PACKAGE INSERT FOR SEREFLO HFA INHALER

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

SEREFLO 25/50 HFA (Inhaler)

SEREFLO 25/125 HFA (Inhaler)

SEREFLO 25/250 HFA (Inhaler)

COMPOSITION:

SEREFLO 25/50 HFA: Each single actuation provides salmeterol xinafoate equivalent to 25 µg of salmeterol and 50 µg of fluticasone propionate.

SEREFLO 25/125 HFA: Each single actuation provides salmeterol xinafoate equivalent to 25 µg of salmeterol and 125 µg of fluticasone propionate.

SEREFLO 25/250 HFA: Each single actuation provides salmeterol xinafoate equivalent to 25 µg of salmeterol and 250 µg of fluticasone propionate.

Inactive ingredients are anhydrous ethanol, lecithin and norflurane (HFA-134a).

PHARMACOLOGICAL CLASSIFICATION:

A.21.5.4 Corticosteroids - Other combinations.

PHARMACOLOGICAL ACTION:

SEREFLO HFA contains fluticasone propionate and salmeterol which have differing modes of action. Salmeterol is a selective beta$_2$-adrenoceptor agonist. Salmeterol has been shown to produce long-lasting bronchodilatation of at least 12 hours in subjects with reversible airways obstruction. *In vitro* tests have shown salmeterol to be a potent and long-lasting 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.

In vitro tests have shown fluticasone propionate to have potent glucocorticoid anti-inflammatory action.

Pharmacokinetics:

Following oral administration of fluticasone propionate 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. The plasma elimination half-life is approximately 3 hours. The volume of distribution is approximately 250 litres.

INDICATIONS:

SEREFLO HFA is indicated in the following:

- Regular prophylactic treatment of atopic asthma in children and adults, who have been stabilised on identical dosages of the components of **SEREFLO HFA** given concurrently.

CONTRA-INDICATIONS:

SEREFLO HFA is contra-indicated in:

- Patients with a history of hypersensitivity to any of the ingredients.

WARNINGS:

Children who are taking **SEREFLO HFA** may be more susceptible to infections, such as chickenpox or measles. Thus care should be taken to avoid exposure to chickenpox and measles.

INTERACTIONS:

As a result of the very low plasma concentrations achieved after inhaled dosing, clinically significant drug interactions are unlikely. Care should be taken when co-administering known strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for increased systemic exposure to fluticasone propionate.

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 (see **"Special Precautions"**).

PREGNANCY AND LACTATION:

The use of **SEREFLO HFA** during pregnancy and lactation is not recommended as safety and efficacy have not been established.

Corticosteroids have been shown to be teratogenic in animals; therefore teratogenicity following inhalation cannot be excluded.

DOSAGE AND DIRECTIONS FOR USE:

SEREFLO HFA is for oral inhalation use only. Patients should be made aware that **SEREFLO HFA** must be used regularly for optimum benefit, even when asymptomatic. Patients should be regularly reassessed by a doctor so that the dosage of **SEREFLO HFA** 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.

SEREFLO HFA inhaler 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 **SEREFLO HFA** 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 include administration of antibiotics if an infection is present.

Treatment with **SEREFLO HFA** should not be stopped abruptly.

Recommended doses:

Shake the inhaler well before use.

Adults and adolescents 12 years and older:

Two inhalations of 25 µg salmeterol and 50 µg fluticasone propionate twice daily

OR

Two inhalations of 25 µg salmeterol and 125 µg fluticasone propionate twice daily

OR

Two inhalations of 25 µg salmeterol and 250 µg fluticasone propionate 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 AND SPECIAL PRECAUTIONS:

Side-effects:

As **SEREFLO HFA** contains fluticasone propionate and salmeterol, 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:

The following side-effects have been reported with the use of salmeterol:

Metabolism and nutrition disorders:

The following side-effects have been reported and frequencies are unknown:

Hypokalaemia may occur.

Nervous system disorders:

Frequent: Headache.

Less frequent: Tremor.

Cardiac disorders:

Less frequent: Palpitations.

The following side-effects have been reported and frequencies are unknown:

Cardiac dysrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) may occur in some patients.

Skin and subcutaneous tissue disorders:

The following side-effects have been reported and frequencies are unknown:

Hypersensitivity reactions, including rash, oedema and angioedema.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps.

The following side-effects have been reported and frequencies are unknown:

There have been reports of arthralgia.

<u>Fluticasone propionate:</u>

The following side-effects have been reported with the use of fluticasone:

Infections and infestations:

Frequent: Oropharyngeal candidiasis, influenza, upper respiratory infections.

Less frequent: Vaginal candidiasis.

Immune system disorders:

Less frequent: Angioedema, hypersensitivity-induced bronchospasm, hypersensitivity reaction (immediate or delayed), such as skin rash or urticaria, systemic eosinophilic conditions (e.g. Churg-Strauss syndrome), peripheral oedema, facial oedema, oropharyngeal oedema.

Endocrine disorders:

Less frequent: Cushingoid features, Cushing's syndrome.

Metabolism and nutrition disorders:

Less frequent: Adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density.

Psychiatric disorders:

Frequent: Insomnia.

Less frequent: Sleep disorders, aggression, agitation, depression, restlessness.

The following side-effects have been reported and frequencies are unknown:

Anxiety and behavioural changes.

Nervous system disorders:

Less frequent: Dizziness, giddiness, migraine.

Eye disorders:

Less frequent: Cataract, glaucoma, increased intra-ocular pressure, conjunctivitis, eye irritation.

Respiratory, thoracic and mediastinal disorders:

Frequent: Bronchitis, nasal problems, such as nasal congestion, nasal discharge, rhinitis, pain in nasal sinuses or sinusitis, nasopharyngitis, and hoarseness.

Less frequent: Paradoxical bronchospasm, wheezing after dosing, otitis media, dysphonia, epistaxis, irritation due to inhalant, sneezing.

Gastrointestinal disorders:

Frequent: Diarrhoea.

Less frequent: Throat irritation, gastroenteritis/colitis, abdominal pain or discomfort, nausea.

Skin and subcutaneous tissue disorders:

Less frequent: Skin rash (cutaneous hypersensitivity reaction), dermatitis, ecchymoses, or contusions, pruritus.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia.

Reproductive system and breast disorders:

Less frequent: Pelvic inflammatory disease, vaginitis/vulvovaginitis, dysmenorrhoea.

General disorders:

Frequent: Malaise.

Less frequent: Fatigue, weight gain.

<u>Salmeterol and fluticasone propionate combination:</u>

Additional to the above, the following side-effects have been reported with inhaled salmeterol and fluticasone propionate combination:

Infections and infestations:

Less frequent: Viral gastrointestinal infection, viral respiratory infection.

Blood and lymphatic system disorders:

The following side-effects have been reported and frequencies are unknown:

Eosinophilia.

Nervous system disorders:

Less frequent: Nervousness.

The following side-effects have been reported and frequencies are unknown:

Neuropathy.

Eye disorders:

Less frequent: Keratitis.

Cardiac disorders:

Less frequent: Rapid heart rate.

Respiratory, thoracic and mediastinal disorders:

Frequent: Choking, stridor or laryngeal spasm, irritation, or swelling, pharyngitis, upper respiratory inflammation.

Less frequent: Blood in nasal mucosa, chest pain, cough, rhinorrhoea.

Skin and subcutaneous tissue disorders:

The following side-effects have been reported and frequencies are unknown:

Vasculitic rash.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle pain.

Special Precautions:

Treatment with **SEREFLO HFA** inhaler should not be stopped abruptly as adrenal insufficiency may be precipitated in this way. Hoarseness and candidiasis (thrush) of the mouth and throat can occur. Such patients may find it helpful to gargle with water after using the **SEREFLO HFA** inhaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the **SEREFLO HFA** inhaler.

Cutaneous hypersensitivity reactions have been reported. Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. **SEREFLO HFA** inhaler should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted.

Systemic corticosteroid effects may occur in patients on **SEREFLO HFA** 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, such as contained in **SEREFLO HFA**. 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.

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 steroids 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 **SEREFLO HFA**, 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 **SEREFLO HFA** is titrated to the lowest dose at which effective control is maintained.

It is recommended that the height of children receiving prolonged treatment with **SEREFLO HFA** is regularly monitored. Patients in a medical or surgical emergency, who require high doses of **SEREFLO HFA** 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 **SEREFLO HFA** 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 **SEREFLO HFA** 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. **SEREFLO HFA** 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:

SEREFLO HFA is unlikely to produce an effect.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The signs and symptoms of salmeterol overdosage are tremor, headache and tachycardia. The preferred antidote for overdosage with salmeterol inhaler is a cardioselective 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:

SEREFLO 25/50 HFA: A white homogenous suspension aerosol for inhalation.

SEREFLO 25/125 HFA: A white homogenous suspension aerosol for inhalation.

SEREFLO 25/250 HFA: A white homogenous suspension aerosol for inhalation.

PRESENTATION:

SEREFLO 25/50 HFA: Carton containing a pressurised aluminium container with a plastic actuator, with or without a long mouthpiece plastic actuator (Gentle-Haler); or a pressurised aluminium container sealed inside a breath-activated plastic actuator with a dose counter (Synchrobreathe). Each container provides 120 metered dose inhalations.

SEREFLO 25/125 HFA: Carton containing a pressurised aluminium container with a plastic actuator, with or without a long mouthpiece plastic actuator (Gentle-Haler); or a pressurised aluminium container sealed inside a breath-activated plastic actuator with a dose counter (Synchrobreathe). Each container provides 120 metered dose inhalations.

SEREFLO 25/250 HFA: Carton containing a pressurised aluminium container with a plastic actuator, with or without a long mouthpiece plastic actuator (Gentle-Haler); or a pressurised

aluminium container sealed inside a breath-activated plastic actuator with a dose counter (Synchrobreathe). Each container provides 120 metered dose inhalations.

STORAGE INSTRUCTIONS:

Store in a cool dry place, at or below 25 ºC.

Avoid storage in direct sunlight and heat.

The canister is pressurised; it should not be broken, punctured or burnt, even when apparently empty.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

SEREFLO 25/50 HFA: A42/21.5.4/0218

SEREFLO 25/125 HFA: A42/21.5.4/0219

SEREFLO 25/250 HFA: A42/21.5.4/0220

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

CIPLA MEDPRO (PTY) LTD

Rosen Heights

Pasita Street

Rosen Park

Bellville

7530

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