SEREVENT INHALER CFC-FREE
Proposed PI

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

SEREVENT INHALER CFC-FREE

Salmeterol xinafoate 25 µg (micrograms)

Metered-dose inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Pressurised metered-dose inhaler delivering 25 micrograms salmeterol (as xinafoate) with each actuation.

3. PHARMACUTICAL FORM:

Metered-dose inhaler.

SEREVENT INHALER CFC-FREE is a metered-dose aerosol inhaler comprising of a suspension of salmeterol xinafoate in a non-CFC propellant Norflurane.

4. CLINICAL PARTICULARS:

4.1 Indications:

Asthma:

Adults:

Long-term maintenance treatment of reversible airways obstruction, in asthma, chronic bronchitis and emphysema.

Children 4 years and older:

Maintenance treatment of reversible airways obstruction in asthma including long-lasting prevention of exercise-induced bronchospasm.

SEREVENT INHALER CFC-FREE should be used only as an adjunct to corticosteroids in the management of asthma.

SEREVENT INHALER CFC-FREE is not intended for use in acute attacks of asthma, in view of the slow onset of action.

4.2 Posology and method of administration:

SEREVENT INHALER CFC-FREE: administered by the inhaled route only.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should not be increased.

Adults: Two inhalations (2 x 25 micrograms of salmeterol) twice daily.

Children 4 years and older: Two inhalations (2 x 25 micrograms of salmeterol) twice daily.

There are insufficient clinical data to recommend the use of SEREVENT INHALER CFC-FREE in children below 4 years of age.

Elderly: There is no need to adjust the dose in the elderly.

In order to gain full therapeutic benefit, regular usage of SEREVENT INHALER CFC-FREE is recommended in the treatment of asthma. The onset of the bronchodilator effect of SEREVENT INHALER CFC-FREE usually occurs in approximately 10-30 minutes or longer. The full benefits will be apparent after the 1st or 2nd dose of the medicine.

If symptoms persist, patients should take a short-acting inhaled beta$_2$-agonist for relief. However, this need is usually an indication that control of their airways obstruction is

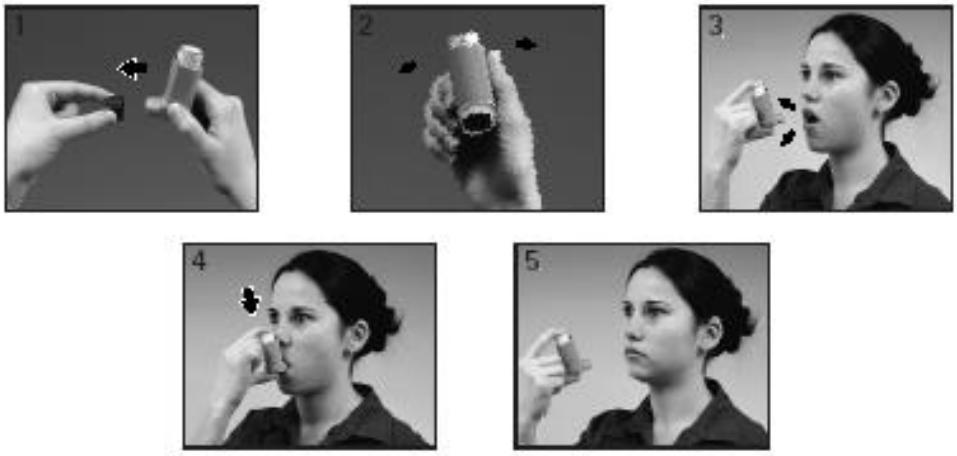
suboptimal and that other treatment should be considered. This may involve commencing or increasing the dose of prophylactic treatment.

Instructions on the use of the Inhaler

Testing the inhaler:

Before using a canister of SEREVENT INHALER CFC-FREE for the first time, remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, hold the inhaler between fingers and thumb with the thumb at the base, below the mouthpiece and release puffs of SEREVENT INHALER CFC-FREE into the air, to ensure 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 remove the mouthpiece cover, shake the inhaler well and release two puffs of SEREVENT INHALER CFC-FREE into the air.

Using the inhaler:



1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.

4. Hold the inhaler upright between fingers and thumb with the thumb on the base, below the mouthpiece.
5. Breathe out as far as is comfortable and then place the mouthpiece in the mouth between the teeth and close the lips around it, but do not bite it.
6. Just after starting to breathe in through the mouth, press firmly down on the top of the inhaler to release SEREVENT INHALER CFC-FREE, while still breathing in steadily and deeply.
7. While holding the breath, take the inhaler from the mouth and take the finger from the top of the inhaler. Continue holding the breath for as long as is comfortable.
8 To take the second inhalation, keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Afterwards, rinse the mouth with water and spit it out.
10. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

Cleaning:

The 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, tissue or cottonbud.
4. Replace the mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications:

Hypersensitivity to salmeterol or to any other ingredient of SEREVENT INHALER CFC-FREE.

Co-administration with ketoconazole.

4.4 Special warnings and precautions for use:

SEREVENT INHALER CFC-FREE should not be initiated in patients with significantly worsening or acutely deteriorating asthma.

Patients with asthma should receive optimal anti-inflammatory therapy with corticosteroids before starting maintenance treatment with SEREVENT INHALER CFC-FREE.

Maintenance treatment with SEREVENT INHALER CFC-FREE is not a substitute for inhaled or oral corticosteroids, but its use is complementary to them.

Patients must be advised not to stop or reduce corticosteroid therapy without medical advice.

SEREVENT INHALER CFC-FREE should not be used as the only or the main treatment in patients with severe or unstable asthma.

SEREVENT INHALER CFC-FREE is not intended to relieve acute asthma symptoms, for which an inhaled short-acting bronchodilator is required.

Sudden and progressive deterioration of asthma is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy.

Increasing use of SEREVENT INHALER CFC-FREE to relieve symptoms, indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought.

Patients who have to take increasing doses of other beta$_2$-agonists in addition to salmeterol for relief of symptoms should seek urgent medical advice.

The dose of SEREVENT INHALER CFC-FREE should not be increased beyond the maximum recommended dose. The dose of SEREVENT INHALER CFC-FREE should be individualised to the patient's needs and should be the lowest possible dose that keeps the patient symptom-free or fulfils the therapeutic objective.

Patients should be educated to recognise the signs of deteriorating asthma control and the need to seek medical attention promptly in such circumstances.

Pharmacological side effects of SEREVENT INHALER CFC-FREE, such as tremor, palpitations and headache 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. SEREVENT INHALER CFC-FREE should be discontinued immediately, the patient assessed and if necessary, alternative therapy instituted.

Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occur, especially at higher than therapeutic doses. For this reason, SEREVENT INHALER CFC-FREE should be used with caution in patients with pre-existing cardiovascular disease.

A decrease in serum potassium (hypokalaemia) may occur. Therefore, SEREVENT INHALER CFC-FREE should be used with caution in patients predisposed to low levels of serum potassium.

Increases in blood glucose levels have been reported (see section 4.8) and this should be considered when prescribing SEREVENT INHALER CFC-FREE to patients with a history of diabetes mellitus.

SEREVENT INHALER CFC-FREE should be administered with caution in patients suffering from hyperthyroidism.

A large study (SMART) comparing the safety of salmeterol or placebo added to usual therapy showed an increase in asthma-related deaths in patients receiving salmeterol.

Long-acting beta$_2$-agonists, such as SEREVENT INHALER CFC-FREE should be prescribed together with corticosteroids (see section 4.1).

An interaction study showed that concomitant use of systemic ketoconazole significantly increases exposure to salmeterol. This may lead to prolongation in the QTc interval. Caution should be exercised when strong CYP3A4 inhibitors are co-administered with salmeterol.

4.5 Interactions with other medicines and other forms of interaction:

Beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

In a placebo-controlled, crossover interaction study in 15 healthy subjects, co-administration of salmeterol (50 µg twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1,4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia (see section 4.3).

A repeat-dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin.

Caution is recommended when co-administering strong CYP3A4 inhibitors such as ritonavir with salmeterol.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of SEREVENT INHALER CFC-FREE in pregnancy has not been established.

Lactation:

There is no experience of the use of SEREVENT INHALER CFC-FREE in nursing mothers.

4.7 Effects on ability to drive and use machines:

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable 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.

Clinical Trial Data:

The following frequencies are estimated at the standard dose of 50 micrograms twice daily.

Immune system disorders:

Uncommon: Hypersensitivity Reactions: rash

***Nervous system disorders*:**

Common: tremor and headache

Tremor occurs more commonly when administered at doses higher than 50 micrograms twice daily.

Cardiac disorders:

Common: palpitations

Uncommon: tachycardia

Tachycardia occurs more commonly when administered at doses higher than 50 micrograms twice daily.

Musculoskeletal and connective tissue disorders:

Common: muscle cramps.

Post-marketing Data:

Immune system disorders: anaphylactic reactions including oedema, angioedema, bronchospasm and anaphylactic shock

Metabolism and nutrition disorders: hyperglycaemia

Cardiac disorders: cardiac dysrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles

Respiratory, thoracic and mediastinal disorders: oropharyngeal irritation and paradoxical bronchospasm

Musculoskeletal and connective tissue disorders: arthralgia.

Reporting of side effects:

If you get side effects, talk to your doctor or pharmacist or nurse. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of SEREVENT INHALER CFC-FREE.

4.5 Overdose

In overdose, the side effects will be elicited and exacerbated (see section 4.8). These include tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia.

If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 10.2.1. Medicines acting on respiratory system - bronchodilators, inhalants

Salmeterol is a selective long-acting beta$_2$-adrenoreceptor agonist.

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

D2. In man, salmeterol inhibits the early and late phase response to inhaled allergen and after single dosing attenuates bronchial hyperresponsiveness.

5.2 Pharmacokinetic properties:

Salmeterol acts locally in the lung therefore plasma levels are not predicative of therapeutic effect.

In addition, there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the active substance in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/ml or less) achieved after inhaled dosing.

Salmeterol is extensively metabolised to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Chlorofluorocarbon (CFC)-free propellant Norflurane (HFA 134_a).

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from frost, heat and direct sunlight.

Replace the mouthpiece cover firmly and snap it into position.

Pressurised container: Do not expose to temperatures higher than 50 ºC. Do not puncture, break or burn the canister, even when apparently empty.

DO NOT PUT THE METAL CONTAINER IN WATER.

Keep out of reach of children

6.5 Nature and contents of container:

The suspension is contained in an aluminium alloy can, internally coated with a specified fluoropolymer and sealed with a metering valve. Each canister is fitted with a plastic actuator incorporating an atomising nozzle and fitted with a dustcap.

Canisters contain at least 120 actuations.

A single canister is packed into a carton.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICAT OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue, Epping Industria 1, 7460

8. REGISTRATION NUMBER:

A40/10.2.1/0064

9. DATE OF FIRST AUTHORISATION

Date of first registration: 01 December 2006

10. DATE OF REVISION OF TEXT:

23 January 2023

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