AUSTRALIAN PRODUCT INFORMATION – ARIDOL (MANNITOL) POWDER FOR INHALATION COMPOSITE PACK

1 NAME OF THE MEDICINE

Mannitol

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Mannitol is the only ingredient in the contents of Aridol hard gelatin capsules. Colouring agents are used on the cap and body of the 0 mg capsule, the caps of the 5, 10, 20 and 40 mg capsules (the bodies of the other capsules are clear). The colouring agents are titanium dioxide (0, 5, 10, 20 and 40 mg), yellow iron oxide (10 mg) and red iron oxide (20 and 40 mg). The delivered dose from each of the 5, 10, 20 and 40mg capsules is approximately 3, 8, 16 and 31mg, respectively.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Aridol is indicated for identifying bronchial hyperresponsiveness to assist in the diagnosis of asthma.

4.2 DOSE AND METHOD OF ADMINISTRATION

Aridol is supplied in kit form containing sufficient capsules to complete one complete challenge, and the inhalation device (Osmohaler™).

Prior to the challenge, spirometry should be performed and the reproducibility of the resting FEV_1 established.

The patient should be seated comfortably and encouraged to maintain good posture to assist the effective delivery of Aridol to the lungs. The test should proceed as follows:

1. Apply nose clip and subject should be directed to breathe through the mouth
2. Insert 0 mg capsule into inhalation device. Puncture capsule by depressing buttons on side of device slowly, and once only (a second puncture may fragment the capsules)
3. The patient should exhale completely, before inhaling from device in a controlled rapid deep inspiration
4. At the end of deep inspiration, start 60 second timer, subject should hold breath for 5 seconds and exhale through mouth before removal of nose clip
5. At the end of 60 seconds, measure the FEV_1 in duplicate (this becomes **baseline FEV_1**)
6. Insert 5 mg capsule into inhalation device, and proceed as above
7. Repeat steps 1 – 4 following the dose steps in Table 1 below until the patient has a positive response or 635mg has been administered.

Table 1: DOSE STEPS FOR ARIDOL CHALLENGE			
Dose #	**Dose mg**	**Cumulative Dose mg**	**Capsules per dose**
1	0	0	1
2	5	5	1
3	10	15	1
4	20	35	1
5	40	75	1
6	80	155	2 x 40 mg
7	160	315	4 x 40 mg
8	160	475	4 x 40 mg
9	160	635	4 x 40 mg

A positive response is achieved when the patient experiences either of the following:

15% fall in FEV_1 from baseline (0 mg dose)

or

10% incremental fall in FEV_1 between doses

Examples of positive tests:

1. FEV_1 fall following dose step 2: 3%
   FEV_1 fall following dose step 3: 8%
   FEV_1 fall following dose step 4: 16%
   - as the total fall is 16% (≥15%), the test is positive

2. FEV_1 fall following dose step 2: 3%
   FEV_1 fall following dose step 3: 14%
   - although the total fall is <15%, the incremental fall is 11% (≥10%) and the test is positive

Points to remember:

1. There should be minimal delay between FEV_1 measurement and the next dose so that the osmotic effect in the airway is cumulative.
2. At least 2 repeatable FEV_1 measures should be obtained after each dose.
3. The 80 and 160 mg doses are administered in multiples of 40 mg capsules (i.e., 2 x 40 mg and 4 x 40 mg, respectively). There is no interval between administering multiple capsules for these doses. One capsule should be followed immediately by the next until that total dose has been inhaled.
4. After inhalation of each dose, the capsule should be checked to ensure it is empty. A second inhalation from the same capsule may be required if the dose has not been entirely dispersed from the capsule.
5. The gelatin capsules may fragment when punctured. To minimise the possibility of this occurring, each capsule should not be punctured more than once.
6. A new inhalation device is to be used for each test which should not be cleaned during the test.

As with all challenge tests, most patients recover spontaneously. Those with a positive challenge result should receive a standard dose of a $beta_2$ agonist to expedite recovery. Following administration of a $beta_2$ agonist FEV_1 usually recovers within 10-20 minutes. Patients should be monitored until their FEV_1 is to within 5% of baseline levels.

4.3 CONTRAINDICATIONS

Known hypersensitivity to mannitol or any of the excipients.

Aridol should not be given to patients with conditions that may be compromised by induced bronchospasm or repeated blowing manoeuvres. These include: aortic or cerebral aneurysm, uncontrolled hypertension, myocardial infarction or a cerebral vascular accident in the previous six months.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Aridol is to be administered by inhalation only. The Aridol inhalation test should be conducted only under the supervision of a physician or other appropriate trained personnel thoroughly familiar with all aspects of bronchial provocation tests and the management of acute bronchospasm. Patients should not be left unattended during the procedure once the administration of Aridol has begun.

Medications to treat severe bronchospasm must be present in the testing area including bronchodilators and oxygen.

General precautions when conducting spirometry and bronchial provocation testing should be observed, including using caution in patients with the following: ventilatory impairment (resting FEV_1 of less than 70% of normal predicted values or an absolute value of 1.5L in adults); spirometry induced bronchoconstriction, haemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent eye surgery, unstable angina, inability to perform spirometry of acceptable quality or upper or lower respiratory tract infection in the previous 2 weeks.

If a patient has spirometry induced asthma or the FEV_1 fall following the 0 mg capsule is greater than 10%, a standard dose of bronchodilator should be given and the Aridol challenge discontinued.

Use in the elderly
Aridol has been given to a limited number of elderly patients

Paediatric use
The Aridol test should not be used in patients below 6 years of age due to their inability to produce acceptable quality spirometric measurements.

The pivotal trial enrolled 138 children (125 asthmatic and 13 non-asthmatic subjects). Also there have been a small number of other studies investigating the safety and efficacy of Aridol in children. It appears the sensitivity and specificity as well as adverse event profile is comparable with adults. The mean maximum fall in FEV_1 was approx 21% in children which was the same as in adults.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Regular use of inhaled corticosteroids reduces the airway sensitivity to Aridol and in many individuals, complete inhibition of the airway response occurs.

The following should be withheld before conducting an Aridol test as they may affect the results:

Medicines: Recommended periods for withholding medicines before the Aridol test are listed in Table 2 below.

Table 2: Recommended periods for withholding medicines before the Aridol test

Time to Withhold	Medication
6-8 hours	**INHALED NON-STEROIDAL ANTI-INFLAMMATORY AGENTS** e.g. sodium cromoglycate, nedocromil sodium
8 hours	**SHORT-ACTING BETA$_2$ AGONISTS** eg salbutamol, terbutaline
12 hours	**INHALED CORTICOSTEROIDS** e.g. beclomethasone dipropionate; budesonide; fluticasone propionate
12 hours	**IPRATROPIUM BROMIDE**
24 hours	**INHALED CORTICOSTEROIDS PLUS LONG-ACTING BETA$_2$ AGONISTS** eg fluticasone and salmeterol; budesonide and eformoterol
24 hours	**LONG-ACTING BETA$_2$ AGONISTS** e.g. salmeterol; eformoterol
24 hours	**THEOPHYLLINE**
72 hours	**TIOTROPIUM BROMIDE**
72 hours	**ANTIHISTAMINES** eg cetirizine, fexofenadine and loratadine
4 days	**LEUKOTRIENE-RECEPTOR ANTAGONISTS** e.g. montelukast sodium

Foods: Ingestion of significant quantities of coffee, tea, cola drinks, chocolate or other food containing caffeine may decrease bronchial responsiveness. These substances should be withheld on the day of the test.

Exercise: Vigorous exercise should not be performed prior to testing on the day of the test.

Smoking: Patients should refrain from smoking for at least 6 hours prior to testing.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
The effect of inhaled mannitol on fertility has not been investigated.

Use in pregnancy – Pregnancy Category B2
Animal reproduction studies have not been carried out with inhaled mannitol. However, studies with orally administered mannitol indicate no teratogenic effects in mice or rats, at doses of up to 1.6g/kg, or in hamsters at 1.2g/kg. The effects of a possible hyperresponsiveness reaction on the mother and/or the foetus are unknown and therefore Aridol should not be given to pregnant women.

Use in lactation
It is not known whether this drug is excreted in human milk. Many compounds are excreted in human milk, and therefore caution should be exercised when mannitol is administered to breastfeeding women.

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)

A positive result with Aridol may produce symptoms of bronchospasm such as chest tightness, cough or wheezing.

Most patients experience cough during the challenge; however, it is only occasional in the vast majority of patients (83%) experiencing cough. In the remainder, it is frequent enough to cause some delay in continuation of the challenge (16%) or discontinuation (1%). Pharyngolaryngeal pain, a commonly reported adverse event, may be reduced if the mouth is rinsed after the test.

Adverse events were monitored in the pivotal clinical trial from the beginning of the challenge to a week following the challenge day. Due to the short half-life of mannitol, the causal link would be expected to diminish over that time. Most adverse events were reported to be mild and transient. The following is a table of adverse events reported in the trial (compared to hypertonic saline) at an incidence of 1% or more.

Table 3: Adverse events reported in the pivotal clinical trial (compared to hypertonic saline) at an incidence of 1% or more

Adverse event	Mannitol (%)	Hypertonic saline (%)
Ophthalmic		
Eye pruritus	1.0	0.6
Gastrointestinal		
Nausea	4.3	3.0
Upper abdominal pain	1.9	1.4
Diarrhoea	1.3	0.6
Vomiting	1.3	0.9
Infections		
Nasopharyngitis	1.4	3.1
Upper respiratory tract infection	1.3	1.7
Musculosketal		
Back pain	1.0	0.6
Neuronal		
Headache	17.2	19.0
Dizziness	1.1	1.3
Respiratory		
Pharyngolaryngeal pain	5.1	3.0
Cough*	2.2	2.4
Rhinorrhoea	2.1	1.4
Throat irritation	1.3	0.2
Asthma aggravated	1.1	1.3
Chest tightness	1.0	0.6
Dyspnoea	1.0	0.8
Sneezing	0.8	1.1
Nasal congestion	0.6	1.1
Wheezing	0.5	1.1

Adverse event	Mannitol (%)	Hypertonic saline (%)
General		
Fatigue	1.1	0.5
* Cough was defined as an adverse event during the challenge only if it led to discontinuation of the challenge		

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

Susceptible persons may suffer a hyperresponsiveness reaction from an overdose. The reaction can be treated with a bronchodilator. There is some experience with Aridol in clinical studies where patients experienced a 15% fall and inhaled a further dose. These studies used 20-25% as the target FEV_1 fall. The maximum fall measured was 50.2%. If excessive bronchoconstriction occurs, a $beta_2$ agonist should be given, and oxygen if necessary.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
When inhaled, mannitol induces an increase in osmolarity in the airways similar to other bronchial provocation tests such as hypertonic saline, exercise and the hyperpnea of dry air. The increase in osmolarity is associated with the release of a wide variety of mediators of bronchoconstriction from inflammatory cells within the airways. These mediators then act via specific receptors on bronchial smooth muscle to cause contraction and the airways to narrow. The airway response is most pronounced (hyperresponsiveness) in patients with asthma and exercise-induced asthma. The airway response to Aridol is measured using the forced expiratory volume in one second (FEV_1). The sensitivity to mannitol is reported as the delivered dose of mannitol to cause a 15% reduction in FEV_1.

The involvement of airway inflammation has been demonstrated by a reduction in the sensitivity to inhaled mannitol following treatment with inhaled corticosteroids. The involvement of mediators has been demonstrated by the reduction in response to mannitol after specific antagonists. The histamine antagonist, fexofenadine, has been shown to reduce the airway sensitivity to mannitol. The time to recover to baseline FEV_1 is reduced after treatment with the cysteinyl leukotriene receptor antagonist, montelukast although there was no effect observed on the sensitivity to mannitol. Nedocromil sodium, a drug that inhibits mast cell mediator release as well as reducing sensory nerve activation, has been shown to reduce sensitivity to mannitol and in some cases the airway response to mannitol was inhibited.

Clinical trials
The pivotal trial in the clinical development program was a controlled, randomised, crossover study which compared Aridol with hypertonic (4.5%) saline in identifying bronchial hyperresponsiveness. The study enrolled 646 subjects of whom 592 completed both arms of the trial. The study enrolled both asthmatic (n=551) and non-asthmatic (n=95) subjects aged 6 to 83 years.

The mannitol challenge test was positive (15% fall in FEV_1) in 296 subjects at a mean dose of 186 mg. In non-asthmatic subjects the mean maximum fall in FEV_1 was 4.95% +/- 4.7%. Compared to the hypertonic saline challenge, the mannitol challenge had a sensitivity of 81% and a specificity of 87%. The mean maximum FEV_1 fall (±SD) for the two challenges was comparable: 21.02% (± 5.7) for mannitol and 21.34% (± 5.9) for hypertonic saline.

Following completion of the two challenge tests, a respiratory physician assessed the data and categorised the subjects as being asthmatic or non-asthmatic on the basis of their medical history, history of respiratory symptoms, and the results of the hypertonic saline challenge. Compared to this clinical diagnosis, the mannitol challenge had a sensitivity of 60%, and a specificity of 95%. The hypertonic saline challenge had a sensitivity of 65% and a specificity of 95%. The positive and negative predictive values for the mannitol challenge were 98.3% and 33.9% respectively, resulting in positive and negative likelihood ratios of 12.55 and 0.42 respectively.

Of the 196 subjects classified as asthmatic by the respiratory physician, but having a negative mannitol challenge, 159 (81%) were taking glucocorticosteroids, 72.7% had no wheezing in the week prior to the challenge and 65.6% had not used a reliever puffer more than once in the previous week. It is important to consider current glucocorticosteroid therapy when interpreting indirect challenge test results.

5.2 PHARMACOKINETIC PROPERTIES

There are no pharmacokinetic data available for mannitol following inhalation using a dry powder inhaler although limited animal data on mannitol solution indicates an absorption half-life of approximately 0.2-1 hours. Following absorption, the pharmacokinetic profile of inhaled mannitol can be expected to follow that of intravenous administered mannitol.

When administered intravenously, mannitol is eliminated largely unchanged by glomerular filtration and 80% of the dose is excreted in the urine within 3 hours. The elimination half-life in adults is approximately 1-2 hours. In the presence of renal failure, the half-life is extended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Mannitol was not genotoxic in *Salmonella typhimurium* and *E. coli* strain WP2. Negative results were also recorded in *Saccharomyces cerevisiae*, rat bone marrow cells and human WI-38 cells. Doses of up to 5 g/kg by gavage were also negative in a dominant lethal assay in rats.

Carcinogenicity
Dietary mannitol (≤5%) given for 2 years had no significant effect on tumour incidence in $B6C3F_1$ mice and F344 rats. Animal carcinogenicity studies have not been carried out with inhaled mannitol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 and 3 – Qualitative and quantitative composition and Pharmaceutical Form.

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

Aridol should be stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Aridol is provided as a complete diagnostic kit. Each kit contains:

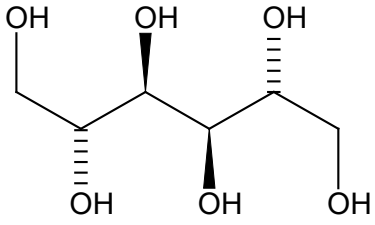
- 1 x empty clear capsule printed with two white bands
- 1 x 5mg white/clear capsule
- 1 x 10 mg yellow/clear capsule
- 1 x 20mg pink/clear capsule
- 15 x 40mg red/clear capsule
- 1 x Inhalation device (Osmohaler™)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Also known as D-mannitol.

Mannitol is a hexahydric alcohol. The powder is a white or almost white, crystalline powder of free-flowing granules. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism.

The empirical formula is $C_6H_{14}O_6$. Molecular weight is 182.2

CAS number
69-65-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

Pharmaxis Ltd.
20 Rodborough Road
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9 DATE OF FIRST APPROVAL

22 March 2006

10 DATE OF REVISION

11 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat