PROPOSED PACKAGE INSERT FOR

DUOLIN HFA (METERED DOSE INHALER)

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

DUOLIN HFA (Metered dose inhaler)

COMPOSITION:

DUOLIN HFA: Each metered dose contains ipratropium bromide monohydrate equivalent to ipratropium 20 mcg and salbutamol sulphate equivalent to salbutamol 100 mcg in each actuation.

Inactive ingredients include HFA-227 propellant gas and lactose monohydrate.

Contains lactose.

PHARMACOLOGICAL CLASSIFICATION:

A 10.2.1 Bronchodilators – inhalants.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. It inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. The bronchodilation following inhalation of ipratropium bromide is primarily local and site

specific to the lung and not systemic in nature.

Salbutamol sulphate is a beta$_2$-adrenergic agent which acts on airway smooth muscle resulting in relaxation.

DUOLIN HFA metered dose inhaler provides the simultaneous release of ipratropium bromide and salbutamol sulphate allowing the synergistic efficacy on the muscarinic and beta$_2$-adrenergic receptors in the lung to cause bronchodilation.

Pharmacokinetic properties:

Ipratropium bromide is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as compared by blood level and renal excretion studies. The elimination half-life is about 3 – 4 hours after inhalation or intravenous administration. Ipratropium bromide does not penetrate the blood brain barrier.

Salbutamol sulphate is rapidly and completely absorbed following oral administration either by the inhaled or gastric route. Peak plasma salbutamol concentrations are seen within three hours of administration and salbutamol is excreted unchanged in the urine after 24 hours. Intravenous salbutamol will cross the blood brain barrier reaching concentrations amounting to about five percent of the plasma concentrations.

INDICATIONS:

DUOLIN HFA is indicated for the treatment of reversible bronchospasm

associated with obstructive pulmonary disease.

CONTRA-INDICATIONS:

DUOLIN HFA metered aerosol is contra-indicated in:

- Patients with a hypersensitivity to ipratropium bromide, salbutamol or any of the other components of **DUOLIN FHA**.
- Patients with hypertrophic obstructive cardiomyopathy or tachydysrhythmia.
- Patients with a history of hypersensitivity to soya lecithin or related food products, such as soybean and peanut.
- Patients with known hypersensitivity to atropine or its derivatives.
- Pregnancy and lactation, as safety has not been established.
- Children, as safety has not been established.

WARNINGS:

Patients must be instructed in the correct administration of **DUOLIN HFA** metered aerosol. Care must be taken not to expose the eyes to the aerosol of **DUOLIN HFA**. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

Immediate hypersensitivity reactions may occur after administration of **DUOLIN HFA** metered aerosol, as demonstrated by less frequent cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.

INTERACTIONS:

The concurrent administration of xanthine derivatives (e.g. theophylline) as well as

other beta-adrenergics and anticholinergics may increase the side-effects.

Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction (see **"Special Precautions"**).

A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.

DUOLIN HFA should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of **DUOLIN HFA** may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of **DUOLIN HFA**.

Anticholinergic effects of other medicines may be enhanced.

PREGNANCY AND LACTATION:

The use of **DUOLIN HFA** during pregnancy and lactation is not recommended as safety has not been established (see **"CONTRA-INDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

Adults:	Two inhalations four times a day.
(including elderly patients)	The dose may be increased as required up to a limit of 12 inhalations in 24 hours.
Children:	There is no experience of the use of **DUOLIN HFA** in children below the age of 12 years.

Do not exceed the recommended dose.

Patients should be advised to consult a doctor or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea (difficulty in breathing) if additional inhalations do not produce an adequate improvement.

The correct operation of the metered dose inhaler is essential for successful therapy.

Shake the aerosol canister and depress the valve two times before the apparatus is initially used.

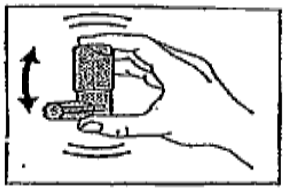


Fig 1

***Instructions for* use:**

1. Remove the protective cap.
2. Shake the metered dose inhaler well before each use (see Fig 1).
3. Breathe out deeply.
4. Hold the metered dose inhaler as shown in Fig 2, and close the lips over the mouthpiece. The arrow and the base of the container should be pointing upwards.

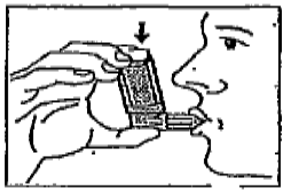


Fig 2

5. Breathe in as deeply as possible, pressing the base of the container firmly at the same time; this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece from the mouth and breathe out. The same action should be repeated for a second inhalation.
6. Replace the protective cap after use.

The container is under pressure and should on no account be opened by force or exposed to temperatures exceeding 50 ℃. As the container is not transparent it is not possible to see when the contents are used up, but shaking the container will show if there is any remaining fluid.

The mouthpiece should always be kept clean and can be washed with warm water. If soap or detergent is used, the mouthpiece should be thoroughly rinsed in clear water.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The following side-effects may occur with the use of **DUOLIN HFA**:

Immune system disorders:

Less frequently: Allergic type reactions, such as skin rash, angioedema of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases. Many of the patients had a history of allergy to other

medicines and/or foods, including soybean (see **"CONTRA-INDICATIONS"**).

Hypersensitivity reactions may include paradoxical bronchospasm, angioedema, urticaria, hypotension, and collapse.

Metabolism and nutrition disorders:

Frequency unknown: Hypokalaemia, hyperglycaemia.

Psychiatric disorders:

Frequent: Nervousness.

Nervous system disorders:

Frequent: Headache, dizziness.

Eye disorders:

Frequency unknown: Acute angle-closure glaucoma (see **"Special Precautions"**).

Cardiac disorders:

Frequent: Tachycardia, palpitations, cardiac dysrhythmias (particularly after high doses).

Frequency unknown: Myocardial ischaemia.

Vascular disorders:

Frequency unknown: Decrease in diastolic blood pressure, increase in systolic blood pressure, peripheral vasodilation.

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough, local irritation, and dysphonia.

Less frequent: Inhalation induced bronchospasm.

Gastrointestinal disorders:

Frequent: Constipation, dryness of the mouth.

Less frequent: Nausea, vomiting.

Frequency unknown: Gastrointestinal motility disturbances, dyspepsia.

Skin and subcutaneous tissue disorders:

Less frequent: Rash, pruritus.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Fine tremor of skeletal muscles.

Less frequent: Myalgia/muscle cramps.

Renal and urinary disorders:

Less frequent: Urinary retention.

Special Precautions:

Ocular complications:

There have been reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has escaped into the eyes.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

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In the following conditions **DUOLIN HFA** should only be used after careful risk/benefit assessment, especially when higher than recommended doses are used: insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

In the case of acute, rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

Prolonged use:

If bronchial obstruction deteriorates, it is inappropriate and possibly hazardous to simply increase the use of **DUOLIN HFA** beyond the recommended dose over extended periods of time. If higher than recommended doses of **DUOLIN HFA** are required to control symptoms, the patient's therapy plan should be reviewed by a doctor.

Potentially serious hypokalaemia may result from **DUOLIN HFA** therapy. Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.
Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm.

Hypokalaemia may result in an increased susceptibility to dysrhythmias in patients receiving digoxin. It is recommended that serum potassium levels are monitored in such situations. Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances. A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.

DUOLIN HFA contains lactose. Patients who are lactose intolerant and who accidentally swallow **DUOLIN HFA** may experience unwanted side-effects, such as nausea, cramping, bloating, diarrhoea, and flatulence. **DUOLIN HFA** should not be used by patients with rare hereditary problems or a history of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Effects on the ability to drive and use machines:

DUOLIN HFA is unlikely to affect your ability to drive or use machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

The effects of overdosage are expected to be primarily related to salbutamol. The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, dysrhythmias and flushing.

Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disturbances) are mild and transient in nature in view of the wide therapeutic range and topical administration.

Therapy:

Administration of sedatives, tranquillisers, in severe cases intensive therapy. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent but due care and attention should be used in administering these medicines in patients with a history of bronchospasm. Further treatment is symptomatic and supportive.

IDENTIFICATION:

White homogenous suspension aerosol for inhalation, in propellant HFA-227

supplied in a pressurised container.

PRESENTATION:

Carton containing a pressurised aluminium container which delivers ipratropium bromide monohydrate equivalent to ipratropium 20 mcg and salbutamol sulphate equivalent to salbutamol 100 mcg in each actuation. Each container provides 200 metered dose inhalations.

STORAGE INSTRUCTIONS:

Store in a cool dry place at or below 25 ℃. Avoid storage in direct sunlight or heat.

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

STORE THIS MEDICINE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

To be allocated.

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

CIPLA MEDPRO (PTY) LTD

Building 9, Parc du Cap,

Mispel Street, Bellville

7530, RSA

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

02 July 2012