

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022368Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: October 5, 2010

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 22-368

Applicant Name: Pharmaxis Ltd

Date of Submission: April 7, 2010

PDUFA Goal Date: October 7, 2010

Proprietary Name: Aridol

Established Name: Mannitol Inhalation Powder

Dosage form: Inhalation powder in gelatin capsules, and inhaler device

Strength: 0, 5, 10, 20, and 40 mg gelatin capsules

Proposed Indications: Assessment of bronchial hyperresponsiveness

Action: Approval

1. Introduction

Pharmaxis Ltd originally submitted this 505(b)(1) application on February 27, 2009, for use of Aridol (mannitol inhalation powder) in a single patient use inhaler as a single use product for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older. Assessment of bronchial hyperresponsiveness is usually done as an aid in the diagnosis of asthma. The proposed testing regimen is for a patient to serially inhale mannitol powder supplied at doses of 0, 5, 10, 20, 40, 80, 160, 160, and 160 mg. Spirometry is performed immediately after each serial inhalation. Dosing is stopped and the test is called positive when either FEV1 decreases 15% or more from baseline or decreases $\geq 10\%$ from the value obtained following the immediate previous dose. Testing is negative if all doses of mannitol are inhaled (635 mg total) without decreases in overall FEV1 $\geq 15\%$ or a decrease $\geq 10\%$ from the value obtained following the immediate previous dose. A complete response action on the original submission was taken on December 23, 2009, because the Office of Compliance made a withhold recommendation due to violations seen in the testing sites. The applicant submitted a response to the complete response action on April 7, 2010, addressing this deficiency. This summary review provides an overview of the application and the complete response. The reader is referred to the previous Division Director's review dated December 23, 2009, for details of the original review cycle findings and Agency conclusion.

2. Background

There is currently one other FDA approved drug for use for assessment bronchial hyperresponsiveness. The product is Provocholine (methacholine chloride), which was approved in 1986. A mannitol test for assessment of bronchial hyperresponsiveness is currently approved for marketing in at least 15 countries under the trade name Aridol or

Osmohale. Mannitol inhaled on a chronic basis is also being studied to enhance mucociliary clearance in patients with bronchiectasis, cystic fibrosis, and chronic obstructive pulmonary disease (COPD).

3. Chemistry, Manufacturing, and Controls

The product is a single use test kit consisting of 5 strengths of mannitol: 0 mg, 5 mg, 10 mg, 20 mg, and 40 mg, in hard gelatin capsules, and a hand held dry powder inhaler. The inhaler is similar to other marketed single dose dry powder inhaler devices. To deliver a dose of mannitol, the health care provider will place one capsule in the chamber of the inhaler device, press the push buttons to pierce the capsule on each end, and ask the patient to breathe in rapidly and deeply through the mouthpiece.

The drug substance is manufactured by [REDACTED] (b) (4), and the finished product is manufactured by Pharmaxis Inc. in Australia. The inhaler device is manufactured by [REDACTED] (b) (4). All manufacturing and testing facilities associated with this application have an acceptable inspection status. Testing sites previously found to have violations have either been replaced by the applicant with an acceptable alternate or removed from the application. Pharmaxis has submitted adequate stability data to support expiry of 12 months. All Drug Master Files (DMFs) associated with this application were also found to be acceptable.

Based on limited data available in the application, Pharmaxis Inc. has not fully characterized foreign particulate matter and aerodynamic particle size distribution to set final release specifications. Post marketing commitments are in place to address these two issues.

4. Nonclinical Pharmacology and Toxicology

The nonclinical program for the application focused on the effect of inhaled mannitol on the respiratory system because the toxicological profile of mannitol for non-inhalation use has been well established. Mannitol is non-carcinogenic, non-genotoxic, and non-teratogenic; and it is considered to be generally safe when given orally. Pharmaxis submitted reports of up to 3 and 6 months inhalation toxicology studies in rats and dogs, respectively. The studies showed toxicities in the respiratory system, which included increased incidence of alveolitis and macrophages accumulation in the lung in rats, and laryngeal ulceration in dogs. However, these findings in animals had acceptable safety margins to support the proposed human dosage, hence, are not of concern for the intended Aridol use in humans.

5. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology program submitted was limited because Aridol will be used only as a single dose use product and not chronically, and mannitol is considered to be generally safe when given orally. This limited program is acceptable. Pharmaxis conducted a study in 18 healthy male subjects to compare the bioavailability of mannitol

powder administered by inhalation route to mannitol administered intravenously and orally. The relative bioavailability of inhaled mannitol compared to orally administered mannitol was 96%.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies with Aridol

ID	Study type	Study duration	Patient Age, yr	Test groups	N (ITT)	Study Year#	Countries
301	crossover	Single test	6-83	Mannitol inhalation 4.5% saline inhalation	509	2004	Australia
305	crossover	Single test	6-50	Mannitol inhalation Methacholine inhalation Exercise challenge	654	2006	USA
# Year study subject enrollment ended							

b. Design and conduct of the studies

Study 301 was a multi-center, open-label, operator-blinded, randomized, crossover in design conducted in patients who either carried a definitive diagnosis of asthma or do not have asthma. After screening and randomization, study subjects underwent either a mannitol or 4.5% saline challenge test 1 week apart. Subjects were considered positive to either test if at least a 15% reduction in FEV1 from baseline occurred. The primary efficacy endpoint was to estimate and compare the sensitivity and specificity of the mannitol challenge with respect to the 4.5% saline challenge. Safety assessments were limited to physical examination and recording of adverse events.

Study 305 was a multi-center, open-label, operator-blinded, randomized, crossover in design conducted in patients with symptoms suggestive of asthma but without a definitive diagnosis of asthma. During the course of the study subjects underwent three separate bronchial challenge tests utilizing exercise, Aridol, and methacholine. A positive exercise test was defined as a decrease in FEV1 $\geq 10\%$, a positive Aridol test was defined by either a decrease in FEV1 by $\geq 15\%$ from baseline or a between-dose fall in FEV1 $\geq 10\%$, and a positive methacholine response was defined as a decrease in FEV1 $\geq 20\%$ after breathing methacholine at a concentration less than or equal to 16 mg/mL. The sensitivity and specificity of Aridol and methacholine challenges were assessed relative

to exercise testing which served as a common comparator. The objectives of the study were to: (1) Estimate sensitivity and specificity of Aridol to detect bronchial hyperresponsiveness, as manifested by a positive exercise challenge, i.e., within a 10% margin of the point estimates. (2) Demonstrate that Aridol challenge test sensitivity for bronchial hyperresponsiveness is significantly greater than 60%; and (3) Demonstrate that Aridol specificity is significantly greater than that seen with methacholine to detect bronchial hyperresponsiveness. Safety assessments were limited to physical examination and recording of adverse events.

c. Efficacy findings and conclusions

The submitted clinical studies are adequate to support the use of Aridol for assessment of bronchial hyperresponsiveness in subjects 6 years of age and older.

Study 301 allowed estimation of sensitivity and specificity of Aridol with respect to physician diagnosis of asthma. The sensitivity of Aridol in subjects with a physician diagnosis of asthma was 58% [(54%, 62%, 95th CI)] compared to a sensitivity of the physician diagnosis in the same population of 97% [(95%, 98%, 95th CI)]. The specificity of Aridol in subjects without asthma was 95% [(90%, 99%, 95th CI)] compared to the physician diagnosis in the same population of 98% [(95%, 100%, 95th CI)]. Comparative data to 4.5% saline is of no utility because it is not recognized as a bronchial challenge test in the United States.

Study 305 was conducted by Pharmaxis at the Division's request to provide data in patients with symptoms suggestive of asthma but without a definitive diagnosis of asthma, because this is the population on which the test will be performed. Pharmaxis included exercise challenge test as a common denominator to compare mannitol and methacholine because exercise challenge is a recognized test in patients with asthma. Results of the study are shown in Table 2 and Figure 1 below.

The sensitivity and specificity of Aridol and methacholine were comparable in this study population, and both were statistically significantly higher than 50% for the overall study population, a level of success that could be achieved by chance alone (Table 2). The fall in FEV1 associated with administration of increasing dose of mannitol is greater in the exercise positive subject than in the exercise negative subjects and this relationship is similar to that of methacholine (Figure 1). This analysis further supports efficacy.

Table 2. Comparison of sensitivity and specificity (calculated relative to exercise challenge) for Aridol and methacholine (Study 305)

Population	Treatment	Sensitivity % (95% CI)	Specificity % (95% CI)
Overall (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 (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 (n=70)	Aridol	55 (37, 72)	62 (46, 77)

Population	Treatment	Sensitivity % (95% CI)	Specificity % (95% CI)
	Methacholine	65 (48, 81)	64 (49, 79)
	Difference	-10 (32, 13)	-3 (-24, 19)

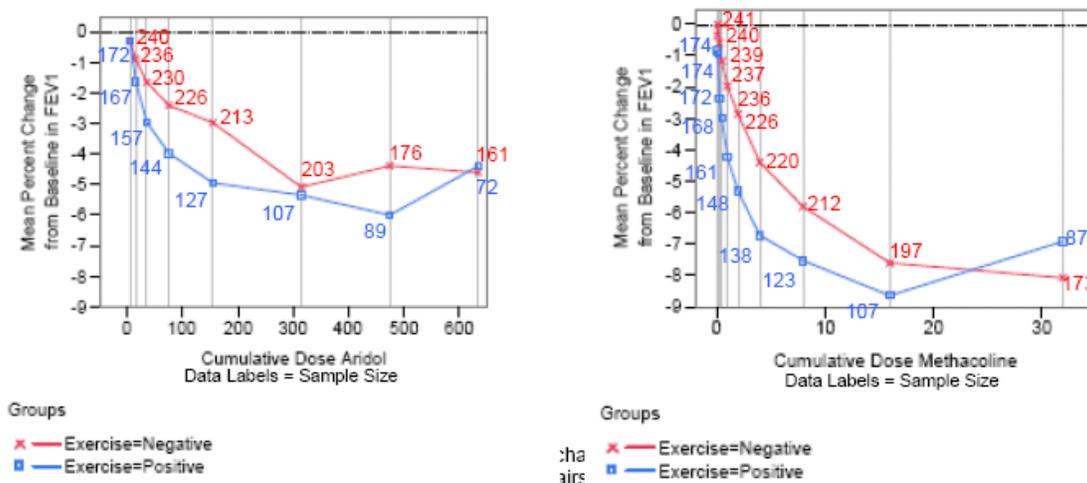


Figure 1. Mean percent change from baseline in FEV1 with Aridol or methacholine by exercise stratum

8. Safety

a. Safety database

The safety assessment of Aridol is based on studies shown in Table 1. The primary safety database is comprised of the two pivotal studies that consist of 1082 unique subjects (577 females and 505 males). The safety database is adequate and typical for other similar applications.

b. Safety findings and conclusion

The safety data do not raise any obvious safety concern for Aridol that will preclude approval. The studies did not investigate the long-term effects of Aridol, or the effects of Aridol on blood chemistry, hematology, urinalysis, or ECG parameters. This is appropriate because mannitol is considered generally safe when given orally and the dose given by inhalation route for bronchial hyperresponsiveness test is much smaller considering the amount generally used orally.

There were no deaths in the clinical program. There was one serious adverse event of appendicitis in the program that was considered unrelated to the study drug. Common adverse events were related to the respiratory tract, which is expected of the drug and the study population. A major safety concern of bronchial hyperresponsiveness testing is large decrease in FEV1 during the test. Frequency of subjects with decreases in FEV1 $\geq 30\%$ was 3% for Aridol compared to 12% for methacholine. Aridol will have a boxed warning regarding the potentials for bronchospasm and recommendations on safe administration of the test.

One limitation of the safety database is paucity of data in older subjects, an age group where co-morbid conditions such as cardiovascular and chronic respiratory disease other than asthma is common. Study 305 excluded enrollment of subjects 50 years of age and older due to physical demands of the exercise challenge. Pharmaxis had agreed to conduct a required post-marketing study to assess the safety of Aridol in older subjects.

c. REMS/RiskMAP

There are no substantial safety concern that would require REMS and RiskMAP. The major safety concern with Aridol is large decrease in FEV1 during the test, which will be reflected as a boxed warning. Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test.

9. Advisory Committee Meeting

An advisory committee for Aridol was held on November 20, 2009. The Committee voted with an overall majority that the submitted data provide substantial and convincing evidence to support approval of Aridol for testing of bronchial hyperresponsiveness. The Committee commented that the data for ages 50 years and older was limited, but recommended that Aridol be made available for patients 6 years of age and older. The Committee commented on the low sensitivity of Aridol as well as methacholine for diagnosis of asthma, but noted that neither Aridol nor methacholine is a diagnostic test for asthma. The Committee stated that in some situations Aridol will provide useful information that will help clinicians make a diagnosis of asthma. The Committee did not want the Aridol test to be overused as a screening test for asthma.

10. Pediatric

Pharmaxis submitted a request for a waiver for studies for children below 6 years of age based on the inability of children below 6 years of age to perform serial spirometry reliably, which is required for the Aridol bronchial challenge test. The Division agreed that a waiver in children below 6 years of age is reasonable. The request was discussed at the PERC meeting on October 7, 2009, during which the committee also agreed that a waiver is appropriate.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two sites that enrolled large number of patients in study 305. Audit of the sites did not reveal any major irregularities. During review of this application the clinical team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. None of the investigators had significant equity interest in Pharmaxis.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Aridol was reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Pharmaxis submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. The labeling contains a Boxed Warning for bronchospasm. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, SEALD, and by DDMAC. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. The Division and Pharmaxis have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, OBP, and DMEPA, and found to be acceptable after agreed upon revisions were made.

d. Patient Labeling and Medication Guide

There is no patient labeling and medication guide. The Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test. There are clinician Instructions for Use which, with agreed upon revisions, is acceptable to the Division, DMEPA, and Pharmaxis.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Pharmaxis has submitted adequate data to support efficacy and safety of Aridol in a single patient use inhaler as a single use product for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment of Aridol in a single patient use inhaler as a single use product for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older supports its approval. The submitted clinical studies demonstrate that the proposed serial increasing dose of Aridol provides acceptable data as a test of bronchial hyperresponsiveness. The safety profile of Aridol as a single use product is also acceptable. The adverse event profile was predictable and not of concern. The major safety concern with Aridol is acute bronchospasm during the test, which will be reflected

as a boxed warning. Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

Pharmaxis had agreed to conduct a required post-marketing study to assess the safety of Aridol in subjects 50 years of age and older as discussed in section 8b above (Clinical Safety).

Pharmaxis has not fully characterized foreign particulate matter and aerodynamic particle size distribution to set final release specification. Post -marketing commitments are in place to address these two issues as discussed in section 3 above (Chemistry, Manufacturing, and Controls).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
10/05/2010