SUMMARY REVIEW OF REGULATORY ACTION

Date:	December 23, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-368
Applicant Name:	Pharmaxis Ltd
Date of Submission:	February 27, 2009
PDUFA Goal Date:	December 27, 2009
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:	Complete Response

1. Introduction

Pharmaxis Ltd submitted this 505(b)(1) application 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 ≥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 ≥15% or a decrease ≥10% from the value obtained following the immediate previous dose. The application is based on clinical efficacy and safety study. This review will provide an overview of the application with a focus on the clinical program.

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 placed 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 (b) (4), and the finished product is manufactured by Pharmaxis Inc in Australia. The inhaler device is manufactured by (b) (4). 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.

The overall recommendation from Office of Compliance is a withhold recommendation due to some GMP violations seen in three testing sites.

(b) (4)

Based on this recommendation from the Office of Compliance, CMC is recommending a Complete Response action pending an acceptable overall recommendation from the Office of Compliance for all manufacturing and testing sites listed in the application.

Based on limited data available in the application, (b) (4) Post approval agreements are in place to address these two issues. These by themselves do not preclude approval and will be noted as agreements in the action letter.

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 indacaterol maleate

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 types of bronchial challenge tests utilizing exercise, Aridol, and methacholine. A positive

exercise test was defined as a decrease in FEV1 ≥ 10%, a positive Aridol test was defined by either a decrease in FEV1 by ≥ 15% from baseline or a between-dose fall in FEV1 ≥ 10%, and a positive methacholine response was defined as a decrease in FEV1 ≥ 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 bronchla 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 if approved. 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 1 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 that 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)
	Methacholine	65 (48, 81)	64 (49, 79)
	Difference	-10 (32, 13)	-3 (-24, 19)

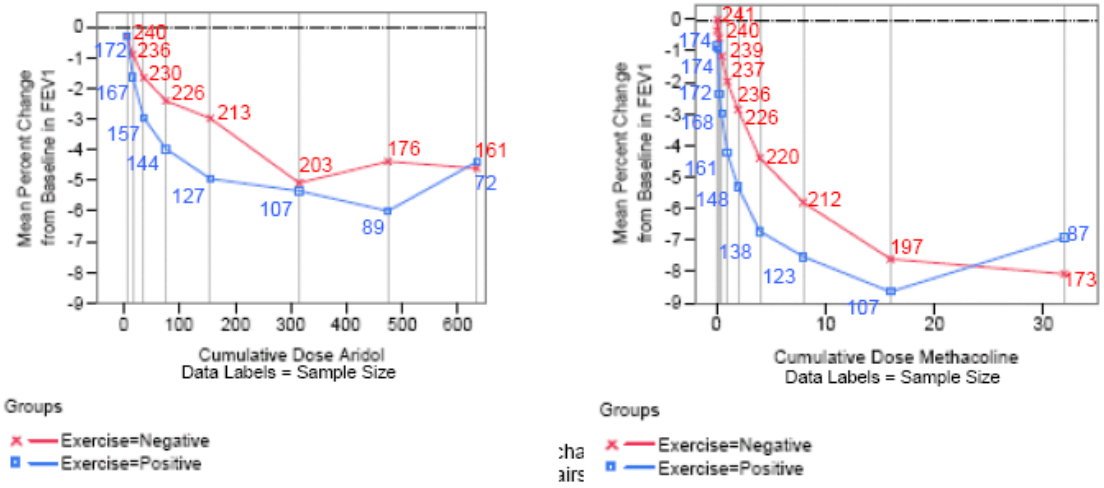

Figure 1. Mean percent change from baseline in FEV1 with Aridol or methacholine by exercise stratum

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 considered 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 ≥30% was 6% for Aridol compared to 12% for methacholine. Aridol will have a boxed warning regarding the potentials for bronchospasms and recommendations on safe administration of the test.

(b) (4)

(b) (4) Since the application will not be approved, Pharmaxis will be given the option of addressing this requirement in their response to the action.

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

(b) (4)

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. However, the application cannot be approved because the Office of Compliance has made a withhold recommendation due to violations seen in the testing sites (see section 3 above). Based on this recommendation from the Office of Compliance, CMC is recommending a Complete Response action pending an acceptable overall recommendation from the Office of Compliance for all manufacturing sties listed in the application. Therefore, the action on this application will be Complete Response.

b. Risk Benefit Assessment

An overall risk and benefit assessment of this application cannot be made because as noted in section 3 and section 13a the Office of Compliance has identified violations in the drug product testing site. This deficiency will preclude approval. From a pure clinical standpoint, the submitted data otherwise would have supported approval of Aridol for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older. 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

(b) (4)

(b) (4) Since the application will not be approved in this review cycle, Pharmaxis will be given the option of addressing this requirement in their response to the action.

(b) (4) Post approval agreements are in place to address these two issues. These by thmeselves do not preclude approval and will be noted in the action letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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BADRUL A CHOWDHURY
12/23/2009