SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

PROVENTIL, 100 µg, Pressurised metered-dose inhaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains salbutamol sulphate equivalent to 100 micrograms of salbutamol.

Contains alcohol (ethanol); 4,32 mg per metered dose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Pressurised metered-dose inhaler.

Metered-dose aerosol inhaler containing a homogeneous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PROVENTIL is indicated for relief of bronchospasm in:

- Bronchial asthma of all types
- Chronic bronchitis
- Emphysema

4.2 Posology and method of administration

Posology

One or two inhalations repeated four-hourly if required. The bronchodilator effect of each administration of PROVENTIL lasts for at least four hours and more frequent use should be unnecessary. The patient can readily recognise any reduction in the length of action and should be instructed to consult a doctor if the effect of a previously adequate dose lasts for less than three hours.

PROVENTIL acts rapidly and may be used when necessary to relieve attacks of acute dyspnoea. Doses may be taken prophylactically before exertion to prevent exercise-induced asthma. Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as the condition is potentially life-threatening.

Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60 % predicted at baseline with greater than 30 % variability, usually not returning entirely to normal after a bronchodilator. These patients will require inhaled corticosteroid therapy.

Failure to respond promptly or fully to such rescue medication signals a need for urgent medical advice and treatment.

Method of administration

PROVENTIL is administered by the inhaled route only, to be breathed in through the mouth.

Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the medicine to the lungs.

4.3 Contraindications

- Hypersensitivity to salbutamol sulphate or to any of the excipients listed in section 6.1.
- PROVENTIL is not appropriate for managing premature labour.
- PROVENTIL should not be used for threatened abortion.

4.4 Special warnings and precautions for use

PROVENTIL should be administered cautiously to patients suffering from thyrotoxicosis.

PROVENTIL should be used with caution in patients with cardiovascular disorders especially ischaemic heart disease, angina, tachycardia, dysrhythmias and hypertension. Patients with underlying severe heart disease (e.g. ischaemic heart disease, dysrhythmia or severe heart failure) who are using PROVENTIL should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

PROVENTIL should be used with caution in patients known to have received other sympathomimetic medicine.

PROVENTIL and beta-blocking medicines, such as propranolol, should not be prescribed together.

Increasing use of PROVENTIL may be a sign of worsening asthma. Under these conditions, a reassessment of the patient's therapy plan may be required. Sudden and progressive deterioration in asthma control is potentially life threatening and concomitant glucocorticosteroid therapy should be considered.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

In patients considered at risk, daily peak flow monitoring may be instituted.

In the event of a previously effective dose of PROVENTIL failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

Particular caution is advised in acute severe asthma as hypokalaemia may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in such situations.

High dosages may increase the risk of serious side effects, including cardiac dysrhythmias. The risk is further aggravated if administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias or in the presence of hypoxia and acidosis. The maximum dose should not be exceeded.

Paradoxical bronchospasm may occur with an immediate increase in wheezing after

dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. PROVENTIL should be discontinued immediately, the patient assessed, and if necessary, a different fast acting bronchodilator instituted for on-going use.

PROVENTIL contains a small amount of alcohol (ethanol). Each actuation (puff) from this inhaler contains about 4,32 mg of ethanol.

The use of salbutamol as contained in PROVENTIL may lead to a positive test for a prohibited substance in competitive sport activities.

4.5 Interaction with other medicines and other forms of interaction

PROVENTIL and non-selective beta-blocking medicines such as propranolol, should not usually be prescribed together.

Sympathomimetics should be used with caution in patients undergoing anaesthesia with cyclopropane, halothane or other halogenated anaesthetics as ventricular fibrillation may be induced.

An increased risk of dysrhythmias may also occur if administered concomitantly with cardiac glycosides, quinidine or tricyclic antidepressants.

Sympathomimetic amines should not be given to patients receiving mono-amine oxidase inhibitors or within 14 days of termination of mono-amine oxidase inhibitor therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnant women has not been established. Studies in animals have shown reproductive toxicity (see section 5.3).

No controlled clinical trials with salbutamol have been conducted in pregnant women. Reports of various congenital anomalies following intrauterine exposure to salbutamol (including cleft palate, limb defects and cardiac disorders) have been received. Some of the mothers were taking multiple medications during their pregnancies.

Breastfeeding

Safety during breastfeeding has not been established. As salbutamol is probably secreted in breast milk, its use in nursing mothers requires careful consideration.

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	Frequency	Description
Immune system disorders	*Less frequent*	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.
Metabolism and nutrition disorders	*Less frequent*	Hypokalaemia, potentially serious hypokalaemia may result from *beta*$_2$ agonist therapy.
Nervous system disorders	*Frequent*	Tremor, headache.
	Less frequent	Hyperactivity.
	Frequency unknown	Agitation, nervousness, fatigue, fear, restlessness, dizziness, confusion, insomnia*
Cardiac disorders	*Frequent*	Tachycardia.
	Less frequent	Palpitations, cardiac dysrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).
	Frequency unknown	Myocardial ischaemia* (see section 4.4).
Vascular disorders	*Less frequent*	Peripheral vasodilatation.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Paradoxical bronchospasm.
Gastrointestinal disorders	*Less frequent*	Mouth and throat irritation.
	Frequency unknown	Loss of appetite, nausea, vomiting.*
Musculoskeletal and connective tissue disorders	*Less frequent*	Muscle cramps.

*reported spontaneously in post-marketing data therefore frequency regarded as unknown

Other effects that may occur with sympathomimetic medicines include difficulty in micturition, urinary retention, dyspnoea, altered metabolism, sweating and hypersalivation.

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. Healthcare 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.

4.9 Overdose

Signs and Symptoms

The most common signs and symptoms of overdose with PROVENTIL are beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia (see sections 4.4 and 4.8). Agitation, hallucinations and irritability have been reported.

Hypokalaemia may occur following overdose with PROVENTIL. Serum potassium levels should be monitored. Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnoea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Treatment:

Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 10.2.1 Medicines acting on respiratory system. Bronchodilators. Inhalants

Pharmacotherapeutic group: Adrenergics, inhalants. Selective beta-2-adrenoreceptor agonists.

ATC Code: R03AC02

Salbutamol is a selective beta-2-adrenoceptor agonist. At therapeutic doses it acts on the beta-2-adrenoceptors of bronchial muscle providing short acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

Special Patient Populations

Reports from paediatric clinical studies conducted at the recommended dose in patients < 4 years with bronchospasm associated with reversible obstructive airways disease, have shown that PROVENTIL has a safety profile comparable to that in children ≥ 4 years, adolescents and adults.

5.2 Pharmacokinetic properties

Absorption

After administration by the inhaled route between 10 and 20 % of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The

fraction deposited in the airways is absorbed into the pulmonary tissues and circulation but is not metabolised by the lung. On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged active and as the phenolic sulphate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first pass metabolism to the phenolic sulphate.

Distribution

Salbutamol is bound to plasma proteins to the extent of 10 %.

Biotransformation

Salbutamol is cleared partly renally as unchanged active, and partly by hepatic metabolism to the inactive 4'-O-sulphate (phenolic sulphate) which is also excreted primarily in the urine.

The half-life ranges from 0,5 to 4 hours.

Elimination

Both unchanged active and conjugate are excreted primarily in the urine. The faeces are a minor route of excretion. Most of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours.

5.3 Preclinical safety data

In common with other potent selective β_2-agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9,3 % of foetuses were found to have cleft palate at 2,5mg/kg dose. In rats, treatment at the levels of 0,5, 2,32, 10,75 and 50 mg/kg/day orally throughout pregnancy resulted in no significant foetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. Reproductive studies in the rabbit at doses of 50 mg/kg/day orally (i.e. much higher than the normal human dose) have shown foetuses with treatment related changes; these included open eyelids (ablepharia), secondary palate clefts (palatoschisis), changes in ossification of the frontal bones of the cranium (cranioschisis) and limb flexure.

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post-partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofoetal development, litter size, birth weight or growth rate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dehydrated alcohol, HFA-134a, Oleic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Replace the mouthpiece cover firmly and snap it into position.

Store at or below 25 °C.

Do not freeze.

Protect from frost and direct sunlight.

The canister is pressurised and should not be punctured or burnt even if it seems empty.

6.5 Nature and contents of container

PROVENTIL is a metered aerosol comprising an aluminium canister, fitted with a metering valve, delivering salbutamol sulphate equivalent to 100 µg salbutamol per inhalation with a specially designed actuator with dust cap. Each canister delivers 200 puffs.

This is then packed inside a carton containing a leaflet.

6.6 Special precautions for disposal and other handling

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

52/10.2.1/0726

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 March 2022

10 DATE OF REVISION OF THE TEXT

26 March 2021