AUSTRALIAN PRODUCT INFORMATION –

AIROMIR® AUTOHALER® (SALBUTAMOL SULFATE) METERED DOSE AEROSOL AND AIROMIR® INHALER (SALBUTAMOL SULFATE) METERED DOSE INHALATION AEROSOL

1 NAME OF THE MEDICINE

Salbutamol sulfate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Airomir contains microcrystalline salbutamol sulfate suspended in norflurane (1,1,1,2-tetrafluoroethane), a non-CFC propellant which does not deplete ozone from the atmosphere. Each metered dose delivers an amount of salbutamol sulfate equivalent to 100 µg of salbutamol. Airomir also contains oleic acid and ethanol. Excipients with known effects: alcohol (ethanol) 21 % v/v.

Airomir Autohaler is a breath actuated inhaler which automatically releases the dose of medication during inhalation through the mouthpiece and overcomes the need for patients to coordinate actuation with inspiration. Airomir Inhaler is a conventional press and breathe metered dose inhaler. There are no differences in formulation between the Autohaler and Inhaler products.

3 PHARMACEUTICAL FORM

Airomir Autohaler is a metered dose inhalation aerosol. Each unit delivers salbutamol sulfate equivalent to salbutamol 100 µg per metered dose.

Airomir Inhaler is a metered dose inhalation aerosol. Each unit delivers salbutamol sulfate equivalent to salbutamol 100 µg per metered dose.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma or in other situations known to induce bronchospasm.

The Autohaler device is of value in patients who are unable to achieve coordination using metered dose inhalers. No advantage over other metered dose inhalers is claimed for patients who do not have difficulty with coordination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Airomir is therapeutically equivalent to CFC salbutamol pressurised inhalers. Patients can be switched from CFC salbutamol pressurised inhaler to Airomir at the same dosage without loss of therapeutic effect.

Adults: 1 to 2 inhalations every four hours as necessary to obtain relief of bronchospasm. If previously effective doses do not provide relief, other treatment should be instituted promptly.

Children: As for adults.

Elderly: Dosage should at first be lower than for younger adults but may be increased gradually to the usual adult level if necessary.

Impaired Hepatic or Renal Function: Since salbutamol is extensively metabolised in the liver, any liver function impairment may necessitate a reduction in dosage. Similarly impairment in renal function may also require a dosage reduction since a large proportion of inhaled salbutamol is excreted in the urine.

Note: An increase in the use of salbutamol required to control asthma symptoms may indicate deterioration in the patient's asthma. If so, a re-assessment of the patient's treatment regimen may be required. Should inhalation therapy fail to relieve asthma symptoms, other treatments should be implemented immediately in order to avoid a potential medical emergency.

Patients who are unable to successfully coordinate actuation of their metered dose inhaler with inhalation (including virtually all children) will benefit from substituting their conventional press and breathe metered dose inhaler with the Autohaler or using a spacer device.

Where a spacer is considered necessary the AeroChamberPlus™ has been shown to be compatible with Airomir Inhaler. Use of an AeroChamberPlus™ spacer with Airomir Inhaler reduces the amount of drug deposited in the oropharynx without affecting drug deposition in the lungs. A change in the make of spacer or a change in the formulation of the drug used may be associated with alterations in the amount of drug delivered to the lungs, the clinical significance of which is uncertain. In these situations the patient should be monitored for any loss of asthma control. For instructions on the proper use of spacers refer to *Instructions for Prescribers* in section *4.4: SPECIAL WARNINGS AND PRECAUTIONS FIR USE*.

4.3 CONTRAINDICATIONS

Known hypersensitivity to salbutamol sulfate or other sympathomimetics, or to any other ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The results of animal experiments indicate that high dosages of some sympathomimetic agents may cause cardionecrosis. In view of this evidence the possibility of cardiac lesions occurring in humans cannot be excluded. The administration of Airomir by inhalation results in low salbutamol plasma concentrations so the risk of this effect is correspondingly reduced.

Airomir contains norflurane, a non-CFC propellant. In animal studies norflurane has been shown to have no significant pharmacological effects, except at very high exposure concentrations when necrosis and a relatively weak cardiac sensitising effect were found. The potency of the cardiac sensitisation of norflurane was less than that of trichlorofluoromethane (CFC-11). Large doses of CFC propellants have been reported in animals to produce cardiac arrhythmias and sensitise their hearts to adrenaline-induced arrhythmias. Data in humans are limited. Inhalations of the maximum recommended dose of Airomir produce low concentrations of propellant in the plasma.

Excessive use of Airomir is potentially hazardous, both from the propellant as well as from the possibility of overdosage with the active medication. Patients should therefore be warned not to exceed the recommended dose. Additionally, overuse of inhaled salbutamol may cause a worsening of hypoxaemia.

Use with caution in the following circumstances

Cardiac disease: When Airomir is used at the recommended doses the blood concentrations of salbutamol are usually too low to produce a significant systemic effect. However, prescribers should be aware of the possibility of the unwanted stimulation of cardiac adrenergic receptors and care should be taken in patients with hypertension, coronary artery disease and myocardial insufficiency.

Cardiac arrhythmias: Salbutamol may predispose to the occurrence of cardiac arrhythmias or may exacerbate existing arrhythmias. This effect may be due to a direct chronotropic effect and to the reduction of serum potassium. Care should be taken when using salbutamol in patients who have arrhythmias or who are receiving drugs such as digitalis or diuretics which do not spare potassium. Caution should also be taken when using salbutamol with anaesthetic agents which sensitise the myocardium to sympathomimetic agents.

Hypokalaemia: Potentially serious hypokalaemia may result from β_2-agonist therapy mainly from parenteral and nebulised administration. This effect may be potentiated in patients with hypoxia or those treated concomitantly with theophylline, steroids or diuretics. Caution should be taken in these patients.

Diabetes mellitus: When given by inhalation at recommended doses salbutamol should have little or no hyperglycaemic effect; however care should be taken initially in using salbutamol in diabetics.

Hyperthyroidism: Salbutamol should be used with caution in patients with thyrotoxicosis.

Lactic Acidosis: Lactic acidosis has been reported very rarely in association with high therapeutic doses of intravenous and nebulised short-acting β-agonist therapy, mainly in patients treated for an acute asthma exacerbation (see section 4.8 (UNDESIRABLE EFFECTS)). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting β-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Instructions for Prescribers

Asthma management should be adjusted according to individual need based on lung function and clinical monitoring. Increasing use of β_2-agonist may be a sign of worsening asthma. Under these conditions a re-assessment of the patients' therapy plan may be required and concomitant glucocorticosteroid therapy should be considered. This is important since poor asthma control can result in potential life-threatening situations and increased use of β_2-agonists may cause deterioration of asthma control.

Patients should be informed of the importance of correct inhaler technique (either breath-actuated inhaler or conventional inhaler). To ensure correct use of Airomir Autohaler and Inhaler refer patients to the Patient Instruction Leaflet accompanying each unit. If necessary, correct technique should be demonstrated to patients, particularly first-time users and those with poor coordination.

It is advisable to check the patient's compliance and inhaler technique before increasing the dose. Patients should be advised to seek medical advice when the bronchodilator effect is reduced and not to increase the dose over that prescribed. Patients should be warned that excessive use of inhaled salbutamol may result in significant adverse effects and/or loss of asthma control. Patients should also be advised not to use other asthma medications at the same time as Airomir unless on medical advice.

If using a spacer, the patient should be instructed to breathe in and out several times after each release into the spacer. Any delay should be kept to a minimum.

Because of electrostatic charge, leading to adherence of drug particles to the wall of the spacer, spacers should be washed in warm water with kitchen detergent and left to drain dry (without rinsing) before initial use and at least monthly thereafter. A cloth should not be used to dry the spacer, as this can produce more static electricity.

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Beta-adrenergic blockers specifically antagonise the action of salbutamol and other sympathomimetics on the airways. Use of these drugs is also generally contraindicated in asthma because they tend to increase airways resistance.

Concomitant use of theophylline (and other xanthine derivatives), steroids and diuretics may potentiate salbutamol-induced hypokalaemia in acute severe asthma. In those circumstances and in other situations (such as hypoxia) likely to potentiate salbutamol-induced hypokalaemia, serum potassium levels should be monitored.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy – Pregnancy Category B1

There is no experience of Airomir in pregnant women. An inhalation reproductive study with Airomir Inhaler in rats did not exhibit any teratogenic effects. Salbutamol does however cross the placenta. In some rodent studies large doses of salbutamol have been shown to be teratogenic although the relevance of these findings to humans is unknown. Safe use in pregnancy has not been established; therefore Airomir should not be used during pregnancy unless the benefits outweigh the potential risk.

Use in lactation

There is no experience of Airomir in lactating women. It is unknown whether salbutamol is excreted in breast milk. Airomir should therefore not be used in women who are breast-feeding unless the benefits of therapy outweigh the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse effects of salbutamol sulfate are generally extensions of its sympathomimetic actions. Their rates of occurrence are dependent on route of administration as well as dose.

Clinical Trial Data

In a 12-week, double-blind, double-dummy study which compared Airomir, CFC salbutamol pressurised inhaler and a placebo (norflurane) inhaler in 565 asthmatic patients, the adverse events reported as probably or possibly related to study treatment, given as 2 puffs four times daily for 12 weeks, and with an incidence of 1% or greater are presented in the table below. A dash represents an incidence of less than 1%.

Adverse event	Airomir N=193	CFC-salbutamol N=186	Placebo (norflurane) N=186
Application site disorders:			
Inhalation site sensation	5%	6%	2%
Inhalation taste sensation	4%	3%	3%
Cough	3%	2%	2%
Increased asthma symptoms	2%	1%	8%
Autonomic Nervous system disorders:			
Flushing	-	1%	-
Body as a whole – general disorders:			
Headache	6%	8%	5%
Central & Peripheral nervous system disorders:			
Tremor	7%	5%	2%
Dizziness	4%	5%	3%
Hyperkinesia	1%	-	-
Gastro-intestinal system disorders:			
Nausea	3%	3%	2%
Flatulence	2%	-	-
Dyspepsia	1%	-	-
Vomiting	1%	-	-
Heart rate and rhythm disorders:			
Tachycardia	5%	2%	-
Palpitation	1%	2%	2%
Musculo-skeletal system disorders:			
Myalgia	1%	-	-
Psychiatric disorders:			
Nervousness	7%	6%	2%
Somnolence	2%	1%	-

Adverse event	Airomir N=193	CFC-salbutamol N=186	Placebo (norflurane) N=186
Insomnia	1%	1%	1%
Respiratory disorders:			
Acute asthma episode	4%	4%	6%
Increased asthma symptoms	2%	2%	6%
Pharyngitis	2%	-	3%
Respiratory disorder	-	-	1%
Skin and appendages disorders:			
Rash	-	1%	-

Post Marketing Data

In a 3-month post marketing surveillance study, 5,402 patients receiving CFC-salbutamol pressurised inhaler were switched to Airomir. The reported adverse reactions which were considered to be probably or possible related to treatment are presented below in the following frequency categories within body system:

very common	≥ 10%
common	≥1% and <10%
uncommon	≥0.1% and <1%
rare	≥0.01% and <0.1%
very rare	<0.01%

Central & peripheral nervous system disorders: Uncommon: headache, tremor, dizziness. Rare: paraesthesia, leg cramps, dysphonia.

Respiratory system disorders: Uncommon: pharyngitis, bronchospasm, increased asthma symptoms, coughing. Rare: dyspnoea, acute asthma episode, upper respiratory tract infection, tracheitis, bronchitis, rhinitis.

Gastro-intestinal system disorders: Uncommon: nausea. Rare: dry mouth, vomiting, stomatitis, abdominal pain, dyspepsia, tongue discolouration, anorexia.

Body as a whole - general disorders: Uncommon: chest pain. Rare: inadequate response, decrease therapeutic response, rigours, malaise, fever, oedema.

Heart rate and rhythm disorders: Uncommon: palpitation

Application site disorders: Rare: inhalation site sensation, inhalation taste sensation, cough, increased asthma symptom, application site reaction, dysphonia.

Musculo-skeletal disorders: Rare: myalgia, arthralgia

Skin & appendages disorders: Rare: pruritus, rash, skin disorder

Psychiatric disorders: Rare: nervousness, depression, paroniria, agitation, emotional lability (mood swing), abnormal thinking, euphoria.

Resistance mechanism disorders: Rare: infection

Myo endo pericardial & valve disorders: Rare: angina pectoris

Platelet, bleeding & clotting disorders: Rare: epistaxis

Reproductive disorders female: Rare: breast pain

Autonomic nervous system disorders: Rare: flushing, saliva altered

Special senses other, disorders: Rare: taste perversion

Lactic acidosis has been reported very rarely in patients receiving intravenous and nebulised salbutamol therapy for the treatment of acute asthma exacerbation.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms: The symptoms of overdosage are the same as the adverse effects of salbutamol, the most significant being tachycardia and/or muscle tremor. With the metered dose inhalers some toxicity may be due to the aerosol propellant.

Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting β-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: Monitor biochemical abnormalities particularly hypokalaemia. Hypokalaemia should be treated with potassium replacement if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Salbutamol is a direct acting sympathomimetic agent which mainly has β-adrenergic activity and a high degree of selectivity for β2-adrenoceptors. As a predominantly β2-adrenoceptor stimulant, salbutamol's bronchodilating action is relatively more prominent than its cardiac effects. Salbutamol is chemically related to adrenaline, noradrenaline and isoprenaline but it has a longer duration of action than these compounds. This is possibly due to its resistance to catechol-O-methyl transferase (COMT), an inactivating enzyme which occurs in association with sympathetic receptors.

The β-sympathetic agonists act primarily through activation of adenylate cyclase which catalyses the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Cyclic AMP mediates the effects of the β-agonists on sympathetic receptors. Increased cAMP concentrations also inhibit release of mediators of immediate hypersensitivity from mast cells, as well as relaxing bronchial smooth muscle. Stimulation of β2-receptors causes relaxation of the smooth muscle of the bronchi, uterus and blood vessels, decreases the duration of skeletal muscle contraction and increases glycolysis and glycogenolysis.

Airomir contains the sulfate salt of salbutamol, which has been shown to be clinically equivalent to salbutamol base when administered in equivalent doses by metered-dose inhaler.

Clinical trials

In a 12-week, randomised, double-blind, double-dummy, active- and placebo-controlled study, 565 adult patients with asthma were evaluated for the bronchodilator efficacy of Airomir (193 patients) in comparison to a CFC salbutamol pressurised inhaler (186 patients). Serial FEV1 (Forced Expiratory Volume) measurements demonstrated that two inhalations of Airomir produced significantly greater improvement in pulmonary function than placebo and produced outcomes which were clinically comparable to a CFC salbutamol pressurised inhaler. The mean time to onset of a 15% increase in FEV1 was 6 minutes and the mean time to peak effect was 50 minutes. The mean duration of effect as measured by a 15% increase in FEV1 was 3 hours. No statistically significant or clinical meaningful differences were seen in the safety parameters, including the overall adverse event rates, heart rate, blood pressure, serum potassium or ECG interval changes between Airomir and CFC-salbutamol pressurised inhaler.

In a 4-week, randomised, open-label, parallel study, 63 children with asthma were evaluated for the bronchodilator efficacy of Airomir (33 patients) in comparison to CFC-salbutamol pressurised inhaler (30 patients). Serial FEV1 measurements demonstrated that two inhalations of Airomir produced a clinically comparable bronchodilator effect compared to CFC salbutamol pressurised inhaler. Analysis of all safety parameters revealed that Airomir has a similar safety profile to CFC salbutamol pressurised inhaler.

In the 12-month studies there were 337 adult patients assigned to Airomir and 132 to CFC salbutamol pressurised inhaler (2 puffs twice daily and prn). There were no significant differences between Airomir and CFC salbutamol pressurised inhaler treatment groups for total reported adverse events, clinically meaningful changes in laboratory tests or physical examinations (changes in pulse rate, blood pressure, serum potassium and ECG intervals). Baseline lung function, assessed as the FEV1 obtained at visits prior to dosing did not change in either group over the one year treatment periods. No significant differences in bronchodilator efficacy were found between Airomir and CFC salbutamol pressurised inhaler throughout the studies.

Forty eight asthmatic patients (adults) completed 16 puffs cumulative dose, cross-over studies comparing Airomir to CFC salbutamol pressurised inhaler. The efficacy equivalence between Airomir and CFC salbutamol pressurised inhaler was confirmed by the comparable FEV1 responses, while equivalence in safety was confirmed by comparable falls in serum potassium, changes in vital signs (heart rate, blood pressure) and ECG intervals.

5.2 PHARMACOKINETIC PROPERTIES

When Airomir is inhaled at the recommended doses salbutamol is delivered topically to the lung such that its effects are apparent within minutes. Because of the small amount of drug administered and due to its gradual absorption from bronchi, plasma levels of salbutamol are extremely low after oral inhalation. Salbutamol is not metabolised in the lung.

Swallowed salbutamol is readily absorbed from the gastrointestinal tract and undergoes extensive pre-systemic metabolism by conjugation to a 4'-0-sulfate ester in the gastrointestinal tract and the liver. Its systemic bioavailability is about 50 %.

Salbutamol and its metabolites are rapidly excreted in the urine and faeces. About 80 % of a single dose is recovered in urine within 24 hours. Following oral inhalation unchanged salbutamol accounts for approximately 30 % of the excreted dose in the urine. The elimination half-life of salbutamol is about 3-6 hours. Salbutamol is not significantly bound in plasma. The elimination of salbutamol may be altered by changes to hepatic or renal function; consequently dosage reduction may be required in patients with hepatic or renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

There are no reasons to consider norflurane as a potential mutagen, clastogen or carcinogen judging from in-vitro and in-vivo studies which include long-term administration by inhalation in rodents.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Airomir should be stored below 30 °C, away from direct heat or sunlight. As the canister is pressurised, no attempt should be made to puncture it or dispose of it by burning.

6.5 NATURE AND CONTENTS OF CONTAINER

Airomir Autohaler and Airomir Inhaler* are each available in pack sizes of 100* and 200 doses. Each unit is supplied with an actuator.

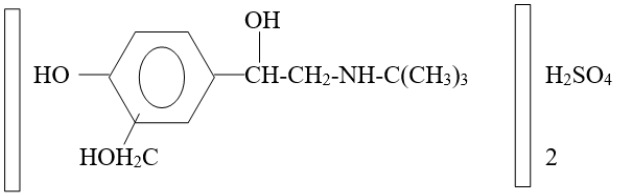
* Not currently marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy. [optional – use one of these statements only]

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl) ethanol sulfate.

Salbutamol sulfate is a white or almost white powder. It is soluble in water but is only slightly soluble in alcohol, chloroform and ether. 1.2 mg of salbutamol sulfate is equivalent to 1.0 mg of salbutamol base.

Molecular formula is $C_{13}H_{21}NO_3.½H_2SO_4$

CAS number: 51022-70-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S3) Pharmacist Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited

Level 10, 12 Help Street

Chatswood NSW 2067

Australia

Toll free: 1800 630 056

9 DATE OF FIRST APPROVAL

Airomir Autohaler: 6 January 1999

Airomir Inhaler: 19 August 1998

10 DATE OF REVISION

24 April 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Transfer of text from old PI format (without changes) (Nov 2019)
All	Reformatting of approved PI (Nov 2019)

Airomir and Autohaler are registered trademarks of 3M. Aerochamber Plus is a registered trademark of Trudell Medical international.