhalation twice a day) and placebo in adolescents and adult patients with persistent symptomatic asthma despite inhaled corticosteroid or inhaled corticosteroid/LABA therapy. Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to Fp MDPI 55 mcg twice daily during the run-in period. Patients were randomly assigned to receive treatment as follows: 145 patients received placebo, 146 patients received Fp MDPI 113 mcg, 146 patients received Fp MDPI 232 mcg, 145 patients received FS MDPI 14/113 mcg, and 146 patients received FS MDPI 14/232mcg. Baseline FEV_1 measurements were similar across treatments: Fp MDPI 113 mcg 2.069 L, Fp MDPI 232 mcg 2.075 L, FS MDPI 14/113 mcg 2.157 L, FS MDPI 14/232 mcg 2.083 L, and placebo 2.141 L. The primary endpoints for this trial were the change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 analyzed for a subset of 312 patients who performed post-dose serial spirometry.

Table 3: Primary analysis of change from baseline in trough FEV_1 at Week 12 by treatment group Trial 2 (FAS)

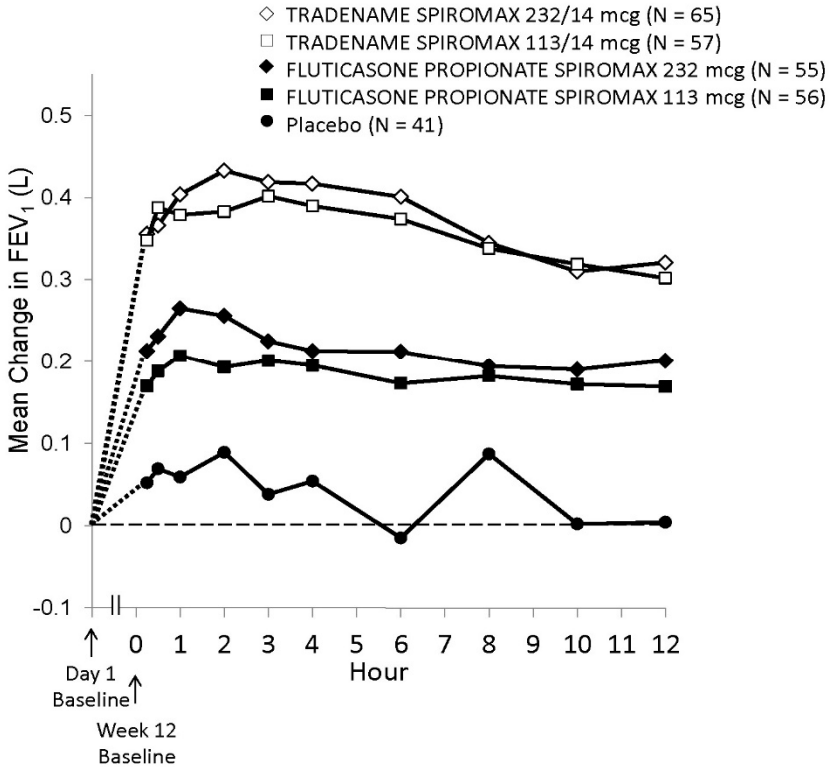
Variable Statistic		Fp MDPI		FS MDPI	
	Placebo (N=143)	**113 mcg BID (N=145)**	**232 mcg BID (N=146)**	**14/113 mcg BID (N=141)**	**14/232 mcg BID (N=145)**
Change in trough FEV_1 (L) at week 12					
LS mean	-0.004	0.119	0.179	0.271	0.272
Comparison to placebo					
Difference of LS mean		0.123	0.183	0.274	0.276
95% CI		(0.038, 0.208)	(0.098, 0.268)	(0.189, 0.360)	(0.191, 0.361)
p-value		0.0047	0.0000	0.0000	0.0000
Comparison to Fp MDPI					
				Compared to 113 mcg:	Compared to 232 mcg:
Difference of LS mean				0.152	0.093
95% CI				(0.066, 0.237)	(0.009, 0.178)
p-value				0.0005	0.0309

Comparisons of combination therapy with monotherapy were not controlled for multiplicity.

FEV_1 = forced expiratory volume in 1 second; FAS = full analysis set; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; BID = twice daily; n = number; LS=least squares; CI = confidence interval

Improvements in lung function occurred within 15 minutes of the first dose (15 minutes post-dose, the difference in LS mean change from baseline in FEV_1 was 0.160 L and 0.187 L compared with placebo for FS MDPI 14/113 mcg and 14/232 mcg, respectively; unadjusted p-value <0.0001 for both doses compared with placebo. Maximum improvement in FEV_1 generally occurred within 3 hours for both FS MDPI dose groups, and improvements were sustained over the 12 hours of testing at weeks 1 and 12 (Figure 2). No diminution in the 12 hour bronchodilator effect was observed with either FS MDPI dose as assessed by FEV_1 following 12 weeks of therapy.

Figure 2: Primary analysis serial spirometry: Mean change from baseline in FEV1 (L) at week 12 by time point and treatment group trial 2 (FAS; Serial spirometry subset)



FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second

Paediatric population

Patients aged 12 through 17 years have been studied. The pooled results from both confirmatory trials for change from baseline in FEV_1 in patient aged 12-17 years are presented below (Table 4). At week 12, changes from baseline in trough FEV_1 were larger for all Fp MDPI and FS MDPI dose groups than for the placebo group across all age groups in both studies similar to the overall results of the trials.

Table 4: Summary of actual values and change from baseline in trough FEV_1 at week 12 by treatment group and age 12-17 Years (FAS)[a]

Time point Statistic	Placebo	Fluticasone Propionate Spiromax		Seffalair Spiromax	
		113 mcg bid	232 mcg bid	14/113 mcg bid	14/232 mcg bid
Baseline					
n	22	27	10	24	12
Mean (SD)	2.330 (0.3671)	2.249 (0.5399)	2.224 (0.4362)	2.341 (0.5513)	2.598 (0.5210)
Median	2.348	2.255	2.208	2.255	2.425

Min, Max	1.555, 3.075	0.915, 3.450	1.615, 3.115	1.580, 3.775	1.810, 3.695
Week 12 Change					
n	22	27	10	24	12
Mean (SD)	0.09 (0.3541)	0.378 (0.4516)	0.558 (0.5728)	0.565 (0.4894)	0.474 (0.5625)
Median	0.005	0.178	0.375	0.553	0.375
Min, Max	-0.850, 0.840	-0.115, 1.650	-0.080, 1.915	-0.265, 1.755	-0.295, 1.335

[a] Full Analysis Set = FAS

The European Medicines Agency has waived the obligation to submit the results of studies with Seffalair Spiromax in all subsets of the paediatric population for the treatment of asthma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

For pharmacokinetic purposes each component can be considered separately.

Salmeterol

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition, there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/mL or less) achieved after inhaled dosing.

Fluticasone propionate

The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5% to 11% of the nominal dose depending on the inhalation device used. In patients with asthma a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Absorption

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose of fluticasone propionate may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and presystemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

Distribution

The disposition of fluticasone propionate is characterised by high plasma clearance (1150 mL/min), a large volume of distribution at steady-state (approximately 300 L), and a terminal half-life of approximately 8 hours. Plasma protein binding is 91%.

Biotransformation

Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 3A4. Other unidentified metabolites are also found in the faeces.

Elimination

The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged drug.

Paediatric population

A pharmacokinetic analysis of patients aged 12 through 17 was performed. Although the subgroups were small, systemic exposure of fluticasone propionate and salmeterol for the 12 to 17 years and ≥18 years subgroups in all treatments was not markedly different to the overall study population. The apparent elimination half-life (t½) was not impacted by age.

5.3 Preclinical safety data

The only safety concerns for human use derived from animal studies of salmeterol and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

In animal reproduction studies, glucocorticosteroids have been shown to induce decreased foetal body weight and/or malformations (cleft palate, skeletal malformations) in rats, mice, and rabbits with subcutaneously administered maternal toxic doses. However, these animal experimental results do not seem to be relevant for man given recommended doses and fluticasone propionate administered via inhalation to rats decreased foetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the maximum recommended human daily inhaled dose on a body surface area (mg/m^2) basis. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Animal studies with salmeterol have shown embryo foetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced abnormalities.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which may include milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

After opening the foil wrap: 2 months.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the mouthpiece cover closed after use.

6.5 Nature and contents of container

The inhaler is white with a semi-transparent yellow mouthpiece cover. The parts of the inhaler coming into contact with the inhalation powder or the patient mucosa are made of acrylonitrile butadiene styrene (ABS), polyethylene (PE), and polypropylene (PP). Each inhaler contains 60 doses and is foil-wrapped with desiccant.

Packs of 1 inhaler.

Multipacks containing 3 (3 packs of 1) inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,

Ridings Point,

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Castleford,

WF10 5HX,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

17/08/2021