Aridol® (mannitol inhalation powder)
Bronchial Challenge Test Kit

A bronchial challenge test that’s not so challenging

Each Aridol® kit contains one inhaler and dry powder capsules to conduct one test:
- No dilution protocol or nebulizer required
- 24-hour shelf life
- Reproducible
- Time to conduct a positive test:
  - Aridol® 20 minutes
  - Methacholine: 45 minutes
- Sensitivity and specificity equal to methacholine

Ensuring a safe and reliable bronchial challenge test

Guidance for Conducting a Time-Sensitive Aridol® Bronchial Challenge Test

The Aridol® challenge should be completed in 35 minutes or less. Aridol® is not a stand alone test or a screening test for asthma. Bronchial challenge testing with Aridol® should be used only as part of a physician’s overall assessment of asthma.

Indication
Mannitol, the active ingredient in Aridol®, acts as a bronchoconstrictor and may cause severe bronchospasm. Bronchial challenge testing with Aridol® is for diagnostic purposes only. Bronchial challenge testing with Aridol® should only be conducted by trained professionals under the supervision of a physician.

Important Safety Information
Aridol® is not a stand alone test or a screening test for asthma. Bronchial challenge testing with Aridol® should be used only as part of a physician’s overall assessment of asthma.

WARNING: RISK OF SEVERE BRONCHOSPASM

The precise mechanisms through which Aridol® causes bronchoconstriction are not known. Aridol® is a cumulative dose-response bronchial challenge test that should be administered by a trained healthcare professional. Aridol® should not be used to screen for asthma. Aridol® can cause bronchoconstriction in patients with asthma. Severe bronchospasm can result in severe respiratory symptoms. Healthcare professionals must monitor patients during the challenge and be prepared to treat severe bronchoconstriction.

Time-Savers
Increasing the ease and efficiency of the challenge:

1. Use a pair of medical gloves to maintain bronchial irritant exposure to the subject throughout the challenge.
2. Prior to the challenge, have the patient sit or lie supine for 5 minutes to allow any vagal effects to subside and to allow the test to progress more smoothly.
3. Encourage the patient to take small sips of water during the challenge. This will decrease the dryness of the mouth and throat and increase the ease of inhalation.
4. Encourage the patient to take small sips of water after the challenge. This will decrease the dryness of the mouth and throat and increase the ease of swallowing.

Static
Static can sometimes occur in low humidity environments. A static charge can sometimes make the capsules difficult to remove from the chamber. Healthcare professionals have found the following techniques helpful:

1. Remove only one dose from the blister pack at a time.
2. Use a pair of metal tweezers to maximize efficiency in removing the capsules from the foil and placing them into the inhaler.
3. Scor the foil enclosing the capsules on the dosing card with tweezers prior to beginning the challenge. This will increase the ease of removing the capsules for placement into the inhaler device.
4. Use a pair of metal tweezers to remove capsules from the blister pack and insert into the inhaler.
5. Scor the foil enclosing the capsules on the dosing card with tweezers prior to beginning the challenge. This will increase the ease of removing the capsules for placement into the inhaler device.

Cough
Inhaling dry powder directly into the back of the throat can be difficult to remove from the chamber. Healthcare professionals have found the following techniques helpful:

1. Give the patient a sip of water before administering the next dose so that the osmotic effect in the airway is cumulative. Following the administration of a dose containing multiple capsules should be done in minimal time.
2. Tilt their head back while inhaling the dry powder. This may help to relieve any irritation in the back of the throat caused by inhaling dry powder.
3. Have them move the water around the inside of their mouth and then swallow.
4. Ensur the patient does not exhale or cough into the inhaler.
5. Dislodge the capsule from the piercing chamber and allow it to move into the spinning chamber.

Dispensing and Administration of a single dose containing multiple capsules should be done in minimal time.

Some techniques that have been found to be helpful in the reaction of the patient are:

1. Provide a cup of hot water and a straw for the patient to drink. This will decrease the dryness of the mouth and throat and increase the ease of swallowing.
2. Have them inhale the dry powder directly into the back of the throat. This will decrease the dryness of the mouth and throat and increase the ease of swallowing.
3. Encourage them to use a nebulizer or a metered dose inhaler to deliver the dose. This will decrease the dryness of the mouth and throat and increase the ease of swallowing.

References:
Aridol® (mannitol inhalation powder)
Bronchial Challenge Test Kit

Guidance for Conducting a Time-Sensitive Aridol Bronchial Challenge Test

The Aridol challenge should be completed in 35 minutes or less. Bronchial challenge testing with Aridol is contraindicated in patients with clinically apparent asthma or very low baseline pulmonary function tests (e.g., FEV1 <1-1.5 liters or <70% of the predicted values).

1. Remove the dry powder from the blister pack when you are ready to administer the dose. One dose may be administered by a trained healthcare professional.

2. Instruct the patient to inhale the powder by taking a deep breath from the base of the inhaler. Ensure they inhale at an even steady rate. Inhaling dry powder too quickly will increase the chance of cough.

3. Once the patient has inhaled the dose, they should hold their breath for 20 seconds.

4. Give the patient a sip of water. The precise mechanisms through which Aridol causes bronchoconstriction are not known.

Other information:
- Time-Savers
- Static
- Cough

Please see accompanying Full Prescribing Information including Boxed Warning, Test Kit Instructions and Important Safety Information on the reverse side.

References:
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARIDOL safely and effectively. See full prescribing information for ARIDOL.

ARIDOL® (mannitol inhalation powder)
Bronchial Challenge Test Kit
Initial U.S. Approval: 1964

WARNING: RISK OF SEVERE BRONCHOSPASM
See full prescribing information for complete boxed warning.
Mannitol, the active ingredient in ARIDOL, acts as a bronchoconstrictor and may cause severe bronchospasm. Bronchial challenge testing with ARIDOL is for diagnostic purposes only. Only trained professionals under the supervision of a physician who are familiar with the management of acute bronchospasm should perform bronchial challenge testing with ARIDOL. Medications (such as short acting inhaled beta-agonist) and equipment to treat severe bronchospasm must be present in the testing area. Because of the potential for severe bronchoconstriction, bronchial challenge testing with ARIDOL should not be performed in any patient with clinically apparent asthma or very low baseline pulmonary function tests (e.g., FEV₁ < 1.5 liters or < 70% of the predicted values) (5.1)

INDICATIONS AND USAGE

Mannitol, the active ingredient in ARIDOL, is a sugar alcohol indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. (1)

Limitations of Use: ARIDOL is not a stand alone test or a screening test for asthma. Bronchial challenge testing with ARIDOL should be used only as part of a physician's overall assessment of asthma.

DOSAGE AND ADMINISTRATION

For Oral Inhalation Use Only

• One ARIDOL test kit contains dry powder mannitol capsules in graduated doses and a single patient use inhaler necessary to perform one bronchial challenge test. (2)
• The mannitol capsules supplied in the ARIDOL kit are to be used with the single patient use inhaler device (2). Discard the inhaler after use.
• Capsule contents are to be inhaled in increasing dosage until either a positive response (15% reduction in FEV₁ from baseline or a 10% incremental reduction in FEV₁ between consecutive doses) is achieved or all capsules are inhaled (maximum total dose 635mg) (2)
• Starting and maximum dose is the same for children (> 6 years old) and adults (2)

Inhalation powder. One test kit contains dry powder mannitol capsules in graduated doses of 0mg, 5mg, 10mg, 20mg, and 40mg and one single patient use dry powder inhaler device (2, 3)

CONTRAINdicATIONS

• Known hypersensitivity to mannitol or to the gelatin used to make the capsules (4)
• Conditions that may be compromised by induced bronchospasm or repeated spirometry maneuvers (4)

WARNINGS AND PREcautions

• Severe bronchospasm: ARIDOL may cause severe bronchospasm in susceptible patients. Administer by trained professionals under the supervision of a physician. Medications and equipment to treat severe bronchospasm must be present in the testing area. (5.1)
• Subjects with co-morbid conditions: Use with caution in patients with conditions that may increase sensitivity to the bronchoconstricting or other potential effects of ARIDOL such as: severe cough, ventilatory impairment, unstable angina, or active upper or lower respiratory tract infection that may worsen with use of a bronchial irritant. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (rate 1%) were headache, pharyngolaryngeal pain, throat irritation, nausea, cough, rhinorrhea, dyspnea, chest discomfort, wheezing, retching and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmaxis Inc. at 1-888-659-6396 or email at adverse.events@pharmaxis.com.au or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Revised October 2010

See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

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* Sections or subsections omitted from the full prescribing information are not listed
Table 1: Mannitol dose steps for bronchial challenge testing with ARIDOL

<table>
<thead>
<tr>
<th>Dose #</th>
<th>Dose mg</th>
<th>Cumulative Dose mg</th>
<th>Capsules per dose</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
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<tr>
<td>9</td>
<td>160</td>
<td>635</td>
<td>4 x 40 mg</td>
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</tbody>
</table>

A positive response is achieved when the patient experiences a 15% reduction in FEV₁ from baseline (or a 10% incremental reduction in FEV₁, between consecutive doses). The test result is expressed as a PD₁₀₀.

 Patients with either a positive response to bronchial challenge testing with ARIDOL or significant respiratory symptoms should receive a standard dose of a short acting inhaled beta-agonist and monitored until fully recovered to within baseline.

3 DOSAGE FORMS AND STRENGTHS

ARIDOL is a bronchial challenge test kit. Each kit contains one, single patient use, dry powder inhaler device and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation as described below:

Blisters pack 1:
- Marked 1 – 1 x empty clear capsule
- Marked 2 – 1 x 5 mg white/clear capsule printed with 5 mg
- Marked 3 – 1 x 10 mg yellow/clear capsule printed with 10 mg
- Marked 4 – 1 x 20 mg pink/clear capsule printed with 20 mg

Blisters pack 2:
- Marked 5 – 1 x 40 mg red/clear capsule printed with 40 mg
- Marked 6 – 2 x 40 mg red/clear capsules printed with 40 mg
- Marked 7 – 4 x 40 mg red/clear capsules printed with 40 mg

Blisters pack 3:
- Marked 8 – 4 x 40 mg red/clear capsules printed with 40 mg
- Marked 9 – 4 x 40 mg red/clear capsules printed with 40 mg

4 CONTRAINDICATIONS

ARIDOL use is contraindicated in:
- Patients with known hypersensitivity to mannitol or to the gelatin used to make the capsules
- Patients with conditions that may be compromised by induced bronchospasm or repeated spirometry maneuvers. Some examples include: aortic or cerebral aneurysm, uncontrolled hypertension, recent myocardial infarction or cerebral vascular accident [see Warnings and Precautions (5.2)].

5 WARNINGS & PRECAUTIONS

5.1 Severe Bronchospasm

Mannitol, the active ingredient in ARIDOL, acts as a bronchoconstrictor and may cause severe bronchospasm in susceptible patients. The test should only be conducted by trained professionals under the supervision of a physician familiar with all aspects of the bronchial challenge test and the management of acute bronchospasm. Patients should not be left unattended during the bronchial challenge test. Medications and equipment to treat severe bronchospasm must be present in the testing area.

If a patient has a ≥10% reduction in FEV₁ (from pre-challenge FEV₁), on administration of the 0 mg capsule, the ARIDOL bronchial challenge test should be discontinued and the patient should be given a dose of a short acting inhaled beta-agonist and monitored accordingly.

Patients with either a positive response to bronchial challenge testing with ARIDOL or significant respiratory symptoms should receive a short acting inhaled beta-agonist. Subjects should be monitored until fully recovered to within baseline.

5.2 Subjects with Co-morbid Conditions

Bronchial challenge testing with ARIDOL should be performed with caution in patients with conditions that may increase sensitivity to the bronchoconstricting or other potential effects of ARIDOL such as severe cough, ventilatory impairment, spirometry-induced bronchoconstriction, hemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent intraocular surgery, unstable angina, or active upper or lower respiratory tract infection.

6 ADVERSE REACTIONS

Mannitol, the active ingredient in ARIDOL, is a sugar alcohol that may cause severe bronchospasm in susceptible subjects [see Warnings and Precautions (5.1)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population for the ARIDOL bronchial challenge test consisted of 1,082 subjects (577 females and 505 males) including patients with asthma, symptoms suggestive of asthma, and healthy individuals from 6 to 83 years of age who participated in the two clinical trials (Studies 1 and 2). The racial distribution of subjects was 84% Caucasian, 5% Asian, 4% Black, and 7% Other. Children and adolescents comprised 23% of the total study population with 118 children aged 6-11 years and 128 adolescents aged 12-17 years.

Adverse reactions were reported at the time of the testing procedure and for one day thereafter. No serious adverse reactions were reported following bronchial challenge testing with ARIDOL in either trial.

Five adult subjects (0.6%) discontinued from the studies within a day following bronchial challenge testing with ARIDOL because of cough, decreased lung function, feeling jittery, sore throat, and throat irritation. One adult subject (0.3%) discontinued following the methacholine bronchial challenge test because of dizziness. One pediatric subject (0.4%) discontinued from the studies within a day following bronchial challenge testing with ARIDOL because of retching.

Table 2 displays the combined common adverse reactions (≥1%) within a day after bronchial challenge testing with ARIDOL or methacholine in the overall population for Studies 1 and 2.

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<td>635</td>
<td>4 x 40 mg</td>
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</tbody>
</table>
The maximum reduction in FEV₁, following bronchial challenge testing with ARIDOL was 46%, compared to 54% for exercise testing and 67% for the methacholine challenge. The incidences in decreases in FEV₁, ≥30% and ≥60% following ARIDOL, methacholine, and exercise challenges for Studies 1 and 2 is shown in Table 3.

Table 3: Incidence of decreases in FEV₁, ≥30% or ≥60% (overall population, Studies 1 and 2)

<table>
<thead>
<tr>
<th>Challenge</th>
<th>No. Exposed</th>
<th>N (%) with Fall in FEV₁, ≥30%</th>
<th>N (%) with Fall in FEV₁, ≥60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
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<tr>
<td>Exercise</td>
<td>435</td>
<td>27 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Methacholine</td>
<td>420</td>
<td>51 (12%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>ARIDOL</td>
<td>419</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIDOL asthmatics</td>
<td>536</td>
<td>23 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>ARIDOL Non-asthmatics</td>
<td>91</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There were no differences in the incidence of adverse reactions based on gender or race. The clinical trials did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently compared to subjects below 65 years of age.

Children and Adolescents Aged 6 to 17 Years: Overall, the types and severities of adverse reactions in children were similar to those observed in the adult population. As in the adult population, the adverse reactions of pharyngolaryngeal pain, nausea, and headache were the more common with incidences of 4%, 3%, and 3%, respectively. There were no major differences in the types of adverse reactions observed in children 6-11 years of age compared to adolescents 12-17 years old.

The decrease in FEV₁, in children and adolescents who received the ARIDOL bronchial challenge test was similar to that of the adult population with 5%, 15% and 9% of pediatric subjects who had bronchial challenge testing with ARIDOL, methacholine and exercise, respectively, experiencing reduction in FEV₁, ≥30%. No patient who had bronchial challenge testing with ARIDOL or exercise had a decrease in FEV₁, ≥60%, whereas, one adolescent patient (aged 12 years) who received methacholine had a decrease in FEV₁, ≥60%.

6.2 Post-Marketing Experience

The following adverse reactions have been identified post approval outside the U.S. of the ARIDOL bronchial challenge test kit: cough, gagging, wheeze, and decreased forced expiratory volume. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with mannitol, the active ingredient in ARIDOL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled clinical studies of mannitol in pregnant women. Bronchial challenge testing with ARIDOL should be performed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Mannitol was not teratogenic. Mannitol did not cause any embryofatal malformations when given to pregnant rats and mice at oral doses approximately 20 and 10 times the maximum recommended human daily inhalation dose (MRHIDD) in adults, respectively, on a mg/m² basis [see Animal Toxicology and/or Pharmacology (13.2)].

8.2 Labor and Delivery

The effects of a possible hyperresponsiveness reaction on a mother or child during labor or delivery are not known, and therefore bronchial challenge testing with ARIDOL should not be administered during labor or delivery.

8.3 Nursing Mothers

It is not known whether mannitol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mannitol is given to a nursing mother.

8.4 Pediatric Use

A total of 2,464 children and adolescents ages 6 to 17 years were studied in the two clinical trials [see Clinical Studies (14)].

The mean and median maximum percentage reduction in FEV₁, in patients with a positive ARIDOL challenge test in children and adolescents 6 to 17 years of age (19% and 18%, respectively) showed no apparent difference compared to the adult population (19% and 18%, respectively).

The safety profile of the ARIDOL bronchial challenge test in children and adolescents 6 to 17 years of age was similar to the adult population in two clinical studies [see Adverse Reactions (6)].

Bronchial challenge testing with ARIDOL should not be performed in children less than 6 years of age due to their inability to provide reliable spirometric measurements.

8.5 Geriatric Use

There was insufficient number of subjects 50 years of age and older in the clinical program. Therefore, the safety and efficacy of bronchial challenge testing with ARIDOL in the older population cannot be adequately assessed. It is unknown whether any differences in the safety and efficacy of bronchial challenge testing with ARIDOL exist between subjects 50 years of age and older and younger subjects.

8.6 Hepatic and Renal Impairment

Formal pharmacokinetic studies with mannitol, the active ingredient, in ARIDOL, have not been conducted in patients with hepatic or renal impairment. However, an increase in systemic exposure of mannitol can be expected in patients with renal impairment based on the kidney being its primary route of elimination.

Given parenterally, mannitol is used as an osmotic diuretic in a variety of clinical situations including acute renal failure where the osmotic effects of mannitol inhibit the rate of water re-absorption and maintain the rate of urine production.

10 OVERDOSAGE

Mannitol, the active ingredient in ARIDOL, is to be administered only by inhalation. Susceptible persons may experience excessive bronchospasm from an overdose. If such bronchospasm occurs, immediately administer a short acting inhaled beta-agonist and other medical treatments such as oxygen, as necessary.

11 DESCRIPTION

D-mannitol (referred to throughout as mannitol), the active ingredient in ARIDOL is a hexahydrated alcohol, that is a sugar alcohol, with the following chemical name (2R,3R,4R,5R)-hexan-1,2,3,4,5,6-hexol and chemical structure:

Mannitol is a white or almost white crystalline powder of free-flowing granules with an empirical formula of C₆H₁₄O₆ and molecular weight of 182.2. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism.

The ARIDOL bronchial challenge test kit contains one single patient use dry powder inhaler and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation. All except the 0 mg printed hard gelatin capsules contain dry powder mannitol for oral inhalation. The accompanying dry powder inhaler is a plastic device used for inhaling the capsules. All doses are to be administered using the same device supplied with each kit without washing or sterilizing the device at anytime during the test.

To use the delivery system, a mannitol capsule is placed in the well of the inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The mannitol dry powder is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

There are no inactive ingredients in the mannitol capsules supplied with the ARIDOL bronchial challenge test kit. The 0 mg capsule and the bodies of the 5, 10, 20 and 40 mg capsules are clear. The white capsules (5 mg) contain titanium dioxide and yellow iron oxide. The pink caps (10 mg) contain red iron oxide. The yellow capsules (20 mg) contain red iron oxide. The red caps (40 mg) contain titanium dioxide and red iron oxide. The inhaler is a plastic device used for administering mannitol to the lungs. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the delivered dose from the inhaler from each of the 5, 10, 20, and 40 mg capsules is approximately 3.4, 7.7, 16.5 and 34.1 mg, respectively. Peak inspiratory flow rates (PIFR) achievable through the inhaler were evaluated in healthy and asthmatic individuals ranging from 7 to 65 years of age and with % FEV₁, of predicted ranging from 67% to 123%. PIFR achieved in the study was at least 70.8 L/min in all subjects assessed. The mean PIFR was 118.2 L/min and approximately ninety percent of each population studied generated a PIFR through the device exceeding 90 L/min.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms through which inhaled mannitol causes bronchoconstriction are not known.
12.2 Pharmacodynamics
The response to inhaled mannitol is reported as the delivered dose of mannitol causing a 15% reduction in FEV₁, and is expressed as PD₁₅.

12.3 Pharmacokinetics
Absorption: The rate and extent of absorption of mannitol after oral inhalation was generally similar to that observed after oral administration. In a study of 18 healthy adult male subjects the absolute bioavailability of mannitol powder following oral inhalation was 59% while the relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%. Following oral inhalation of 635 mg, the mean mannitol peak plasma concentration (Cmax) was 13.71 mcg/mL while the mean extent of systemic exposure (AUC) was 73.15 mcg·hr/mL. The mean time to peak plasma concentration (Tmax) after oral inhalation was 1.5 hour.

Distribution: Based on intravenous administration, the volume of distribution of mannitol was 34.3 L.

Metabolism: The extent of metabolism of mannitol appears to be small. This is evident from a urinary excretion of about 87% of unchanged drug after an intravenous dose to healthy subjects.

Elimination: Following oral inhalation, the elimination half-life of mannitol was 4.7 hours. The mean terminal elimination half-life for mannitol in plasma remained unchanged regardless of the route of administration (oral, inhalation, and intravenous). The urinary excretion rate versus time profile for mannitol was 4.7 hours. The mean terminal elimination half-life for mannitol in plasma

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In 2-year carcinogenicity studies in rats and mice mannitol did not show evidence of carcinogenicity at oral dietary concentrations up to 5% (or 7,500 mg/kg on a mg/kg basis). These doses were approximately 55 and 30 times the MRHID, respectively, on a mg/m² basis.


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

13.2 Animal Toxicology and/or Pharmacology
Reproductive Toxicology Studies
Mannitol did not cause any embryofetal malformations when given to pregnant rats and mice at oral doses of 1.6 g/kg each (approximately 20 and 10 times the MRHID in adults, respectively, on a mg/m² basis).

14 CLINICAL STUDIES
The effectiveness of the ARIDOL bronchial challenge test kit in assessing bronchial hyperresponsiveness in adults and children 6 years of age and older was assessed in two clinical studies. Study 1 was an operator-blinded, open-label crossover trial that assessed the sensitivity and specificity of bronchial challenge testing with ARIDOL and methacholine. The study endpoint of interest was an estimation of the sensitivity and specificity of bronchial challenge testing with ARIDOL with respect to a physician’s clinical diagnosis of asthma. Following completion of the bronchial challenge tests with ARIDOL and hypertonic saline, a respiratory physician assessed the data and categorized the subjects as having or not having asthma. The sensitivity of the ARIDOL bronchial challenge test in subjects with a physician diagnosis of asthma was 58% (95% CI) compared to a sensitivity of the physician diagnosis in the same population of 97% (95%, 98%, 95% CI). The specificity of the ARIDOL bronchial challenge test in subjects without asthma was 95% (90%, 99%, 95% CI) compared to the specificity of the physician diagnosis of 100% (95%, 100%, 95% CI).

16 HOW SUPPLIED/STORAGE AND HANDLING
ARIDOL is a bronchial challenge test kit. Each kit contains one single patient use, dry powder inhaler device and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation as described below:

Blisters pack "1":
- Marked 1 – 1 x empty clear capsule
- Marked 2 – 1 x 5 mg white/clear capsule printed with 5 mg
- Marked 3 – 1 x 10 mg yellow/clear capsule printed with 10 mg
- Marked 4 – 1 x 20 mg pink/clear capsule printed with 20 mg

Blisters pack "2":
- Marked 5 – 1 x 40 mg red/clear capsule printed with 40 mg
- Marked 6 – 2 x 40 mg red/clear capsules printed with 40 mg
- Marked 7 – 4 x 40 mg red/clear capsules printed with 40 mg

Blisters pack "3":
- Marked 8 – 4 x 40 mg red capsules printed with 40 mg
- Marked 9 – 4 x 40 mg red/clear capsules printed with 40 mg

ARIDOL should be stored below 77°F (25°C) with excursions permitted between 59-86°F (15-30°C). [See USP Controlled Room Temperature]. Do not freeze. Do not refrigerate.

The ARIDOL bronchial challenge test should only be used with the provided inhaler. All remaining unused (opened and unopened) blister packs and the inhaler should be properly discarded at the completion of the test. Be sure to read the accompanying ARIDOL bronchial challenge test kit instructions completely before test initiation. If you have any questions, contact the manufacturer support at 1-888-659-6396.

17 PATIENT COUNSELING INFORMATION
17.1 Severe Bronchospasm
Prior to administration patients should be informed of the potential for bronchial challenge testing with ARIDOL to cause severe bronchospasm and of the potential symptoms they may experience.

17.2 Subjects with Certain Co-morbid Conditions
Bronchial challenge testing with ARIDOL should be performed with caution in patients having severe cough, ventilatory impairment, spirometry-induced bronchoconstriction, hemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent intraocular surgery, unstable angina, or active upper or lower respiratory tract infection or other conditions that may worsen with the use of a bronchial irritant.

Table 4: Comparisons of the sensitivity and specificity (calculated relative to exercise challenge) for the ARIDOL test and methacholine in Study 1

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Population (n=419)</td>
<td>ARIDOL</td>
<td>58 (25, 85)</td>
<td>63 (67, 72)</td>
</tr>
<tr>
<td></td>
<td>Methacholine</td>
<td>71 (92, 84)</td>
<td>59 (39, 77)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>5 (-14, 19)</td>
<td>-1 (-12, 3)</td>
</tr>
</tbody>
</table>

ARIDOL® is a registered trademark of Pharmaxis Ltd
SP-200-01

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Manufactured for:
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ARIDOL® (mannitol inhalation powder) Bronchial Challenge Test Kit Instructions

Inhaler

- **‘Spinning’ Chamber**
- **‘Piercing’ Buttons**
- **Mouthpiece**
- **Filter**

**ARIDOL Bronchial Challenge Test Results**

**Positive ARIDOL Bronchial Challenge Test Result**
A positive response may be achieved in two ways:
1. ≥15% fall in FEV₁ from baseline (using the post 0mg FEV₁, as baseline)
2. ≥10% incremental fall in FEV₁ (between two consecutive mannitol doses)

**Negative ARIDOL Bronchial Challenge Test Result**
An ARIDOL bronchial challenge test result is considered to be negative when a cumulative dose of 635mg of mannitol has been administered and the patient's FEV₁ has not fallen by ≥ 15% from baseline.

**Equipment Required:**
- **ARIDOL Bronchial Challenge Test Kit** (containing mannitol capsules, an inhaler, full prescribing information and instructions)
- **Spirometer & mouthpiece**
- **Nose clip**
- **Timer** (which can be set to 60 seconds)
- **Calculator**
- **Short-acting inhaled beta agonist** (i.e. albuterol) and volumetric spacer (if using a metered dose inhaler)

Medication and emergency equipment should be present in the testing area in accordance with standard bronchial challenge test procedures.

**Important Test Information**

a. The inhaler is for SINGLE PATIENT USE ONLY (one inhaler per ARIDOL bronchial challenge test) and should not be cleaned during the ARIDOL bronchial challenge test. Discard following each ARIDOL bronchial challenge test. Do not sterilize and reuse.

b. When patients are exhaling during the ARIDOL bronchial challenge test, ensure they do so AWAY from the inhaler to minimize humidity within the inhaler.

c. Pierce the capsule only once by fully depressing both piercing buttons on the sides of the inhaler simultaneously. (A second puncture may cause the capsule to split/fragment.)

d. Using rubber/latex gloves when administering the test and handling mannitol capsules may increase static and inhibit capsule movement within the inhaler.

e. If static is an issue or the sound of the capsule ‘rattling’ cannot be heard during inhalation of mannitol, firmly tap the base of the inhaler with one hand while holding the inhaler with the other hand (mouthpiece facing downwards at a 45º angle). This should ensure that the capsule has been ‘dislodged’ and moved from the piercing chamber into the spinning chamber.

f. Inhalation of mannitol may cause a cough and/or dry throat. This is normal and expected when conducting an ARIDOL bronchial challenge test. You can offer the patient water to sip during and after the ARIDOL bronchial challenge test.

g. The ARIDOL bronchial challenge test is time critical and requires an osmotic gradient to be established and maintained. Prolonged intervals between doses may affect the validity of test results and should be avoided.

**Inhaler Instructions**

These instructions show you how to use the inhaler supplied in the ARIDOL® (mannitol inhalation powder) Bronchial Challenge Test Kit.

1. **Remove Cap:** Using both hands, hold the inhaler upright and remove the cap.
2. **Open:** Hold the base of the inhaler firmly with one hand and open the inhaler by rotating the mouthpiece in the direction of the arrow as shown.
3. **Load:** Using dry hands, remove a capsule from the mannitol foil and place into the inhaler as shown. It does not matter which way the capsule is placed in the chamber.
4. **Close:** Keeping the inhaler in an upright position, twist the mouthpiece into the closed position until you hear it ‘click’.
5. **Pierce Capsule:** Hold the inhaler in an upright position and fully depress both piercing buttons on the sides of the inhaler simultaneously and only once (a second puncture may cause the capsule to split/fragment). The piercing action makes holes in the capsule and allows the powder inside the capsule to be released when the patient inhales through the mouthpiece of the inhaler.
6. **Prepare for Inhalation:** Tilt the inhaler so that the mouthpiece faces slightly downward at a 45º angle as shown. This allows the capsule to drop forward into the spinning chamber. A nose clip may be used, if preferred. If so, apply the nose clip to the subject and direct the subject to breathe through his/her mouth. Keep the inhaler tilted in this way and instruct the patient to exhale completely (away from the inhaler).
7. **Inhale:** The patient should tilt his/her head back slightly, keep the inhaler at a 45º angle, raise the inhaler to his/her mouth and ensure they close their lips tightly around the mouthpiece. The patient should take a controlled and deep inhalation. The patient should then hold their breath for five seconds.
8. **Exhale:** Remove the inhaler from the patient’s mouth, allow him/her to exhale and resume normal breathing.
9. **Check:** The mannitol capsule must spin in the inhaler in order to empty. A second inhalation (using the same capsule) may be required immediately if the capsule is not emptied sufficiently following the first inhalation. Check the capsule following each inhalation.

**Please Note:**
The inhaler is designed for SINGLE PATIENT USE ONLY (one inhaler per ARIDOL bronchial challenge test) and should not be cleaned during the ARIDOL bronchial challenge test. Discard the inhaler following each ARIDOL bronchial challenge test. Do not reuse.
**STEP 1:** Patient should be seated for the test. Explain the test procedure; include what is required for an FVC maneuver and FEV₁ measurement and the type of inhalation flow required for the inhaler. Demonstrate as required.

**STEP 2:** Enter the patient’s information in the spirometer as applicable (age, height, race, date of birth, gender, etc.).

**STEP 3:** Determine the pre-challenge FEV₁

Ask the patient to perform an FVC maneuver according to the ATS/ERS Guidelines. The patient’s FEV₁ should be ≥ 70% predicted. The ARIDOL bronchial challenge test should not be performed in patients with an FEV₁ of less than 70% predicted.

**STEP 4:** Calculate the baseline FEV₁ (0mg)

a. Remove the 0mg mannitol capsule from the foil, twist open the inhaler (as per the arrow on the inhaler), place the capsule inside and close the inhaler.

b. A nose clip may be used, if preferred. If so, apply the nose clip to the subject and direct the subject to breathe through his/her mouth.

c. The patient should inhale the dose in the same manner as previous doses, hold their breath for five seconds then exhale.

d. Insert and pierce the first of the four 40mg capsules that comprise the 160mg dose.

e. Ensure the patient is sitting up straight. Ask the patient to exhale (away from the inhaler), seal his/her lips around the inhaler mouthpiece and take a controlled and deep inhalation.

f. Following inhalation, load the second 40mg capsule and give to the patient immediately following exhalation.

**STEP 5:** 5mg capsule

a. Insert the 5mg capsule into the inhaler and pierce the capsule as in Step 4.a & 4.b.

b. Repeat Steps 4.c – 4.f.

c. Following inhalation remove the capsule from the inhaler and check to ensure it has been emptied sufficiently; if not, a second inhalation will be required immediately.

d. Load the 10mg capsule to prepare for the next dose.

e. At 60 seconds following inhalation, immediately measure the patient’s FEV₁ two times (acceptability criteria must be met). Use the highest of these two values to calculate the change in FEV₁.

f. Compare the FEV₁ value at this dose to the target FEV₁, if the FEV₁ value is equal to or below the target value, or there has been a cumulative fall of ≥ 10% from the previous dose, the ARIDOL bronchial challenge test is positive and complete. If not, immediately proceed to the next dose (Step 6).

**STEP 6:** 10mg, 20mg, 40mg Capsules

Administer the 10mg, 20mg and 40mg doses following the directions given in (in Step 5) for the 5mg dose. Each dose is one capsule.

**STEP 7:** 80mg dose (2 x 40mg capsules)

a. Insert and pierce the first of the two 40mg capsules that comprise the 80mg dose.

b. The patient should inhale the dose in the same manner as previous doses, hold their breath for five seconds then exhale.

c. Remove the first 40mg capsule from the inhaler and check to ensure it has been emptied sufficiently; if not, a second inhalation will be required immediately. Do this following the administration of each capsule.

d. Following inhalation, load the second 40mg capsule and give to the patient immediately following exhalation after the first 40mg capsule.

e. Instruct the patient to inhale the second capsule immediately to ensure that the osmotic effect of mannitol is cumulative.

f. Set the timer for 60 seconds when the second 40mg capsule has been inhaled.

g. Instruct the patient to hold their breath for five seconds before exhaling.

h. At 60 seconds following inhalation of the second capsule, immediately measure the patient’s FEV₁ two times (according to ATS/ERS Guidelines). Use the higher of these two values to calculate the change in FEV₁.

i. Compare the FEV₁ value at this dose to the target FEV₁. If the FEV₁ value is equal to or below the target value, or there has been an incremental fall of ≥ 10% from the previous dose, the ARIDOL bronchial challenge test is positive and complete. If not, immediately proceed to the next dose (Step 8).

**STEP 8:** First 160mg dose (4 x 40mg capsules)

a. Insert and pierce the first of the four 40mg capsules that comprise the 160mg dose.

b. The patient should inhale the dose in the same manner as previous doses, hold their breath for five seconds then exhale.

c. Remove capsule from the inhaler and check to ensure it has been emptied sufficiently; if not, a second inhalation will be required immediately. Do this following the administration of each capsule.

d. Following inhalation, load the second 40mg capsule and give to the patient immediately following exhalation.

e. The patient should inhale the contents of the second capsule, hold their breath for five seconds then exhale.

f. Following inhalation, load the third 40mg capsule and give to the patient immediately following exhalation.

g. The patient should inhale the contents of the third capsule, hold their breath for five seconds then exhale.

h. Immediately following inhalation, load the fourth 40mg capsule and give to the patient immediately following exhalation.

i. Instruct the patient to inhale the fourth capsule immediately to ensure that the osmotic effect of mannitol is cumulative.

j. Set the timer for 60 seconds when the fourth 40mg capsule has been inhaled.

k. Instruct the patient to hold their breath for five seconds before exhaling.

l. At 60 seconds following inhalation of the fourth capsule, immediately measure the patient’s FEV₁ two times (according to ATS/ERS Guidelines). Use the higher of these two values to calculate the change in FEV₁.

m. Compare the FEV₁ value at this dose to the target FEV₁. If the FEV₁ value is equal to or below the target value, or there has been an incremental fall of ≥ 10% from the previous dose, the ARIDOL bronchial challenge test is positive and complete. If not, immediately proceed to the next dose (Step 9).

**STEP 9:** Second 160mg dose (4 x 40mg capsules)

Administer the second 160mg dose following the directions given in Step 8.

**STEP 10:** Third 160mg dose (4 x 40mg capsules)

Administer the third 160mg dose following the directions given in Step 8.

At the completion of this dose, 635mg has been administered. If a positive response has not been met, the ARIDOL bronchial challenge test should be considered negative and complete.

**STEP 11:** Following completion of the ARIDOL bronchial challenge test with a positive result or significant respiratory symptoms (e.g. wheezing, dyspnea, cough), you should administer a short-acting inhaled beta agonist and monitor the patient until fully recovered to within baseline. In the case of a negative result, if the patient has significant respiratory symptoms, a short-acting inhaled beta agonist should be administered.