PROFESSIONAL INFORMATION FOR SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/100 CIPLA micrograms / dose inhalation powder, pre-dispensed

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/250 CIPLA micrograms / dose inhalation powder, pre-dispensed

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/500 CIPLA micrograms / dose inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA is a multi – dose plastic inhaler device containing a foil blister strip with 60 blisters.

Each blister contains salmeterol xinafoate equivalent to 50 micrograms of salmeterol and fluticasone propionate 100 micrograms, 250 micrograms or 500 micrograms respectively.

Contains sugar: lactose monohydrate 12,33 mg, 12,18 mg or 11,93 mg respectively.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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 SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA given concurrently.

Chronic Obstructive Pulmonary Disease (COPD)

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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.

4.2 Posology and method of administration

Posology

Adults and adolescents 12 years and older

One inhalation SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/100 CIPLA twice daily, or

One inhalation SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/250 CIPLA twice daily, or

One inhalation SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/500 CIPLA twice daily.

Children 4 years and older

One inhalation SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/100 CIPLA twice daily.

There are no data available for the use of SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA in children under 4 years.

Chronic Obstructive Pulmonary Disease (COPD)

For adult patients the recommended dose is one inhalation SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/250 CIPLA or one inhalation SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/500 CIPLA twice daily.

Special patient groups

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

Patients should be made aware that SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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.

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 SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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.

Method of administration

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA is for oral inhalation use only.

4.3 Contraindications

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA is contraindicated in patients with a history of hypersensitivity to salmeterol, fluticasone or to any of the excipients listed in **section 6.1.**

4.4 Special warnings and precautions for use

- SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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 SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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 **section 4.2**) 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.
- There are cases where 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.
- SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA should be administered with caution in patients with hyperthyroidism.
- Patients on corticosteroid therapy may have adrenocortical suppression.
- There have been isolated reports of contraceptive failure in women using intra-uterine devices and receiving corticosteroid therapy.
- There have been 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.

- Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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, throat and of the oesophagus can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis may be relieved by rinsing the mouth with water and/or brushing the teeth after using SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst continuing with SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA.
- The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.
- An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively across all studies.

  There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid medicines.

  Medical practitioners should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Even though plasma levels of SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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.

4.6 Fertility, 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 medicines 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.

4.7 Effects on ability to drive and use machines

Since SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA may cause blurred vision (see **section 4.8**), the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

As SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected.

Infections and Infestations

Frequent: Pneumonia (in COPD patients), bronchitis

Immune System Disorders

Hypersensitivity reactions with the following manifestations:

Less frequent: Respiratory symptoms (dyspnoea, bronchospasm), anaphylactic reactions including anaphylactic shock

Endocrine Disorders

Less frequent: Cushing's syndrome, Cushingoid features

Metabolism and Nutrition Disorders

Less frequent: Hyperglycaemia

Psychiatric Disorders

Less frequent: Anxiety, sleep disorders, behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children),

Frequency unknown: Depression, aggression (predominantly in children)

Eye Disorders

Frequency unknown: Vision, blurred

Cardiac Disorders

Less frequent: Tachycardia, angina pectoris

Respiratory, Thoracic and Mediastinal Disorders

Frequent: Nasopharyngitis, throat irritation, sinusitis

Skin and subcutaneous tissue disorders

Frequent: Contusions

Musculoskeletal & Connective Tissue and bone disorders

Frequent: Traumatic fractures, myalgia

Salmeterol

Immune System Disorders

Less frequent: Hypersensitivity reactions: rash, oedema, angioedema (mainly facial and oropharyngeal oedema)

Metabolism and Nutrition Disorders

Frequent: Hypokalaemia

Nervous System Disorders

Frequent: Headache, tremor

Cardiac Disorders

Frequent: Palpitations

Less frequent: Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles)

Respiratory, Thoracic and Mediastinal Disorders

Less frequent: Oropharyngeal irritation

Musculoskeletal and Connective Tissue and bone disorders

Frequent: Muscle cramps, arthralgia

Fluticasone propionate

Infections and Infestations

Frequent: Candidiasis of the mouth and throat (thrush) – see **section 4.4**, increased susceptibility to infections (tuberculosis, septicaemia, fungal infections and viral infections)

Less frequent: Oesophageal candidiasis

Neoplasms benign and malignant

Frequency unknown: Tumour lysis syndrome

Blood and lymphatic system disorders

Frequency unknown: Menstrual irregularities, amenorrhoea, thromboembolic complications, peptic ulcers

Immune System Disorders

Hypersensitivity reactions with the following manifestations:

Less frequent: Cutaneous hypersensitivity reactions

Endocrine Disorders

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

Frequency unknown: Acute pancreatitis, adrenal atrophy

Metabolism and Nutrition Disorders

Frequent: Increased appetite

Nervous System Disorders

Frequency unknown: Neurological disturbances, benign intracranial hypertension

Eye Disorders

Less frequent: Cataract, glaucoma

Cardiac Disorders

Less frequent: Electrolyte imbalances, cardiac failure

Vascular Disorders

Frequency unknown: Hypertension

Respiratory, Thoracic and Mediastinal Disorders

Frequent: Hoarseness/dysphonia

Less frequent: Paradoxical bronchospasm (see **section 4.4**).

Skin and subcutaneous tissue disorders

Frequency unknown: Hyperhidrosis, skin thinning, bruising, purpura, erythematous lesions, Stevens-Johnson Syndrome, acneform eruptions, hypertrichosis

Musculoskeletal & Connective Tissue and bone disorders

Frequency unknown: Osteoporosis, avascular necrosis of bone

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are

asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

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 medicine. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.5.1 Corticosteroids and analogues

Pharmacotherapeutic group: Adrenergics in combination with corticosteroids or other drugs, excluding Anticholinergics

ATC code: R03AK06

Mechanism of action

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE CIPLA 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* may have a glucocorticoid anti-inflammatory action.

5.2 Pharmacokinetic properties

Following oral administration 87 to 100 % of the dose may be 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

The inhalation powder is contained in a plastic inhaler containing a foil blister strip with a peelable foil laminate lid containing 60 blisters. The inhaler has a numeric dose counter displayed on the top of the device which indicates the number of doses left.

The inhaler is packaged in a plastic-coated, moisture protective foil pouch.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Belville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/100 CIPLA: 54/21.5.1/0109

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/250 CIPLA: 54/21.5.1/0110

SALMETEROL XINAFOATE/FLUTICASONE PROPIONATE 50/500 CIPLA: 56/21.5.1/0068

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 21 November 2023

Latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT