PROFESSIONAL INFORMATION AZMALER

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

AZMALER HFA metered dose inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains salbutamol sulphate equivalent to 100 µg salbutamol.

Contains ethanol (7,498 % *m/v)*: 4.,329 mg in each puff

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

An aluminium canister containing a milky white coloured suspension of salbutamol sulphate with a propellant.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZMALER is indicated for the relief of bronchospasm in all types of bronchial asthma, chronic bronchitis and emphysema.

4.2 Posology and method of administration

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

One (1) or two (2) inhalations, repeated every 4 hours if required. The bronchodilator effect of each administration of AZMALER lasts for at least 4 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 3 hours.

AZMALER 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.

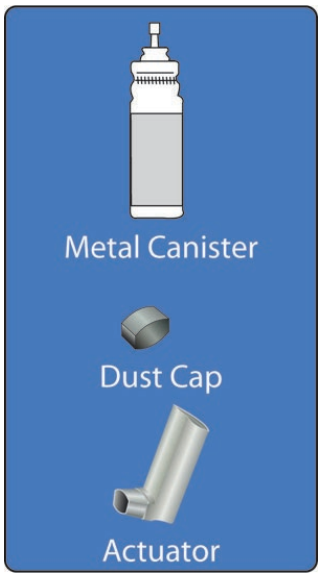
Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as the condition is potentially life-threatening. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and peak expiratory flow (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 or oral corticosteroid therapy.

Failure to respond promptly or fully to rescue medicine, such as AZMALER, signals a need for urgent medical advice and treatment.

Method of administration

AZMALER is administered by the inhaled route only, to be breathed in through the mouth.
Shake well before use.

Parts of the inhaler:



Testing your inhaler:

Before using the inhaler for the first time, remove the dust cap and shake the inhaler well. To test whether the inhaler is in working order, release 2 puffs into the air. If you did not use your inhaler for a few days, test the inhaler by shaking it well and releasing 1 puff into the air before using.

Directions for use for the patient:

Study the directions for use carefully before using the inhaler.

1. Shake well:

Remove the dust cap and ensure that the mouthpiece is clean on the inside and outside. Shake the inhaler before each use.

2. Exhale gently:

Holding the inhaler away from the mouth, breathe out gently (but not fully).

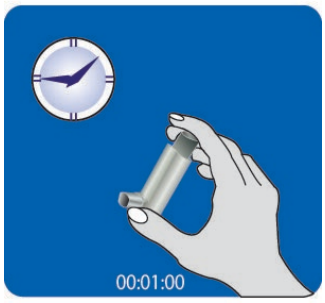
3. Press:

Hold the inhaler between the finger(s) and thumb, place the thumb under the mouthpiece, to support the base. Place the mouthpiece in the mouth, between the teeth, and close the lips around it (make sure not to bite the mouthpiece). After starting to breathe in slowly and deeply through the mouth, press the metal canister down firmly to release the suspension, and continue to breathe in.

4. Hold breath for 10 seconds:

The patient should remove the inhaler from the mouth and continue to hold his/her breath for 10 seconds, or as long as it is comfortable, then breathe out slowly.

5. Second inhalation (if required) – Wait 1 minute:

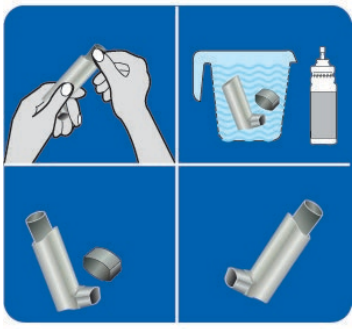


If the patient is to take a second inhalation, he/she should wait for at least one minute before repeating steps 2, 3 and 4. Replace the dust cap on the mouthpiece after use.

NOTE:

Do not rush steps 3 and 4. It is essential that the patient breathe in as slowly as possible when using the inhaler. The patient should check the technique in front of a mirror from time to time. If he/she sees a white mist during the inhalation, he/she may not have closed their lips properly around the mouthpiece, or the patient may not be breathing in as he/she press the canister. This indicates failure of technique. If this happens, the patient must repeat the procedure from step 2 carefully. The patient should consult a healthcare provider if he/she is having any difficulties with the technique.

Directions for cleaning:



It is very important that the actuator (plastic casing) and mouthpiece are cleaned regularly to prevent the build-up of spare suspension. Remove the metal canister and wash the plastic mouthpiece in warm water at least twice a week. Wipe the plastic casing and mouthpiece with a damp cloth. Leave the plastic casing to dry in a warm place overnight. Avoid excessive heat. Replace the metal canister and dust cap. No harm will come from washing the mouthpiece every day. For further assistance or information, the patient should consult a healthcare provider.

4.3 Contraindications

- Patients with a history of sensitivity to salbutamol sulphate or to any of the inactive ingredients of AZMALER (see section 6.1).
- Management of premature labour.
- Threatened abortion.
- Combination with propranolol and other beta-adrenoceptor blocking medicines, as these medicines antagonise the effects of salbutamol, as in AZMALER, and should not be prescribed together (see section 4.5).
- Patients receiving mono-amine oxidase inhibitors, or within 14 days after termination of such therapy.
- Pregnancy and lactation, as adequate and well-controlled studies have not been done (see section 4.6)

4.4 Special warnings and precautions for use

AZMALER should be administered with caution to patients with hyperthyroidism, as risk for cardiovascular effects may be increased. AZMALER should be administered with caution to patients

with cardiovascular disorders (especially ischaemic heart disease, angina, tachycardia, dysrhythmias (such as long QT syndrome) and hypertension).

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 high dose inhaled or oral corticosteroid therapy. With this primary background corticosteroid treatment, AZMALER provides essential rescue medication for a severe asthmatic in treating acute exacerbations. Failure to respond promptly or fully to such rescue medication signals a need for urgent medical advice and treatment.

Patients with cardiovascular disorders who are receiving AZMALER 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. The risk versus benefit should be considered when prescribing AZMALER to patients suffering from cardiac dysrhythmias, coronary insufficiency, hypertension or ischaemic heart disease.

AZMALER and beta-blocking medicines, such as propranolol, should not be used together. Beta-blockers are contraindicated in asthma.

AZMALER should be administered with caution to patients known to have received other sympathomimetic medicine.

Beta$_2$ antagonists such as salbutamol are not appropriate for use alone in the treatment of more than mild asthma.

Increasing use of AZMALER may be indicative of worsening asthma. Under such conditions, a patient's therapy plan may require reassessment and concurrent glucocorticosteroid therapy should be considered. Sudden and progressive deterioration in asthma control is potentially life-threatening. In patients considered at risk, daily peak flow monitoring may be instituted.

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.

Patients should be advised to seek medical advice if a previous effective dose of AZMALER fails to relieve bronchospasm for a minimum of 3 hours.

Potentially serious hypokalaemia may result from AZMALER therapy (see section 4.8). Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and concurrent treatment with medicines causing hypokalaemia, such as diuretics, corticosteroids and xanthine derivatives. Monitoring of serum potassium levels is recommended in such situations.

Cardiac dysrhythmias may occur with overdosage. This risk is further increased if administered concurrently with other medicines that cause hypokalaemia and cardiac dysrhythmias, or in the presence of acidosis and hypoxia. The maximum dose should not be exceeded.

The patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of AZMALER to the lungs (see section

4.2). Patients should be warned that they may experience a different taste upon inhalation compared to their previous inhaler.

AZMALER may cause a fine tremor of skeletal muscle, usually the hands are most obviously affected (see section 4.8). This effect is dose-related.

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing (see section 4.8). This should be treated immediately with an alternative presentation of salbutamol or a different fast-acting inhaled bronchodilator. In this instance, AZMALER should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Regular inhalation of AZMALER**,** although it continues to produce bronchodilatation and increases airway hyperresponsiveness, may reduce the protective effect against bronchoconstriction provoked by stimuli such as bradykinin, methacholine, or allergen.

AZMALER should be given with caution in patients with diabetes mellitus (especially on intravenous use) due to the effects on blood glucose levels. Blood glucose should be monitored since ketoacidosis has been reported.

AZMALER contains a small amount of alcohol (ethanol). This medicine contains 4,329 mg of alcohol (ethanol) in each puff of this inhaler. The amount in each puff of this medicine is equivalent to less than 0,108 ml of beer or 0,433 ml wine.

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

Although no geriatric specific problems have been reported to date, older patients may be more sensitive to the side effects of AZMALER.

4.5 Interaction with other medicines and other forms of interaction

Halogenated anaesthetics:

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

Cardiac glycosides, quinidine or tricyclic antidepressants:

An increased risk of dysrhythmias may occur if AZMALER is used concomitantly with cardiac glycosides, quinidine or tricyclic antidepressants.

Monoamine oxidase inhibitors:

Sympathomimetics such as AZMALER should not be used by patients receiving monoamine oxidase inhibitors or within 14 days of termination of monoamine oxidase inhibitor therapy.

Beta-blocking medicines:

AZMALER and non-selective beta-blocking medicines, such as propranolol, should not be used together as it opposes the bronchodilator effects of AZMALER and may cause serious bronchoconstriction, even if given as eye drops (see section 4.3).

Corticosteroids, diuretics and xanthine derivatives:

AZMALER in combination with corticosteroids, diuretics and xanthine derivatives (e.g. theophylline) increases the risk of hypokalaemia (see section 4.4). Monitoring of serum potassium concentration is recommended in severe asthma, where such combinations are common.

AZMALER should be used 5 minutes prior to the administration of adrenocorticoid or ipratropium inhalations, unless otherwise directed by a medical practitioner.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established (see section 4.3). 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

AZMALER is not likely to affect the ability to drive a vehicle or operate machinery. However, patients should take special care when performing tasks that require their attention, until they know how they will react to **AZMALER**.

4.8 Undesirable effects

Table 1: Tabulated list of adverse reactions		
System Organ Class	**Adverse reactions**	**Frequency**
Immune system disorders	Anaphylactoid reactions (hypersensitivity reactions, including angioedema, urticaria, bronchospasm, hypotension and collapse)	*Less frequent*
Metabolism and nutrition disorders	Hypokalaemia potentially serious hypokalaemia may result from beta$_2$ agonist therapy (see section 4.4).	*Less frequent*
	Altered metabolism, reduced appetite, sweating	*Frequency unknown*
Nervous system disorders	Tremor of skeletal muscle (particularly the hands), headache	*Frequent*
	Hyperactivity	*Less frequent*
	Agitation, nervousness, fatigue, fear, restlessness, dizziness, confusion, insomnia*	*Frequency unknown*
Cardiac disorders	Tachycardia	*Frequent*
	Palpitations, Cardiac dysrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles)	*Less frequent*
	Myocardial ischaemia* (see section 4.4)	*Frequency unknown*
Vascular disorders	Peripheral vasodilatation	*Less frequent*

Respiratory, thoracic and mediastinal disorders	Paradoxical bronchospasm (see section 4.4)	*Less frequent*
	Dyspnoea, coughing	*Frequency unknown*
Gastro-intestinal disorders	Dryness, Mouth and throat irritation	*Less frequent*
	Loss of appetite, nausea, vomiting*,	*Frequency unknown*
Musculoskeletal and connective tissue disorders	Muscle cramps	*Less frequent*

*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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Signs and Symptoms

The most frequent signs and symptoms of overdosage with AZMALER are transient beta agonist pharmacologically mediated effects, including tachycardia, tremor, hyperactivity, metabolic effects (including hypokalaemia, see section 4.4 and 4.8), agitation, hallucinations and irritability.

Hypokalaemia may also occur and hence, 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

Discontinuation of AZMALER treatment should be considered in the treatment of overdosage. Appropriate symptomatic therapy, such as cardio selective beta-blocking medicines in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations), but should be used with caution in patients with a history of bronchospasm. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 10.2.1 Medicines acting on respiratory system. Bronchodilators. Inhalants.

ATC code: R03AC02

Salbutamol is a selective β_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 AZMALER has a safety profile comparable to that in children ≥ 4 years, adolescents and adults.

5.2 Pharmacokinetic properties

Absorption

Approximately 10 – 20 % of the dose reaches the lower airways after administration by the inhaled route. 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.

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

Distribution

Protein binding is negligible (10 %).

Salbutamol is metabolised mainly by sulphation and excreted in the urine, both as free drug and conjugated metabolite (phenolic sulphate).

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 by inhalation is excreted within 72 hours.

5.3 Preclinical safety data

In common with other potent selective β2-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

Ethanol (7,5 % *m/v*)

HFA-134a propellant gas

Oleic acid

6.2 Incompatibilities

None

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 30 °C.

Protect from frost and direct sunlight.

The canister should not be damaged, punctured or burnt, even when apparently empty.

Do not use after the expiry date stated on the label.

Do not dispose of unused medicine in drains or sewerage systems e.g.toilets.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

AZMALER is a metered dose inhaler comprising of an aluminium canister with a metered valve contained within an actuator. The actuator has a blue body and a light blue cap with “SQUARE” logo embossed on the cap. Each canister provides 200 inhalations.

6.6 Special precautions for disposal and other handling

Not applicable

7. HOLDER OF ~~THE~~ CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia, 1827

South Africa

8. REGISTRATION NUMBER

49/10.2.1/0135

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 January 2020

10. DATE OF REVISION OF THE TEXT

20 March 2025