

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22368Orig1s000

LABELING

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)

-----DOSAGE FORMS AND STRENGTHS-----

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

-----DRUG INTERACTIONS-----

No formal drug-drug interaction studies have been conducted with ARIDOL

-----See 17 for PATIENT COUNSELING INFORMATION-----

Revised:

FULL PRESCRIBING INFORMATION: CONTENTS*

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: RISK OF SEVERE BRONCHOSPASM**

3
4 **Mannitol, the active ingredient in ARIDOL, acts as a bronchoconstrictor and may cause severe**
5 **bronchospasm. Bronchial challenge testing with ARIDOL is for diagnostic purposes only.**
6 **Bronchial challenge testing with ARIDOL should only be conducted by trained professionals**
7 **under the supervision of a physician familiar with all aspects of the bronchial challenge test and**
8 **the management of acute bronchospasm. Medications (such as short acting inhaled beta-**
9 **agonist) and equipment to treat severe bronchospasm must be present in the testing area. If**
10 **severe bronchospasm occurs it should be treated immediately by administration of a short**
11 **acting inhaled beta-agonist. Because of the potential for severe bronchoconstriction, the**
12 **bronchial challenge testing with ARIDOL should not be performed in any patient with**
13 **clinically apparent asthma or very low baseline pulmonary function tests (e.g., FEV₁ < 1-1.5**
14 **liters or <70% of the predicted values) [see Warnings and Precautions (5.1)].**

15 **1 INDICATIONS AND USAGE**

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

19 Limitations of Use:

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

22 **2 DOSAGE AND ADMINISTRATION**

23 *Basic Dosing Information*

24 ARIDOL is a test kit containing the required capsules of dry powder mannitol for oral inhalation in
25 graduated doses with the supplied single patient use inhaler necessary to perform one bronchial
26 challenge test. The inhaler should be discarded after use.

27 Do not swallow ARIDOL capsules.

28 The airway response to bronchial challenge testing with ARIDOL is measured using forced
29 expiratory volume in one second (FEV₁).

30 Prior to bronchial challenge testing with ARIDOL, standard spirometry should be performed and the
31 reproducibility of the resting FEV₁ established.

32 An overview of the testing procedure can be found below. See the ARIDOL bronchial challenge test
33 instructions for complete instructions on the dosing and spirometry procedures.

- 34 a. A nose clip may be used if preferred. If so, apply nose clip to the subject and direct the
35 subject to breathe through the mouth
- 36 b. Insert 0 mg capsule into inhalation device. Puncture capsule by depressing buttons on side of
37 device slowly, and once only (a second puncture may fragment the capsules)

- 38 c. The patient should exhale completely, before inhaling from device in a controlled rapid deep
39 inspiration
- 40 d. At the end of deep inspiration, start 60 second timer, subject should hold breath for 5 seconds
41 and exhale through mouth before removal of nose clip
- 42 e. At the end of 60 seconds, measure the FEV₁ in duplicate (the measurement after inhaling the
43 0 mg capsule is the baseline FEV₁)
- 44 f. Repeat steps a-e following the mannitol capsule dose steps from Table 1 below until the
45 patient has a positive response or 635 mg of mannitol has been administered (negative test)
- 46

Table 1: Mannitol dose steps for bronchial challenge testing with ARIDOL			
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

47

48 A positive response is achieved when the patient experiences a 15% reduction in FEV₁ from (0 mg)
49 baseline (or a 10% incremental reduction in FEV₁ between consecutive doses). The test result is
50 expressed as a PD₁₅.

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

54 **3 DOSAGE FORMS AND STRENGTHS**

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

58 Blister pack "1":

- 59 • Marked 1 - 1 x empty clear capsule
- 60 • Marked 2 - 1 x 5 mg white/clear capsule printed with 5 mg
- 61 • Marked 3 - 1 x 10 mg yellow/clear capsule printed with 10 mg
- 62 • Marked 4 - 1 x 20 mg pink/clear capsule printed with 20 mg

63 Blister pack “2”:

- 64 • Marked 5 - 1 x 40 mg red/clear capsule printed with 40 mg
- 65 • Marked 6 – 2 x 40 mg red/clear capsules printed with 40 mg
- 66 • Marked 7 – 4 x 40 mg red/clear capsules printed with 40 mg

67 Blister pack “3”:

- 68 • Marked 8 – 4 x 40 mg red/clear capsules printed with 40 mg
- 69 • Marked 9 - 4 x 40 mg red/clear capsules printed with 40 mg

70

71 **4 CONTRAINDICATIONS**

72 ARIDOL use is contraindicated in:

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

78 **5 WARNINGS & PRECAUTIONS**

79 **5.1 Severe Bronchospasm**

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

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

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

92 **5.2 Subjects with Co-morbid Conditions**

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

98 **6 ADVERSE REACTIONS**

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

101 **6.1 Clinical Trials Experience**

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

105 The safety population for the ARIDOL bronchial challenge test consisted of 1,082 subjects (577
 106 females and 505 males) including patients with asthma, symptoms suggestive of asthma, and healthy
 107 individuals from 6 to 83 years of age who participated in the two clinical trials (Studies 1 and 2). The
 108 racial distribution of subjects was 84% Caucasian, 5 % Asian, 4 % Black, and 7 % Other. Children
 109 and adolescents comprised 23% of the total study population with 118 children aged 6-11 years and
 110 128 adolescents aged 12-17 years.

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

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

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

Table 2: Adverse reactions with an incidence $\geq 1\%$ within a day after bronchial challenge testing (overall population, Studies 1 and 2 combined)		
Adverse Reactions	Treatment	
	ARIDOL (N=1046) n (%)	Methacholine Challenge (N=420) n (%)
Headache	59 (6)	4 (1)
Pharyngolaryngeal pain	25 (2)	0
Throat irritation	19 (2)	1 (<1)
Nausea	19 (2)	0
Cough	17 (2)	8 (2)
Rhinorrhea	16 (2)	0
Dyspnea	15 (1)	21 (5)
Chest discomfort	13 (1)	18 (4)
Wheezing	8 (1)	6 (1)
Retching	6 (1)	0
Dizziness	5 (1)	13 (3)

121

122 The maximum reduction in FEV₁ following bronchial challenge testing with ARIDOL was 46%,
 123 compared to 54% for exercise testing and 67% for the methacholine challenge. The incidences in

124 decreases in FEV₁ ≥ 30% and ≥ 60% following ARIDOL, methacholine, and exercise challenges for
 125 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)			
Challenge	No. Exposed	N (%) with Fall in FEV₁ ≥30%	N (%) with Fall in FEV₁ ≥60%
Study 1			
Exercise	435	27 (6%)	0
Methacholine	420	51 (12%)	3 (1%)
ARIDOL	419	3 (1%)	0
Study 2			
ARIDOL asthmatics	536	23 (4%)	0
ARIDOL Non-asthmatics	91	0	0

126

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

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

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

141 **6.2 Post-Marketing Experience**

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

146 **7 DRUG INTERACTIONS**

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

149 **8 USE IN SPECIFIC POPULATIONS**

150 **8.1 Pregnancy**

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

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

158 **8.2 Labor and Delivery**

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

162 **8.3 Nursing Mothers**

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

165 **8.4 Pediatric Use**

166 A total of 246 children and adolescents ages 6 to 17 years were studied in the two clinical trials [*see*
167 *Clinical Studies (14)*].

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

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

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

175 **8.5 Geriatric Use**

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

181 **8.6 Hepatic and Renal Impairment**

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

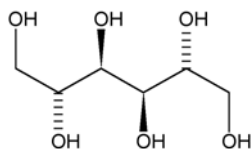
186 Given parenterally, mannitol is used as an osmotic diuretic in a variety of clinical situations including
187 acute renal failure where the osmotic effects of mannitol inhibit the rate of water re-absorption and
188 maintain the rate of urine production.

189 **10 OVERDOSAGE**

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

194 **11 DESCRIPTION**

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



199 Mannitol is a white or almost white crystalline powder of free-flowing granules with an empirical
200 formula of $C_6H_{14}O_6$ and molecular weight of 182.2. Mannitol is freely soluble in water, and very
201 slightly soluble in alcohol. Mannitol shows polymorphism.

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

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

211 There are no inactive ingredients in the mannitol capsules supplied with the ARIDOL bronchial
212 challenge test kit. The 0 mg capsule and the bodies of the 5, 10, 20 and 40 mg capsules are clear. The
213 white caps (5 mg) contain titanium dioxide. The yellow caps (10 mg) contain titanium dioxide and
214 yellow iron oxide. The pink caps (20 mg) and red caps (40 mg) contain titanium dioxide and red iron
215 dioxide. The inhaler is a plastic device used for administering mannitol to the lungs. The amount of
216 drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory

217 time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the delivered
218 dose from the inhaler from each of the 5, 10, 20 and 40 mg capsules is approximately 3.4, 7.7, 16.5
219 and 34.1 mg, respectively. Peak inspiratory flow rates (PIFR) achievable through the inhaler were
220 evaluated in healthy and asthmatic individuals ranging from 7 to 65 years of age and with % FEV₁ of
221 predicted ranging from 67% to 123%. PIFR achieved in the study was at least 70.8 L/min in all
222 subjects assessed. The mean PIFR was 118.2 L/min and approximately ninety percent of each
223 population studied generated a PIFR through the device exceeding 90 L/min.

224 **12 CLINICAL PHARMACOLOGY**

225 **12.1 Mechanism of Action**

226 The precise mechanisms through which inhaled mannitol causes bronchoconstriction are not known.

227 **12.2 Pharmacodynamics**

228 The response to inhaled mannitol is reported as the delivered dose of mannitol causing a 15%
229 reduction in FEV₁ and is expressed as PD₁₅.

230 **12.3 Pharmacokinetics**

231 *Absorption:* The rate and extent of absorption of mannitol after oral inhalation was generally similar
232 to that observed after oral administration. In a study of 18 healthy adult male subjects the absolute
233 bioavailability of mannitol powder following oral inhalation was 59% while the relative
234 bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%.
235 Following oral inhalation of 635 mg, the mean mannitol peak plasma concentration (C_{max}) was 13.71
236 mcg/mL while the mean extent of systemic exposure (AUC) was 73.15 mcg•hr/mL. The mean time to
237 peak plasma concentration (T_{max}) after oral inhalation was 1.5 hour.

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

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

241 *Elimination:* Following oral inhalation, the elimination half-life of mannitol was 4.7 hours. The mean
242 terminal elimination half-life for mannitol in plasma remained unchanged regardless of the route of
243 administration (oral, inhalation, and intravenous). The urinary excretion rate versus time profile for
244 mannitol was consistent for all routes of administration. The total clearance after intravenous
245 administration was 5.1 L/hr while the renal clearance was 4.4 L/hr. Therefore, the clearance of
246 mannitol was predominately via the kidney. Following inhalation of 635 mg of mannitol in 18 healthy
247 subjects, about 55% of the total dose was excreted in the urine as unchanged mannitol. Following oral
248 or intravenous administration of a 500 mg dose, the corresponding values were 54% and 87% of the
249 dose, respectively.

250 *Hepatic and Renal Impairment:* Formal pharmacokinetic studies using ARIDOL have not been
251 conducted in patients with hepatic or renal impairment. Since the drug is eliminated primarily via the
252 kidney, an increase in systemic exposure can be expected in renally impaired patients.

253 **13 NONCLINICAL TOXICOLOGY**

254 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

255 In 2-year carcinogenicity studies in rats and mice mannitol did not show evidence of carcinogenicity
256 at oral dietary concentrations up to 5% (or 7,500 mg/kg on a mg/kg basis). These doses were
257 approximately 55 and 30 times the MRHDID, respectively, on a mg/m² basis.

258 Mannitol tested negative in the following assays: bacterial gene mutation assay, in vitro mouse
259 lymphoma assay, in vitro chromosomal aberration assay in WI-38 human cells, in vivo chromosomal
260 aberration assay in rat bone marrow, in vivo dominant lethal assay in rats, and in vivo mouse
261 micronucleus assay.

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

263 **13.2 Animal Toxicology and/or Pharmacology**

264 *Reproductive Toxicology Studies*

265 Mannitol did not cause any embryofetal malformations when given to pregnant rats and mice at oral
266 doses of 1.6 g/kg each (approximately 20 and 10 times the MRHDID in adults, respectively, on a
267 mg/m² basis).

268 **14 CLINICAL STUDIES**

269 The effectiveness of the ARIDOL bronchial challenge test kit in assessing bronchial
270 hyperresponsiveness in adults and children 6 years of age and older was assessed in two clinical
271 studies. Study 1 was an operator-blinded, open-label crossover trial that assessed the sensitivity and
272 specificity of bronchial challenge testing with ARIDOL compared with a methacholine bronchial
273 challenge test in detecting bronchial hyperresponsiveness in subjects with symptoms suggestive of
274 asthma but without a definite diagnosis of asthma. During the course of the study subjects underwent
275 three types of bronchial challenge tests utilizing exercise, ARIDOL, and methacholine. A positive
276 exercise test was defined as a decrease in FEV₁ ≥ 10%, a positive bronchial challenge test with
277 ARIDOL was defined by either a decrease in FEV₁ by ≥ 15% from baseline or a between-dose
278 reduction in FEV₁ ≥ 10%, and a positive methacholine response was defined as a decrease in FEV₁
279 ≥ 20% after breathing methacholine at a concentration less than or equal to 16 mg/mL. The sensitivity
280 and specificity of bronchial challenge testing with ARIDOL and methacholine were then assessed
281 relative to exercise testing which served as a common comparator. The sensitivity and specificity of
282 ARIDOL and methacholine challenges were also assessed using a blinded study physician's diagnosis
283 of asthma at the end of the study. Five-hundred nine subjects aged 6 to 50 years were screened for
284 enrolment with 419 and 420 subjects receiving at least one dose of mannitol, the active ingredient in
285 ARIDOL, or methacholine, respectively. The maximum cumulative dose of mannitol was 635 mg.
286 Bronchial challenge testing with ARIDOL and methacholine demonstrated similar sensitivity and
287 specificity in predicting bronchial hyperresponsiveness defined by a positive exercise challenge
288 (Table 4).

Table 4 Comparisons of the sensitivity and specificity (calculated relative to exercise challenge) for the ARIDOL test and methacholine in Study 1			
Population	Treatment	Sensitivity % (95% CI)	Specificity % (95% CI)
Overall Population (n=419)			
	ARIDOL	58 (50, 65)	63 (57, 69)
	Methacholine	53 (46, 51)	68 (62, 73)
	Difference	5 (-4, 13)	-5 (-12, 3)
Age 6-11 years old (n=36)			
	ARIDOL	67 (47, 87)	47 (21, 72)
	Methacholine	71 (52, 91)	33 (9, 57)
	Difference	-5 (-29, 20)	17 (-29, 62)
Age 12-17 years old (n=70)			
	ARIDOL	55 (37, 72)	62 (46, 77)
	Methacholine	65 (48, 81)	64 (49, 79)
	Difference	-10 (32, 13)	-3 (-24, 19)

289

290

291 Bronchial challenge testing with ARIDOL and methacholine also demonstrated similar sensitivity and
 292 specificity when calculated relative to a blinded study physician’s diagnosis of asthma in subjects at
 293 the end of the study.

294

295 The sensitivity and specificity of bronchial challenge testing with ARIDOL in children and adolescents 6 to 17 years of age in Study 1 was similar to that in the overall population (Table 4).

296

297 Study 2 was a crossover study comparing bronchial challenge testing with ARIDOL to hypertonic
 298 (4.5%) saline in identifying bronchial hyperresponsiveness in subjects 6 to 83 years of age with
 299 (n=551) and without (n=95) asthma. In this study the efficacy endpoint of interest was an estimation
 300 of the sensitivity and specificity of bronchial challenge testing with ARIDOL with respect to a
 301 physician’s clinical diagnosis of asthma. Following completion of the bronchial challenge tests with
 302 ARIDOL and hypertonic saline, a respiratory physician assessed the data and categorized the subjects
 303 as having or not having asthma. The sensitivity of the ARIDOL bronchial challenge test in subjects
 304 with a physician diagnosis of asthma was 58% [(54%, 62%, 95th CI)] compared to a sensitivity of the
 305 physician diagnosis in the same population of 97% [(95%, 98%, 95th CI)]. The specificity of the
 306 ARIDOL bronchial challenge test in subjects without asthma was 95% [(90%, 99%, 95th CI)]
 compared to the specificity of the physician diagnosis of 98% [(95%, 100%, 95th CI)].

307

16 HOW SUPPLIED/STORAGE AND HANDLING

308

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

311

Blister pack “1”:

312

- Marked 1 - 1 x empty clear capsule

313

- Marked 2 - 1 x 5 mg white/clear capsule printed with 5 mg

314

- Marked 3 - 1 x 10 mg yellow/clear capsule printed with 10 mg

315

- Marked 4 - 1 x 20 mg pink/clear capsule printed with 20 mg

- 316 Blister pack “2”:
317 • Marked 5 - 1 x 40 mg red/clear capsule printed with 40 mg
318 • Marked 6 – 2 x 40 mg red/clear capsules printed with 40 mg
319 • Marked 7 – 4 x 40 mg red/clear capsules printed with 40 mg

- 320 Blister pack “3”:
321 • Marked 8 – 4 x 40 mg red/clear capsules printed with 40 mg
322 • Marked 9 - 4 x 40 mg red/clear capsules printed with 40 mg

323
324 NDC-44178-XXX-XX

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

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

332 **17 PATIENT COUNSELING INFORMATION**

333 **17.1 Severe Bronchospasm**

334 Prior to administration patients should be informed of the potential for bronchial challenge testing
335 with ARIDOL to cause severe bronchospasm and of the potential symptoms they may experience.

336 **17.2 Subjects with Certain Co-morbid Conditions**

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

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345 Frenchs Forest NSW 2086
346 AUSTRALIA

347
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354
355 ARIDOL™ is a registered trademark of Pharmaxis Ltd

356 SP-200-01