# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Peiotal 25 microgram/125 microgram/dose pressurised inhalation, suspension

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex valve) contains:
25 micrograms of salmeterol (as salmeterol xinafoate) and 125 micrograms of fluticasone propionate. This is equivalent to a delivered dose (ex actuator) of 23 micrograms of salmeterol and 115 micrograms of fluticasone propionate.
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension.
The canister contains a white homogeneous suspension.
The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with purple dust caps.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Peiotal is indicated in the regular treatment of asthma where use of a combination product (long-acting $\beta_2$ agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short- acting $\beta_2$ agonist
or
- patients already adequately controlled on both inhaled corticosteroid and long-acting $\beta_2$ agonist

### 4.2 Posology and method of administration

*Posology*

Patients should be made aware that Peiotal must be used daily for optimum benefit, even when asymptomatic.
Patients should be regularly reassessed by a doctor, so that the strength of Peiotal 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 $\beta_2$ agonist could be titrated to Peiotal 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.

Patients should be given the strength of Peiotal containing the appropriate fluticasone propionate dosage for the severity of their disease. Note: Peiotal 25 microgram /50 microgram strength is not appropriate for adults and children with severe asthma. If an individual patient should require dosages outside the recommended regimen, appropriate doses of $\beta_2$ agonist and/or corticosteroid should be prescribed.

Recommended Doses:

*Adults and adolescents 12 years and older:*

Two inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily.

A short-term trial of Salmeterol/Fluticasone propionate 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.

A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. Peiotal is not intended for the initial management of mild asthma. Peiotal 25 micrograms /50 micrograms strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed-combination can be used in patients with severe asthma.

*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 Peiotal inhaler in children is 100 microgram twice daily.

The safety and efficacy of Peiotal in children aged under 4 years has not been established (see Section 5.1).

Children <12 years old may have difficulties synchronising aerosol actuation with inspiration of breath. Use of an AeroChamber Plus® spacer device with Peiotal is recommended in patients who have, or are likely to have, difficulties in coordinating actuation with inspiration. Only the AeroChamber Plus® spacer device should be used with Peiotal. Other spacing devices should not be used with Peiotal and patients should not switch from one spacer device to another.

A clinical study has shown that paediatric patients using a spacer achieved exposure similar to adults not using spacer and paediatric patients using Fluticasone/Salmeterol inhalation powder (Diskus), confirming that spacers compensate for poor inhaler technique (see section 5.2).

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 use the recommended AeroChamber Plus® spacer device as switching to another spacer device can result in changes in the dose delivered to the lungs (see section 4.4).**

Re-titration to the lowest effective dose should always follow the introduction or change of a spacer device.

*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 propionatein patients with hepatic impairment.

Method of administration: Inhalation use

***Instructions for Use***

Patients should be instructed in the proper use of their inhaler (see patient information leaflet).
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, hold the inhaler between the fingers and thumb with their thumb on the base, below the mouthpiece. To make sure that the inhaler works, the patient should shake it well, point the mouthpiece away from them and press the canister firmly to release a puff into the air. These steps should be repeated a second time, shaking the inhaler before releasing a second puff into the air. The total puffs released into the air, before using the inhaler, should be two.

If the inhaler has not been used for a week or more, or the inhaler gets very cold (below 0°C) the mouthpiece cover should be removed, the patient should shake the inhaler well and should release two puffs into the air.

**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 Peiotal, 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 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 practice 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 minimize the risk of oropharyngeal candidiasis and hoarseness.

*Cleaning (also detailed in patient information leaflet)*:

Your inhaler should be cleaned at least once a week.

1. Remove the mouth piece cover.

2. Do not remove the canister from the plastic casing.

3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.

4. Replace the mouthpiece cover in the correct orientation. This does not require excessive force, the cover should click into position.

DO NOT PUT THE METAL CANISTER IN WATER.

**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**

Peiotal 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 Peiotal 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 Peiotal. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Peiotal.

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 Peiotal. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Peiotal should be used (see section 4.2).

Treatment with Peiotal 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 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 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. Peiotal should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The pharmacological side effects of $\beta_2$ 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 (see section 4.2).

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 (see section 4.5).

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 Salmeterol/Fluticasone inhalation powder (Diskus/Accuhaler) compared with placebo (see section 4.8). In a 3-year COPD study, older patients, patients with a lower body mass index (<25 $kg/m^2$) 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 Peiotal should be re-evaluated. The safety and efficacy of Peiotal has not been established in patients with COPD and therefore Peiotal 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 (see section 4.5).

*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 <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 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 medicinal products 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 in patients with asthma, 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 $C_{max}$ and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

**4.6 Fertility, pregnancy and lactation**

*Fertility*

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

*Pregnancy*

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity related to salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of $\beta_2$ adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

Administration of Peiotal 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.

*Breastfeeding*

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 Peiotal 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 machines**

Peiotal has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**

As Peiotal contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.
Adverse events which have been associated with salmeterol/fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and not known (cannot be estimated from the available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

| System Organ Class | Adverse Event | Frequency |
|---|---|---|
| Infections & Infestations | Candidiasis of the mouth and throat<br>Pneumonia<br>Bronchitis<br>Oesophageal candidiasis | Common<br>Common[1,3]<br>Common[1,3]<br>Rare |
| Immune System Disorders | Hypersensitivity reactions with the following manifestations:<br>Cutaneous hypersensitivity reactions<br>Angioedema (mainly facial and oropharyngeal oedema)<br>Respiratory symptoms (dyspnoea)<br>Respiratory symptoms (bronchospasm)<br>Anaphylactic reactions including anaphylactic shock | <br>Uncommon<br>Rare<br><br>Uncommon<br>Rare<br>Rare |
| Endocrine Disorders | Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density | Rare[4] |
| Metabolism & Nutrition Disorders | Hypokalaemia<br>Hyperglycaemia | Common[3]<br>Uncommon[4] |
| Psychiatric Disorders | Anxiety<br>Sleep disorders<br>Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)<br>Depression, aggression (predominantly in children) | Uncommon<br>Uncommon<br>Rare<br><br>Not Known |
| Nervous System Disorders | Headache<br>Tremor | Very Common[1]<br>Uncommon |
| Eye disorder | Cataract<br>Glaucoma<br>Vision, blurred | Uncommon<br>Rare[4]<br>Not known[4] |
| Cardiac Disorders | Palpitations<br>Tachycardia<br>Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles).<br>Atrial fibrillation<br>Angina pectoris | Uncommon<br>Uncommon<br>Rare<br><br><br>Uncommon<br>Uncommon |
| Respiratory, Thoracic & Mediastinal Disorders | Nasopharyngitis<br>Throat irritation<br>Hoarseness/dysphonia<br>Sinusitis<br>Paradoxical bronchospasm | Very Common[2,3]<br>Common<br>Common<br>Common[1,3]<br>Rare[4] |
| Skin and subcutaneous tissue disorders | Contusions | Common[1,3] |

| | | |
|---|---|---|
| Musculoskeletal & Connective Tissue Disorders | Muscle cramps<br>Traumatic fractures<br>Arthralgia<br>Myalgia | Common<br>Common[1,3]<br>Common<br>Common |

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study
4. See section 4.4

*Description of selected adverse reactions*

The pharmacological side effects of $\beta_2$ 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. Peiotal 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 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 candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the Peiotal.

*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 HPRA Pharmacovigilance
Website: www.hpra.ie.

**4.9 Overdose**

There are no data available from clinical trials on overdose with Peiotal, however data on overdose with both drugs are given below:

The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia. If Peiotal therapy has to be withdrawn due to overdose of the β agonist component of the drug, 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.

**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 stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose. Refer to section 4.4: risk of adrenal suppression.

In cases of both acute and chronic fluticasone propionate overdose, Peiotal 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 and pharmacodynamics effects*

Peiotal contains salmeterol and fluticasone propionate which have differing modes of action.

The respective mechanisms of action of both drugs are discussed below.

*Salmeterol:*

Salmeterol is a selective long-acting (12 hour) $\beta_2$ adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting $\beta_2$ agonists.

*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*

*Salmeterol and Fluticasone pressurized inhalation suspension 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 Salmeterol and Fluticasone pressurized inhalation suspension 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 Salmeterol and Fluticasone pressurized inhalation suspension 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 Salmeterol and Fluticasone pressurized inhalation suspension than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual *well-Controlled* week was 16 days for Salmeterol and Fluticasone pressurized inhalation suspension 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 Salmeterol and Fluticasone pressurized inhalation suspension 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** ( ≤500 microgram BDP or equivalent/day) | 75% | 44% | 60% | 28% |
| **Medium dose ICS** (>500 to 1000 microgram 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 Salmeterol/Fluticasone propionate 50/100 microgram twice daily (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 Salmeterol and Fluticasone pressurized inhalation suspension for two weeks. The study showed that doubling the inhalations of each strength of Salmeterol and Fluticasone pressurized inhalation suspension for up to 14 days resulted in a small increase in βagonist-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 βagonist-related adverse events should be taken into account if doubling the dose of Salmeterol and Fluticasone pressurized inhalation suspension 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.

A multi-centre 8-week, double-blind, study was conducted to evaluate the safety and efficacy of salmeterol-FP metered dose inhaler (25/50 micrograms, 1 or 2 inhalations twice daily) versus FP (50 micrograms, 1 or 2 inhalations twice daily) alone in Japanese paediatric (6-month to 4 years of age) patients with infantile bronchial asthma. Ninety-nine percent (148/150) and ninety-five percent (142/150) of patients randomised to receive salmeterol-FP or FP alone, respectively, completed the double-blind period of the study. The safety of long-term treatment with salmeterol-FP metered dose inhaler (25/50 micrograms, 1 or 2 inhalations twice daily) was evaluated in a 16-week, open-label, extension treatment period. Ninety-three percent (268/288) completed the extension period. The study failed to meet its primary efficacy endpoint of mean change from baseline in total asthma symptom score (double blind period). No statistically significant superiority in favour of salmeterol-FP to FP was demonstrated (95% CI [-2.47; 0.54], p=0.206). There are no obvious differences in the safety profile between salmeterol-FP and FP alone (8-week double-blind period); moreover, no new safety signals were identified with administration of salmeterol-FP in the 16-week open-label extension period. However, the data about efficacy and safety of salmeterol-FP are insufficient to establish the benefit/risk balance of salmeterol-FP in children under 4 years old.

*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 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.

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 characterized 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%.
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 Salmeterol/Fluticasone MDI 25/50 microgram (2 inhalations twice daily with or without a spacer) or Salmeterol/Fluticasone DPI (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 Salmeterol/Fluticasone MDI with spacer (107 pg hr/mL [95% CI: 45.7, 252.2]) and Salmeterol/Fluticasone DPI (Diskus) (138 pg hr/mL [95% CI: 69.3, 273.2]), but lower for Salmeterol/Fluticasone MDI (24 pg hr/mL [95% CI: 9.6, 60.2]). Systemic exposure to salmeterol was similar for Salmeterol/Fluticasone MDI, Salmeterol/Fluticasone MDI with spacer, and Salmeterol/Fluticasone DPI (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 embryofetal 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**

Propellant: norflurane (HFA 134a).

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

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 pressurized canisters, the therapeutic effect of this medicinal product may decrease when the canister is cold.

**6.5 Nature and contents of container**

The suspension is contained in an aluminium alloy pressurized canister sealed with a metering valve.
The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with purple dust caps.

One pressurized canister contains 120 actuations.

Each product pack contains 1 inhaler x 120 actuations per inhaler.

**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**

Genetic S.p.A.
Via G. Della Monica n. 26
Castel San Giorgio
Salerno
84083
Italy

**8 MARKETING AUTHORISATION NUMBER**

PA23010/001/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 7th January 2022
Date of last renewal: 22nd September 2026

**10 DATE OF REVISION OF THE TEXT**

March 2026