SERETIDE Accuhaler

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

SERETIDE 50/100 Accuhaler Powder for Inhalation

SERETIDE 50/250 Accuhaler Powder for Inhalation

SERETIDE 50/500 Accuhaler Powder for Inhalation

COMPOSITION:

SERETIDE Accuhaler is a moulded plastic device containing a foil strip with 60 regularly spaced blisters, each blister containing a mixture of salmeterol xinafoate equivalent to 50 µg of salmeterol and microfine fluticasone propionate (100 µg, 250 µg or 500 µg).

Contains sugar (lactose up to 12,5 mg per blister) as excipient.

PHARMACOLOGICAL CLASSIFICATION:

A 21.5.1 Corticosteroids and analogues

PHARMACOLOGICAL ACTION:

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

Salmeterol is a selective beta$_2$-adrenoceptor agonist. Salmeterol has been shown to produce bronchodilatation of at least 12 hours in subjects with reversible airways obstruction.

In vitro tests have shown salmeterol to be an inhibitor of the release, from human lung, of mast cell derived mediators, such as histamine, leukotrienes and prostaglandin D_2. In man

salmeterol inhibits the early and late phase response to inhaled allergen and after single dosing attenuates bronchial hyperresponsiveness.

Fluticasone propionate *in vitro* has a glucocorticoid anti-inflammatory action.

Following oral administration 87-100 % of the dose is excreted in the faeces, up to 75 % as parent compound depending on the dose. There is a non-active major metabolite.

Following intravenous administration there is rapid plasma clearance suggestive of extensive hepatic extraction. The plasma elimination half-life is approximately 3 hours.

The volume of distribution is approximately 250 litres.

INDICATIONS:

SERETIDE Accuhaler is indicated in the regular prophylactic treatment of atopic asthma in children and adults, who have been stabilised on identical dosages of the components of SERETIDE given concurrently.

Chronic Obstructive Pulmonary Disease (COPD):

SERETIDE Accuhaler is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

SERETIDE is indicated for the symptomatic treatment of patients with severe COPD (FEV1 $<$ 50 % predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

CONTRA-INDICATIONS:

SERETIDE Accuhaler is contra-indicated in patients with a history of hypersensitivity to any of its components.

WARNINGS AND SPECIAL PRECAUTIONS:

SERETIDE Accuhaler is not for relief of acute symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their relief medication available at all times.

Increasing use of short-acting inhaled beta$_2$-agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and may have several causes. Consideration should be given to increasing corticosteroid dosage if not caused by otherwise treatable causes of deterioration.

Treatment with SERETIDE Accuhaler should not be stopped abruptly as adrenal insufficiency may be precipitated in this way.

Systemic corticosteroid effects may occur in patients on fluticasone treatment. Patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate.

Patients with severe asthma may require high dose inhaled (see DOSAGE AND DIRECTIONS FOR USE) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Patients weaned off oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they may need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

In rare cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg-Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

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 adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Patients in a medical or surgical emergency, who require high doses of inhaled steroids and/or intermittent treatment with oral steroids, are at risk of impaired adrenal reserve.

The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of residual impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.

In children taking recommended doses of inhaled fluticasone propionate, adrenal function and adrenal reserve usually remain within the normal range. However, the possible effects of previous or intermittent treatment with oral steroids should not be discounted.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled fluticasone propionate or by giving a systemic steroid and/or an antibiotic if there is an infection.

Special care is necessary in patients with active or quiescent pulmonary tuberculosis.

SERETIDE should be administered with caution in patients with thyrotoxicosis.

Patients on corticosteroid therapy may have adrenocortical suppression.

Effects on ability to drive and use machines:

SERETIDE is unlikely to produce an effect.

Excipient warnings:

Contains lactose/fructose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or

fructose intolerance should not use SERETIDE ACCUHALER. Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

Interaction with other medicaments and other forms of interaction:

Even though plasma levels of SERETIDE are very low, potential interactions with other substrates or inhibitors of CYP3A4 cannot be excluded.

Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

PREGNANCY AND LACTATION:

Fluticasone propionate:

Safety during pregnancy and lactation has not been established.

Corticosteroids have been shown to be teratogenic in animals. As these agents are absorbed when inhaled, teratogenicity following inhalation cannot be excluded.

Salmeterol:

Safety in pregnancy has not been established. There is no experience of the use of salmeterol in nursing mothers.

DOSAGE AND DIRECTIONS FOR USE:

SERETIDE Accuhaler is for oral inhalation use only.

Patients should be made aware that SERETIDE Accuhaler must be used regularly for optimum benefit even when asymptomatic.

Patients should be regularly reassessed by a doctor. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

SERETIDE Accuhaler is not for relief of acute symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their relief medication available at all times.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should be reviewed. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of SERETIDE Accuhaler has failed to give adequate control of reversible obstructive airways disease, the patient should be reviewed. Consideration should be given to additional corticosteroid therapies, and to including administration of antibiotics if an infection is present.

Recommended doses:

Adults and adolescents 12 years and older:

One inhalation (SERETIDE 50/100 Accuhaler) twice daily, or

One inhalation (SERETIDE 50/250 Accuhaler) twice daily, or

One inhalation (SERETIDE 50/500 Accuhaler) twice daily.

Children 4 years and older:

One inhalation (SERETIDE 50/100 Accuhaler) twice daily.

There are no data available for use of SERETIDE Accuhaler in children under 4 years.

Chronic Obstructive Pulmonary Disease (COPD):

For adult patients the recommended dose is one inhalation (SERETIDE 50/250 Accuhaler) or one inhalation (SERETIDE 50/500 Accuhaler) twice daily.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal or hepatic impairment.

SIDE EFFECTS:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) and very rare (< 1/10 000) including isolated reports. Common and uncommon events were generally determined from clinical trial data. The incidence of placebo was not taken into account. Very rare events were generally determined from post-marketing spontaneous data.

As SERETIDE Accuhaler contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected.

Adverse events which have been associated with salmeterol or fluticasone propionate are given below.

Salmeterol:

Immune system disorders:

Hypersensitivity reactions:

Uncommon: rash

Very rare: oedema and angioedema

Metabolism and nutrition disorders:

Frequency unknown: hypokalaemia

Nervous system disorders:

Common: tremor and headache

Cardiac disorders:

Common: palpitations

Very rare: cardiac arrythmias including atrial fibrillation, superventricular tachycardia and extrasystoles

Respiratory, thoracic and mediastinal disorders:

Very rare: oropharyngeal irritation

Musculoskeletal and connective tissue disorders:

Common: muscle cramps

Very rare: arthralgia.

Fluticasone propionate:

Infections and infestations:

Very common: candidiasis of mouth and throat

Candidiasis of the mouth and throat (thrush) may occur. Such patients may find it helpful to gargle with water after using the Accuhaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the SERETIDE Accuhaler

***Immune system disorders*:**

Hypersensitivity reactions with the following manifestations have been reported:

Uncommon: cutaneous hypersensitivity reactions

Endocrine disorders:

Possible systemic effects include (see WARNINGS AND SPECIAL PRECAUTIONS):

Very rare: adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma

Respiratory, thoracic and mediastinal disorders:

Common: hoarseness

Hoarseness may occur. Such patients may find it helpful to gargle with water after using the Accuhaler

Very rare: paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. SERETIDE Accuhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms and signs of salmeterol overdosage are tremor, headache and tachycardia. The preferred antidote for overdosage with salmeterol is a cardio-selective beta-blocking agent. Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

Acute: Inhalation of fluticasone propionate at dosages in excess of those recommended may lead to temporary suppression of adrenal function. This does not necessitate emergency action being taken. In these patients treatment with fluticasone propionate by inhalation should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled fluticasone propionate at doses in excess of those recommended over prolonged periods may lead to some degree of adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment with inhaled fluticasone propionate should be continued at a dose sufficient to control asthma.

IDENTIFICATION:

SERETIDE 50/100, 50/250 and 50/500 Accuhaler are moulded plastic devices containing foil strips with 60 regularly spaced blisters, each blister containing a white powder.

PRESENTATION:

SERETIDE Accuhaler is a two-tone purple, circular moulded plastic device containing a foil strip with 60 regularly spaced blisters, each blister containing a mixture of salmeterol xinafoate equivalent to 50 µg of salmeterol and microfine fluticasone propionate (100 µg, 250 µg or 500 µg). Contains lactose as excipient.

The SERETIDE 50/100 Accuhaler device is labelled with pink lettering.

The SERETIDE 50/250 Accuhaler device is labelled with purple lettering.

The SERETIDE 50/500 Accuhaler device is labelled with black lettering.

The device contains a dose counter which shows the number of doses remaining (60 to 1). To show when the last five doses have been reached, the number appears in red.

STORAGE INSTRUCTIONS:

Store in a dry place at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

SERETIDE 50/100 Accuhaler: 33/21.5.4/0413

SERETIDE 50/250 Accuhaler: 33/21.5.4/0414

SERETIDE 50/500 Accuhaler: 33/21.5.4/0415

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

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MANUFACTURER:

Glaxo Wellcome Production, Zone Industrielle No. 2, 23 Rue Lavoisier, 27000, Evreux,

France

Botswana:
Seretide Accuhaler 50/100 - Reg No BOT0200519 S2
Seretide Accuhaler 50/250 - Reg No BOT0200520 S2
Seretide Accuhaler 50/500 - Reg No BOT0200521 S2

Malawi:
Seretide Accuhaler 50/100 - Reg No PMPB/PL270/189 POM
Seretide Accuhaler 50/250 - Reg No PMPB/PL270/135 POM
Seretide Accuhaler 50/500 - Reg No PMPB/PL270/136 POM

Namibia:
Seretide Accuhaler 50/100 - Reg No 04/21.5.4/0916 NS2
Seretide Accuhaler 50/250 - Reg No 04/21.5.4/0917 NS2
Seretide Accuhaler 50/500- Reg No 04/21.5.4/0918 NS2

Zambia:
Seretide Accuhaler 50/100 - Reg No 179/042 POM
Seretide Accuhaler 50/250 - Reg No 179/043 POM
Seretide Accuhaler 50/500- Reg No 179/044 POM

Zimbabwe:
Seretide Accuhaler 50/100 - Reg No 2000/22.1.4/3678 PP
Seretide Accuhaler 50/250 - Reg No 2000/22.1.4/3679 PP
Seretide Accuhaler 50/500 - Reg No 2000/22.1.4/3680 PP

