SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Saltrol Inhaler 25mcg + 125mcg

Strength: 25mcg + 125mcg
Pharmaceutical/Dosage Form: Inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers Salmeterol (as xinafoate) equivalent to 25mcg of Salmeterol, Ph. Eur. and 125mcg of Fluticasone propionate, Ph. Eur.
Also contains:
CFC-Free propellant, HFA 134a

3. PHARMACEUTICAL FORM

Appearance: Aluminum canister with metering valve containing pressurized liquid fitted over a light purple color actuator along with a dark purple color cap.
Functional Test: Dose delivered when activated
Content Appearance: Upon spraying on black sheet, white smear will appear.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Asthma (Reversible Obstructive Airways Disease):
Salmeterol + Fluticasone Propionate is indicated in the regular treatment of asthma (Reversible Obstructive Airways Disease). This may include:

- Use of combination product Long acting Beta 2 agonist and inhaled corticosteroid is appropiate.
- Patients not adequately controlled with inhaled corticosteroid and as needed inhaled short Beta 2 agonist.
- Patients already adequately controlled on both inhaled corticosteroid and long acting Beta 2 agonist

4.2 Posology and Method of Administration

Salmeterol + Fluticasone Propionate inhaler is for inhalation only.

Patients should be made aware that Inhaler must be used daily for optimum benefit, even when asymptomatic. Patients should be regularly reassessed by a doctor, so that the strength of Inhaler 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. Where the control of symptoms is maintained with the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone.

As an alternative, patients requiring a long- acting β2 agonist could be titrated to Inhaler given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms the dose should be given at night and when the patient has a history of mainly daytime symptoms the dose should be given in the morning.

Asthma (Reversible Obstructive Airways Disease):

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with twice daily Salmeterol + Fluticasone Propionate , titration to the lowest effective dose could include Salmeterol + Fluticasone Propionate given once daily. Patients should be given the strength of Salmeterol + Fluticasone Propionate containing the appropriate Fluticasone propionate dosage for the severity of their disease.

If a patient is inadequately controlled on inhaled corticosteroid therapy alone, substitution with Salmeterol + Fluticasone Propionate at a therapeutically equivalent corticosteroid dose may result in an improvement in asthma control. For patients whose asthma control is acceptable on inhaled corticosteroid therapy alone, substitution with Salmeterol + Fluticasone Propionate may permit a reduction in corticosteroid dose while maintaining asthma control.

Recommended Doses:

Adults and adolescents 12 years and older:

- Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily. or
- Two inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily. or
- Two inhalations of 25 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.

A short-term trial of Salmeterol + Fluticasone Propionate inhaler may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is two inhalations of 25 micrograms salmeterol and 50 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 an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

Paediatric population

Children 4 years and older:

- Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily.

The maximum licensed dose of fluticasone propionate delivered by Salmeterol + Fluticasone Propionate inhaler in children is 100 microgram twice daily.

The safety and efficacy of Salmeterol + Fluticasone Propionate inhaler in children aged under 4 years has not been established Children <12 years old may have difficulties synchronising aerosol actuation with inspiration of breath. Use of a spacer device with Salmeterol + Fluticasone Propionate inhaler is recommended in patients who have, or are likely to have difficulties to coordinate actuation with inspiration. A recent clinical study has shown that paediatric patients using a spacer achieved exposure similar to adults not using spacer and paediatric patients using Diskus, confirming that spacers compensate for poor inhaler technique.

The Volumatic device can be used (depending on National Guidance). Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. Patients should continue to use the same make of spacer device as switching between spacer devices can result in changes in the dose delivered to the lungs.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available for use of Salmeterol + Fluticasone Propionate inhaler in patients with hepatic impairment

Instructions for Use:

Patients should be instructed in the proper use of their inhaler

During inhalation, the patient should preferably sit or stand. The inhaler has been designed for use in a vertical position.

Testing the inhaler:

Before using for the first time patients should remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, hold the inhaler between the fingers and thumb with their thumb on the base, below the mouthpiece and release puffs into the air until the counter reads 120 to make sure that it works. The inhaler should be shaken immediately before releasing each puff. If the inhaler has not been used for a week or more the mouthpiece cover should be removed, the patient should shake the inhaler well and should release two puffs into the air. Each time the inhaler is activated the number on the counter will count down by one.

Use of the inhaler:

1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects
3. Patients should shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.
5. Patients should breathe out as far as is comfortable and then place the mouthpiece in their mouth between their teeth and close their lips around it. Patients should be instructed not to bite the mouth piece.
6. Just after starting to breathe in through their mouth, patients should press firmly down on the top of the inhaler to release Salmeterol + Fluticasone Propionate inhaler, while still breathing in steadily and deeply.
7. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. Patients should continue holding their breath for as long as is comfortable.
8. To take a second inhalation, patients should keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Patients should immediately replace the mouthpiece cover in the correct orientation by firmly pushing and snapping the cap into position. This does not require excessive force, the cover should click into position.

IMPORTANT

Patients should not rush stages 5, 6 and 7. It is important that patients start to breathe in as slowly as possible just before operating their inhaler. Patients should practise in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 3.

Patients should rinse their mouth out with water and spit out, and/or brush their teeth after each dose of medicine, in order to minimise the risk of oropharyngeal candidiasis and hoarseness.

Patients should consider getting a replacement when the counter shows the number 020. The counter will stop at 000 when all the recommended puffs have been used. Replace the inhaler when the counter reads 000.

Patients should never try to alter the numbers on the counter or detach the counter from the metal canister. The counter cannot be reset and is permanently attached to the canister.

Cleaning (also detailed in patient information leaflet):

Cleaning

1. Your inhaler should be cleaned at least once a week.
2. Remove the mouth piece cover.
3. Do not remove the canister from the plastic casing.
4. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
5. Replace the mouthpiece cover in the correct orientation. This does not require excessive force, the cover should click into position.

4.3 Contraindications

Salmeterol + Fluticasone propionate is contraindicated:
- In patients with known hypersensitivity to Salmeterol or Fluticasone propionate or to any excipient of the product.

4.4 Special warnings and special precautions for use

Salmeterol + Fluticasone Propionate inhaler Evohaler 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 inhaler to be used for relief in an acute asthma attack available at all times. Patients should not be initiated on Salmeterol + Fluticasone Propionate inhaler 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 inhaler. 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 inhaler.

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 corticosteroid therapy.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Salmeterol + Fluticasone Propionate inhaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Salmeterol + Fluticasone Propionate inhaler should be used.

Treatment with Salmeterol + Fluticasone Propionate should not be stopped abruptly due to risk of exacerbation. Therapy should be down-titrated under physician supervision.

As with all inhaled medication containing corticosteroids, Salmeterol + Fluticasone Propionate inhaler 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.

Rarely, Salmeterol + Fluticasone Propionate inhaler 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 diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

There have been very rare 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.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Salmeterol + Fluticasone Propionate inhaler Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The pharmacological side 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 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.

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 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 cover should be considered during periods of stress or elective surgery.

Systemic absorption of salmeterol and fluticasone propionate is largely through the lungs. As the use of a spacer device with a metered dose inhaler may increase drug delivery to the lungs it should be noted that this could potentially lead to an increase in the risk of systemic adverse effects.

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.

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 side effects when combining fluticasone propionate with other potent CYP3A inhibitors.

There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in a 3-year study in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving salmeterol and fluticasone propionate as a fixed-dose combination administered via the Diskus/Accuhaler compared with placebo (see section 4.8). In a 3-year COPD study, older patients, patients with a lower body mass index (<25kg/m^2) and patients with very severe disease (FEV_1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Physicians should remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD as the clinical features of such infections and exacerbation frequently overlap. If a patient with severe COPD has experienced pneumonia the treatment with Salmeterol + Fluticasone Propionate inhaler should be re- evaluated. The safety and efficacy of Salmeterol + Fluticasone Propionate inhaler Evohaler has not been established in patients with COPD and therefore Salmeterol + Fluticasone Propionate inhaler. Evohaler is not indicated for use in the treatment of patients with COPD.

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 side effects of salmeterol treatment

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.

Paediatric Population

Children and adolescents <16years 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 corticosteroid is regularly monitored. **The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.**

4.5 Interaction with other medicaments and other forms of interaction

β 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 β2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Concomitant use of other β adrenergic containing drugs can have a potentially additive effect.

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 CYP3A4 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 CYP3A4 inhibitor) 100 mg b.i.d. 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 side effects.
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 cobicistat-containing products, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side effects. Combinations should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

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 Cmax 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 side 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 CYP 3A4 inhibitors

Co-administration of erythromycin (500 mg orally three 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 Cmax and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity related to Salmeterol + Fluticasone Propionate. Animal studies have shown reproductive toxicity after administration of β2 adrenoreceptor agonists and glucocorticosteroids. Administration of Salmeterol + Fluticasone Propionate inhaler to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women

Nursing Mothers
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 breastfeeding or to discontinue Salmeterol + Fluticasone Propionate inhaler therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machine

Salmeterol + Fluticasone propionate inhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Very common:
Headache and nasopharyngitis.

Common:
Candidiasis of the mouth and throat, pneumonia, bronchitis, Oesophageal candidiasis hypokalemia, throat irritation, hoarseness/dysphonia, sinusitis, contusions, muscle cramps, traumatic fractures, arthralgia and myalgia.

Uncommon:
Cutaneous hypersensitivity reactions, respiratory symptoms (dyspnoea), hyperglycemia, anxiety, sleep disorders, tremor, cataract, palpitations, tachycardia, atrial fibrillation and angina pectoris.

Rare:
Oesophageal candidiasis, angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (bronchospasm), anaphylactic reactions including anaphylactic shock, cushing's syndrome, cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children), glaucoma, cardiac arrhythmias (including supraventricular tachycardia and extrasystoles) and paradoxical bronchospasm.

Description of selected adverse reactions

The pharmacological side effects of β2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy. As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Salmeterol/Fluticasone Sandoz should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary. 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. Both hoarseness and incidence of candidiasis may be relieved by rinsing the mouth with water and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with Salmeterol/Fluticasone.

Paediatric population

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

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 national reporting system listed in Appendix V.

4.9 Overdosage

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 ß agonist component of the drug, provision of appropriate replacement steroid

therapy should be considered. Additionally, hypokalemia 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 of inhaled Fluticasone propionate: Adrenal reserve should be monitored and treatment with a systemic corticosteroid may be necessary. When stabilized, treatment should be continued with an inhaled corticosteroid at the recommended dose.

In cases of both acute and chronic Fluticasone propionate overdose, therapy should be continued at a suitable dosage 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:

Salmeterol:
Salmeterol is a selective long-acting (12 hour) ß$_2$ adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor. The pharmacologic effects of ß$_2$ adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Fluticasone propionate:
Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

Clinical efficacy and safety

Seretide Asthma clinical trials

A twelve month study (Gaining Optimal Asthma ControL, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of Seretide versus inhaled corticosteroid (Fluticasone Propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until **total control was achieved or the highest dose of study drug was reached. GOAL showed more patients treated with Seretide achieved asthma control than patients treated with ICS alone and this control was attained at a lower corticosteroid dose.

*Well-controlled asthma was achieved more rapidly with Seretide than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual well-controlled week was 16 days for Seretide compared to 37 days for the ICS group. In the subset of steroid naive asthmatics the time to an individual well controlled week was 16 days in the Seretide treatment compared to 23 days following treatment with ICS.

The overall study results showed:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
Pre-Study Treatment	**Salmeterol/FP**		**FP**	
	WC	**TC**	**WC**	**TC**
No ICS (SABA alone)	78%	50%	70%	40%
Low dose ICS (≤ 500mcg BDP or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (>500-1000mcg BDP or equivalent/day)	62%	29%	47%	16%
Pooled results across the 3 treatment levels	71%	41%	59%	28%

*Well controlled asthma; less than or equal to 2 days with symptom score greater than 1 (symptom score 1 defined as 'symptoms for one short period during the day'), SABA use on less than or equal to 2 days and less than or equal to 4 occasions/week, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.

**Total control of asthma; no symptoms, no SABA use, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy The results of this study suggest that Seretide 50/100mcg bd may be considered as initial maintenance therapy in patients with moderate persistent asthma for whom rapid control of asthma is deemed essential (see section 4.2).

A double-blind, randomised, parallel group study in 318 patients with persistent asthma aged 18 years evaluated the safety and tolerability of administering two inhalations twice daily (double dose) of Seretide for two weeks. The study showed that doubling the inhalations of each strength of

Seretide for up to 14 days resulted in a small increase in β-agonist-related adverse events (tremor; 1 patient [1%] vs 0, palpitations; 6 [3%] vs 1 [<1%], muscle cramps; 6[3%] vs 1 [<1%]) and a similar incidence of inhaled corticosteroid related adverse events (e.g. oral candidiasis; 6 [6%] vs 16 [8%], hoarseness; 2 [2%] vs 4 [2%]) compared to one inhalation twice daily. The small increase in β-agonist-related adverse events should be taken into account if doubling the dose of Seretide is considered by the physician in adult patients requiring additional short-term (up to 14 days) inhaled corticosteroid therapy.

Asthma

The Salmeterol Multi-center Asthma Research Trial (SMART)

The Salmeterol Multi-center Asthma Research Trial (SMART) was a 28-week US study that evaluated the safety of salmeterol compared to placebo added to usual therapy in adult and adolescent subjects. Although there were no significant differences in the primary endpoint of the combined number of respiratory-related deaths and respiratory-related life-threatening experiences, the study showed a significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated with salmeterol versus 3 deaths out of 13,179 patients on placebo). The study was not designed to assess the impact of concurrent inhaled corticosteroid use, and only 47% of subjects reported ICS use at baseline.

Safety and efficacy of salmeterol-FP versus FP alone in asthma

Two multi-centre 26-week studies were conducted to compare the safety and efficacy of salmeterol FP versus FP alone, one in adult and adolescent subjects (AUSTRI trial), and the other in paediatric subjects 4-11 years of age (VESTRI trial). For both studies, enrolled subjects had moderate to severe persistent asthma with history of asthma-related hospitalisation or asthma exacerbation in the previous year. The primary objective of each study was to determine whether the addition of LABA to ICS therapy (salmeterol-FP) was non-inferior to ICS (FP) alone in terms of the risk of serious asthma related events (asthma-related hospitalisation, endotracheal intubation, and death). A secondary efficacy objective of these studies was to evaluate whether ICS/LABA (salmeterol-FP) was superior to ICS therapy alone (FP) in terms of severe asthma exacerbation (defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in patient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids).

A total of 11,679 and 6,208 subjects were randomized and received treatment in the AUSTRI and VESTRI trials, respectively. For the primary safety endpoint, non-inferiority was achieved for both trials (see Table below).

Serious Asthma-Related Events in the 26-Week AUSTRI and VESTRI Trials

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5,834)	FP Alone (n = 5,845)	Salmeterol-FP (n = 3,107)	FP Alone (n = 3,101)
Composite endpoint (Asthma-related hospitalisation, endotracheal intubation,-or death)	34 (0.6%)	33 (0.6%)	27 (0.9%)	21 (0.7%)
Salmeterol-FP/FP Hazard ratio (95% CI)	1.029 (0.638-1.662)[a]		1.285 (0.726-2.272)[b]	
Death	0	0	0	0
Asthma-related hospitalisation	34	33	27	21
Endotracheal intubation	0	2	0	0

a If the resulting upper 95% CI estimate for the relative risk was less than 2.0, then non-inferiority was concluded.
b If the resulting upper 95% CI estimate for the relative risk was less than 2.675, then non inferiority was concluded.
For the secondary efficacy endpoint, reduction in time to first asthma exacerbation for salmeterol FP relative to FP was seen in both studies, however only AUSTRI met statistical significance:

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5,834)	FP Alone (n = 5,845)	Salmeterol-FP (n = 3,107)	FP Alone (n = 3,101)
Number of subjects with an asthma exacerbation	480 (8%)	597 (10%)	265 (9%)	309 (10%)
Salmeterol-FP/FP Hazard ratio (95% CI)	0.787 (0.698, 0.888)		0.859 (0.729, 1.012)	

Paediatric population:

In trial SAM101667, in 158 children aged 6 to 16 years with symptomatic asthma, the combination of salmeterol/fluticasone propionate is equally efficacious to doubling the dose of fluticasone propionate regarding symptom control and lung function. This study was not designed to investigate the effect on exacerbations.

In a trial which randomized children aged 4 to 11 years [n=428], salmeterol/fluticasone propionate DISKUS (50/100 microgram, one inhalation twice daily) was compared with salmeterol/fluticasone propionate MDI (25/50 microgram, two inhalations twice daily) over a 12-week treatment period. The adjusted mean change from baseline in mean morning peak expiratory flow over Weeks 1-12 was 37.7L/min in the DISKUS group and 38.6L/min in the MDI group. Improvements were also seen in both treatment groups on rescue and symptom free days and nights.

Fluticasone propionate containing medications in asthma during pregnancy

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of MCMs following first trimester exposure to inhaled FP alone and salmeterol-FP relative to non-FP containing ICS. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to FP or salmeterol-FP of which 42 diagnosed MCMs were identified. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.1 (95%CI: 0.5 – 2.3) for FP exposed vs non-FP ICS exposed women with moderate asthma and 1.2 (95%CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of MCMs was identified following first trimester exposure to FP alone versus salmeterol-FP. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 FP-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 MCM events per 100 pregnancies).

5.2 Pharmacokinetic properties

When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately. For pharmacokinetic purposes therefore 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 5to11% 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. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose. The disposition of fluticasone propionate is characterised by high plasma clearance (1150mL/min), a large volume of distribution at steady-state (approximately 300L) and a terminal half-life of approximately 8 hours. Plasma protein binding is 91%. 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 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces. 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
The effect of 21 days of treatment with Seretide Inhaler 25/50 microgram (2 inhalations twice daily with or without a spacer) or Seretide Diskus 50/100 microgram (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone propionate was similar for Seretide Inhaler with spacer (107pg hr/mL [95% CI: 45.7, 252.2]) and Seretide Diskus (138pg hr/mL [95% CI: 69.3, 273.2]), but lower for Seretide Inhaler (24pg hr/mL [95% CI: 9.6, 60.2]). Systemic exposure to salmeterol was similar for Seretide Inhaler, Seretide Inhaler with spacer, and Seretide Diskus (126 pg hr/mL [95% CI: 70, 225], 103 pg hr/mL [95% CI: 54, 200], and 110 pg hr/mL [95% CI: 55, 219], respectively).

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. In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol have shown embryofoetal 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. Neither salmeterol xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

The non-CFC propellant, norflurane, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
- Ethanol Absolute
- Sorbitan Trioleate
- Propellant HFA 134a

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years

The expiration date refers to the product correctly stored in the required conditions

6.4 Special precautions for storage

- Do not store above 30°C.
- Protect from direct sunlight, heat and frost.
- Shake well before use.

6.5 Nature and contents of container

Saltrol (Salmeterol + Fluticasone Propionate) Inhaler 25mcg + 125mcg is available in a pack of 1's in a unit carton along with the patient information leaflet. Each canister provides 120 actuations.

6.6 Special precautions for disposal and other handling

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

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

8. DRUG PRODUCT MANUFACTURER

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

NAME OF APPLICANT: GETZ PHARMA NIGERIA LIMITED
PLOT 2, IJAODOLA CLOSE, OFF ADEYEMO ALAKIJA STREET,
IKEJA GRA, LAGOS.

9. NAFDAC REGISTRATION NUMBER

B4-9409