CLINICAL PHARMACOLOGY REVIEW

NDA:	22-368
Proprietary Drug Name:	ARIDOL™
Generic Name:	Mannitol bronchial challenge test
Indication:	Assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma
Dosage Form:	Dry powder capsules
Route of Administration:	Oral inhalation
Applicant:	Pharmaxis Ltd
Clinical Division:	Division of Pulmonary and Allergy Products
Submission Date:	February 27, 2009
PDUFA Date:	December 27, 2009
Reviewer:	Ying Fan, Ph.D.
Team Leader (Acting):	Partha Roy, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed the Clinical Pharmacology information submitted under NDA 22-368 on February 27, 2009 and finds it acceptable provided that a satisfactory agreement is reached between the applicant and the Agency regarding the proposed new language to be included in the package insert.

1.2 Phase IV Commitments

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The sponsor submitted the new drug application for Aridol™ mannitol bronchial challenge test. The proposed indication is the assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma. The previous information concerning this product was submitted under IND 70, 277.

Mannitol is a naturally occurring product found in plants, algae, fungi and some bacteria; also, it is endogenous in humans. When inhaled, mannitol induces an increase in osmolarity in the airways similar to that induced by other bronchial provocation tests, such as hypertonic saline, exercise, and the hyperpnea of dry air. The increase in osmolarity is associated with the release of a wide variety of mediators of bronchoconstriction from inflammatory cells within the airways. These mediators then act via specific receptors on bronchial smooth muscle to cause contraction and consequent narrowing of the airways. The airway response is most pronounced (hyperresponsive) in patients with asthma and exercise-induced asthma.

There is at least one prior example where dry powder mannitol was included as an inactive ingredient in an inhaled formulation, which is inhaled insulin that was approved for oral inhalation use on January 27, 2006 (NDA 21-868, Exubera®). This product employs a drug-device combination consisting of hard gelatin capsules containing (b) (4) mannitol and a proprietary dry powder inhaler. As of November 11, 2008, mannitol bronchial challenge test (BCT) has been approved in 10 countries as Aridol™ (proposed proprietary name), and in 4 countries as Osmohale™. Mannitol is a Generally Recognized As Safe (GRAS) excipient in the US for food substances at intakes of up to 20 g/day without additional labeling.

The current clinical submission comprises of two Phase 3 safety and efficacy studies, one open observational non-drug study, and one definitive pharmacokinetic (PK) and bioavailability (BA) study (DPM-PK-101). At the July 19, 2004, Pre-IND/NDA meeting, Agency agreed that no PK study was necessary for the NDA submission. However, Agency also asked the sponsor to provide information on the fate of the drug in the lungs after inhalation. In addition, Agency suggested the sponsor to collect urine and/or plasma samples to provide information on mass balance of the administered dose and on the absorption of mannitol from the lungs. Based on the comments, the sponsor conducted the PK and BA study (DPM-PK-101) and submitted the

results in this NDA. The objective of PK and BA study is: 1) to determine the absolute BA of mannitol powder for inhalation compared to mannitol administered intravenously; 2) to determine the relative bioavailability of mannitol powder for inhalation compared to mannitol administered orally; 3) to determine the pharmacokinetic parameters of systemically available mannitol after inhalation. The Study DPM-PK-101 was an open-label, randomized, three-way cross over study design in 18 healthy male subjects aged 18-65 years old. Each subject received three treatments: 635 mg mannitol powder for inhalation using a drug powder inhaler, 500 mg mannitol powder administered orally (5 ml of Osmitrol 10% solution), and mannitol 500 mg (5 ml of Osmitrol intravenous infusion 10%) in a commercial formulation for intravenous use. The results indicate that the absolute bioavailability of inhaled mannitol in comparison to intravenously administered mannitol was 59%, based on individual AUC comparisons. The relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%. The median time to reach the mannitol peak plasma concentration (T_{max}) is 1.5 (1-2) hour for inhaled and 1.4 (1-2) hour for oral administration. Dose normalized C_{max} in inhalation was about 18% lower than the oral administration. The mean terminal half-life of mannitol remained constant at approximately 5 hours regardless of the route of administration (Table 1). Urinary excretion rate versus time profile for mannitol was consistent for all routes of administration (Figure 1).

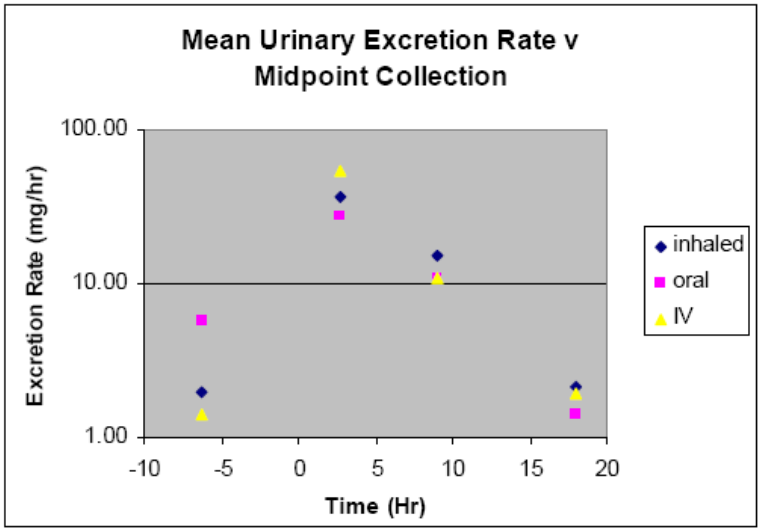
Table 1. Plasma pharmacokinetic results for inhaled mannitol (Mean values ± SD): Study DPM-PM-101

Treatment	Pharmacokinetic Parameters							
	N	T_{max} (hr)	C_{max} (ng/ml)	$T_{1/2}$ (hr)	AUC_{0-24} (ng hr/ml)	AUC_{0-inf} (ng.hr/ml)	C_{max}* (ng/ml)	AUC_{0-inf}* (ng.hr/ml)
635 mg inhalation	18	1.5 ± 0.5	13,706 ± 2638	4.7 ± 1.0	71,457 ± 12586	73,150 ± 12717	10,792 ± 2638	57,599 ± 12717
500 mg oral	18	1.4 ± 0.5	13,094 ± 3085	5.2 ± 1.1	59,776 ± 13596	61,414 ± 14059	13,094 ± 3085	61,414 ± 14509
500 mg iv	18	0.1 ± 0.04	44,322 ±8775**	4.5 ± 1.1	98,719 ± 21735	100,236 ± 21516	44,322 ± 8775	100,236 ± 21561

*values were dose-normalized to 500 mg dose

** mannitol concentration at the 1st sampling time-point (0.1 hr)

Figure 1. Mean urinary excretion rates following single dose administration of 635 mg mannitol powder for inhalation using a drug powder inhaler, 500 mg mannitol powder administered orally (5 ml of Osmitrol 10% solution), and mannitol 500 mg IV (5 ml of Osmitrol intravenous infusion 10%)



Conclusion

The pharmacokinetic data from study DPM-PK101 revealed that systemic exposures of mannitol after inhalation and oral administration were generally similar. The absolute bioavailability of inhaled mannitol in comparison to intravenously administered mannitol was 59%. The relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%, consistent with comparable exposure reported for these two routes of administration. Furthermore, comparable T_{max} and $T_{1/2}$ values between inhalation and oral routes of administration suggest an absence of any change in systemic pharmacokinetic properties of the drug following administration by the inhalation route.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the general attributes of ARIDOL™?

Mannitol is the drug substance in ARIDOL™. It is a hexahydric alcohol with the following chemical structure (Figure 2).

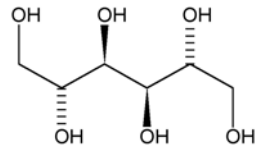


Figure 2. Structural formula of mannitol

Mannitol is a white or almost white crystalline powder of free-flowing granules with an empirical formula of $C_6H_{14}O_6$ and molecular weight of 182.2. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism. Mannitol is spray dried into fine particles. The ARIDOL™ test kit contains printed hard-gelatin capsules containing dry powder mannitol for oral inhalation. There are no inactive ingredients in ARIDOL™. The bodies of the 0, 5, 10, 20 and 40 mg capsules are clear. The white caps (5 mg) contain titanium dioxide. The yellow caps (10 mg) contain titanium dioxide and yellow iron oxide. The pink caps (20 mg) and red caps (40 mg) contain titanium dioxide and red iron dioxide. The delivered dose from each of the 5, 10, 20 and 40 mg capsules is approximately 3.4, 7.7, 16.5 and 34.1 mg, respectively.

DOSAGE FORMS & STRENGTHS

ARIDOL™ is supplied as a complete test kit. Each kit contains 1 proprietary, single-use, dry powder inhaler and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation as described below:

Blister 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

Blister 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

Blister 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

INDICATIONS (as per proposed label)

ARIDOL™ is an indirect bronchial challenge test indicated for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma.

DOSAGE AND ADMINISTRATION

ARIDOL™ is supplied as a complete test kit containing the required capsules of dry powder mannitol in graduated doses and a proprietary single-use inhaler to perform one indirect bronchial challenge test for one patient. The airway response to ARIDOL™ is measured using forced expiratory volume in one second (FEV_1). Prior to the ARIDOL™ test, standard spirometry should be performed and the reproducibility of the resting FEV_1 established.

Aridol™ contains capsules of dry-powder mannitol that are administered by oral inhalation using a single-use disposable dry-powder inhaler. Each Arildol test kit contains 19 capsules, as listed in Table 2.

Table 2: Dose of Capsules and Number of Capsules of Each Dose in Aridol Kit

Number of Capsules	Each Capsule Contains
1	Empty
1	5 mg
1	10 mg
1	20 mg
15	40 mg

As listed in Table 3, nine (9) doses can be administered, up to a maximum cumulative dose of 635 mg.

Table 3: Dose Step-up and Corresponding Cumulative Dose

Step	Dose for Step (mg)	Cumulative Dose (mg)
1	0	0
2	5	5
3	10	15
4	20	35
5	40	75
6	80	155
7	160	315
8	160	475
9	160	635

At baseline and following each dose, a measure of FEV1 is made and the Aridol™ test is continued until either a 15% fall in FEV1 from baseline is reached or a 10% fall from the previous dose occurs (positive tests), or until the full cumulative dose of 635 mg has been administered (negative test).

2.1.2 What is the regulatory background of inhaled mannitol?

(b) (4) mannitol was included as an inactive ingredient in the formulation of inhaled insulin that was approved for oral inhalation use on January 27, 2006 (NDA 21-868, Exubera®). Under the same IND (70,277) as the current mannitol bronchial challenge test (BCT) program, (b) (4) As of November 11, 2008, mannitol BCT has been approved in 10 countries as Aridol™ (proposed proprietary name), and in 4 countries as Osmohale™. Mannitol is a Generally Recognized as Safe (GRAS) excipient in the US for food substances at intakes of up to 20 g/day without additional labeling for oral, intravenous and ocular products.

2.1.3 What is the historical and current use of Mannitol?

Mannitol has been used for many years as laxative and osmotic diuretics in large IV doses. The IV strengths of the mannitol products currently listed in the Orange Book range from 5 gram/100 mL to 20 gram/100 mL. The drug was administered up to 25 to 100 grams via oral and IV routes with no toxicity.

2.2 General Clinical Pharmacology

2.2.1 What are the PK characteristics of mannitol after inhalation administration?

The sponsor evaluated the single-dose pharmacokinetics of mannitol under fasted condition in a randomized, open label, three-way cross-over study (Study DPM-PK-101) in 18 healthy male subjects aged 18-65 years old. Each subject received three treatments: 635 mg mannitol powder for inhalation using a drug powder inhaler, 500 mg mannitol powder administered orally (5 ml of Osmitrol 10% solution), and mannitol 500 mg (5 ml of Osmitrol intravenous infusion 10%) in a commercial formulation for intravenous use. The results are presented below in Table 4. Mannitol was found to be absorbed into the systemic circulation with a median T_{max} of 1.5 (1-2) hours following single dose inhaled administration. The mean (SD) terminal half-life values of mannitol was calculated to be 4.7 (1.0) hrs, respectively.

Table 4. Mean (SD) pharmacokinetic parameters of mannitol following 635 mg inhalation administration of Aridol™.

PK parameters	Aridol™ 635 mg (n=18)
$AUC_{0\text{-}24h}$ (ng*hr/ml)	71,457 (12,586)
$AUC_{0\text{-}inf}$ (ng*hr/ml)	73,150 (12,717)
C_{max} (ng/ml)	13,706 (2,638)
$T_{1/2}$ (h)	4.7 (1.0)
T_{max} (h)	1.5 (1-2)*

* median (range)

2.3 General Biopharmaceutics

2.3.1 What is the bioavailability of mannitol after the inhalation administration compared with the intravenous administration and oral administration?

A pharmacokinetic (PK) and bioavailability (BA) study (Study DPM-PK-101), as described in section 2.2.1 above, was conducted with three primary objectives: 1) to determine the absolute BA of mannitol powder for inhalation compared to mannitol administered intravenously; 2) to determine the relative bioavailability of mannitol powder for inhalation compared to mannitol administered orally; 3) to determine the pharmacokinetic parameters of systemically available mannitol after inhalation. This was particularly necessary because there are no available PK data following inhaled mannitol administration.

The pharmacokinetic parameters of mannitol following inhalation administration of Aridol™, Osmitrol solution, and Osmitrol intravenous infusion are listed in Table 5. The data revealed that the absolute bioavailability of inhaled mannitol in comparison to intravenously administered mannitol was 59% based on individual AUC comparisons. The relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%. The mean time to reach mannitol peak plasma concentration (T_{max}) is 1.5 hour for inhalation administration and 1.4 hour for oral administration. Dose normalized C_{max} in inhalation was 18% lower than oral administration: 10,792 ng/mL and 13,094 ng/mL for inhaled and oral, respectively (Table 5). The mean terminal half-life of mannitol remained constant at approximately 5 hours regardless of route of administration. The plasma concentration-time plots for mannitol after three different routes of administrations further supports the above results (Figure 3).

Figure 3. Mean mannitol plasma concentrations (ng/mL) versus time profiles after administration of 635 mg mannitol powder for inhalation using a drug powder inhaler (A), 500 mg mannitol powder administered orally (5 ml of Osmitrol 10% solution) (B), and mannitol 500 mg (5 ml of Osmitrol intravenous infusion 10%) (C)

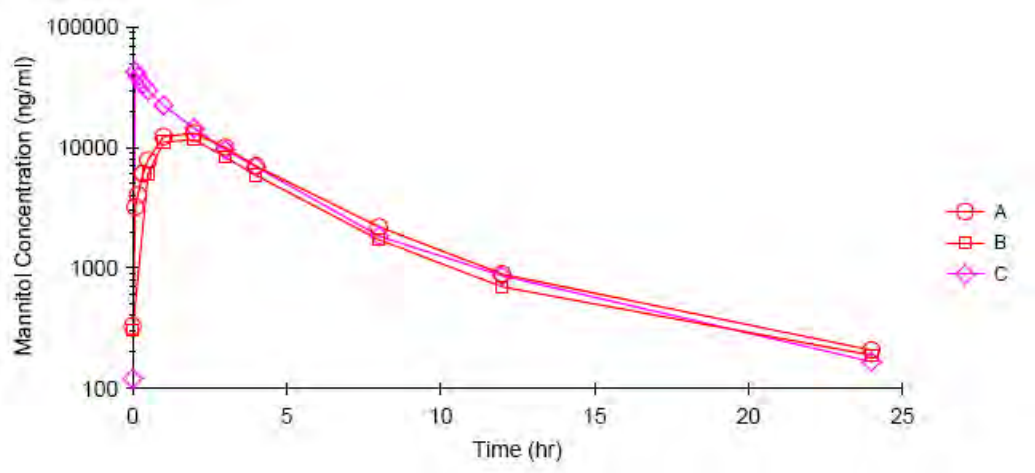


Table 5. PK summary of mannitol following single dose administration of 635 mg mannitol powder for inhalation using a drug powder inhaler, 500 mg mannitol powder administered orally (5 ml of Osmitrol 10% solution), and mannitol 500 mg IV (5 ml of Osmitrol intravenous infusion 10%)

Treatment	Pharmacokinetic Parameters							
	N	T_{max} (hr)	C_{max} (ng/ml)	$T_{1/2}$ (hr)	AUC_{0-24} (ng.hr/ml)	AUC_{0-inf} (ng hr/ml)	C_{max}* (ng/ml)	AUC_{0-inf}* (ng.hr/ml)
635 mg inhalation	18	1.5 ± 0.5	13,706 ± 2638	4.7 ± 1.0	71.457 ± 12586	73,150 ± 12717	10,792 ± 2638	57,599 ± 12717
500 mg oral	18	1.4 ± 0.5	13,094 ± 3085	5.2 ± 1.1	59,776 ± 13596	61,414 ± 14059	13,094 ± 3085	61,414 ± 14059
500 mg iv	18	0.111 ± 0.5	44,322 ± 8775	4.5 ± 1.1	98,719 ± 21735	100,236 ± 21561	44,322 ± 8775	100,236 ± 21561

*values were dose-normalized to 500 mg dose

Figure 4 Mean urinary excretion rates following single dose administration of 635 mg mannitol powder for inhalation using a drug powder inhaler, 500 mg mannitol powder administered orally (5 ml of Osmitrol 10% solution), and mannitol 500 mg IV (5 ml of Osmitrol intravenous infusion 10%)

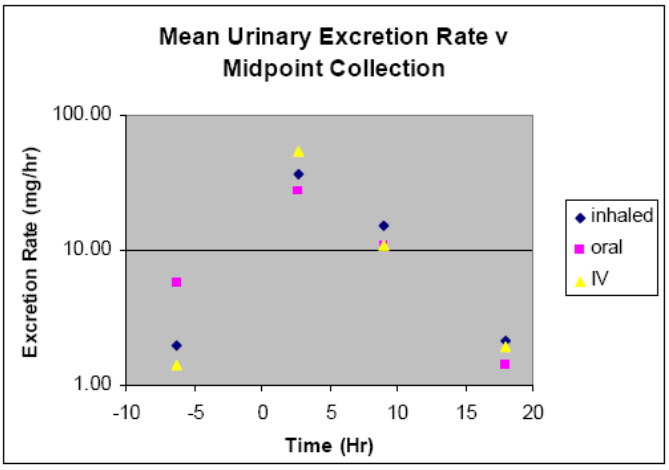


Figure 4 has been constructed using the midpoint time of the collection interval and the mean urinary excretion rate where n ≥16. The measured urinary excretion rate reflects the average plasma concentration rate during the collection interval.

The urinary excretion rate versus time profile for mannitol was consistent for all routes of administration. Calculated mean half lives from urine data are: inhaled: 3.66 ± 0.87 hr; oral: 3.59 ± 1.09 hr; and iv: 3.21 ± 0.46 hr. When compared to the mean (± SD) half lives obtained from plasma, it is evident that these are somewhat shorter (inhaled: 4.7 ± 1.0 hr, oral: 5.2 ± 1.1 hr and iv: 4.5 ±1.1 hr). However, given the standard deviations, and the fewer time points available with

urine data, there is no significant difference between the half life estimates from inhalation and oral administration. The fraction excreted unchanged mannitol in the urine was about 55%, 54% and 87% for inhaled, oral and iv, respectively.

The total clearance (CL) after intravenous administration was found to be 5099 ± 989 ml/hr and the renal clearance (CLr) was 4439 ± 1143 ml/hr. The CLr is nearly comparable to CL, indicating that the clearance of mannitol is predominately renal.

2.4 Analytical Section

2.4.1 Was the suitability of the analytical method supported by the submitted information?

Concentrations of mannitol was determined in serum and urine samples from all human pharmacokinetic studies considered in this review using an HPLC with tandem mass spectrometric detection (LC/MS/MS). The chromatographic separation is performed on a Zorbax (b) (4) µm particle size column using a mobile phase made of acetonitrile:ammonium hydroxide (100:0.1, v/v) and 100 mM ammonium formate:ammonium hydroxide (100:0.1, v/v) a flow rate of 200 µL/min.

A working range of 100 ng/mL (quantitation limit) to 100,000 ng/ml, and 2,000 ng/ml to 200,000 ng/ml were validated for mannitol in human serum and human urine, respectively. The inter-batch accuracy for Mannitol in human serum was determined to be 96.0, 95.6 and 100.0% at 250, 5000 and 80000 ng/mL, respectively. The inter-batch precision of the assay at these concentrations was 7.7%, 6.2% and 4.8%, respectively. The inter-batch accuracy for Mannitol in human urine was determined to be 101.6, 96.8 and 98.1 at 5000, 25000 and 160000 ng/mL, respectively. The inter-batch precision of the assay at these concentrations was 3.8%, 4.0% and 6.2%, respectively. The intra-batch accuracy and precision of the assay satisfied the acceptance criteria (≤ (b) (4) %) for Mannitol in both matrices on all occasions. Table 6 summarizes the finding from the in-study validation of the method.

Table 6. In-study validation for mannitol

	Human serum	Human urine
Linearity	Satisfactory: Standard curve ranged from 100 to 100,000 ng/mL: r^2= 0.9923	Satisfactory: Standard curve ranged from 2,000 to 200,000 ng/mL: r^2= 0.9975
Within-run precision and accuracy	Accuracy: 96.0%, 95.6% and 100.0% at 250, 5000 and 80000 ng/ml, respectively Precision: 7.7%, 6.2%, and 4.8% at 250, 5000 and 80000 ng/ml, respectively	Accuracy: 101.6%, 96.8% and 98.1% at 5000, 25000 and 160000 ng/ml, respectively Precision: 3.8%, 4.0%, and 6.2% at 5000, 25000 and 160000 ng/ml, respectively
Between-run Precision and accuracy	Satisfied the acceptance criteria (≤ (b)(4) %)	Satisfied the acceptance criteria (≤ (b)(4) %)

The dilution accuracy of Mannitol in human serum following a 10-fold dilution of a 200000 ng/mL sample was found to be 93.5% (acceptance criterion 100 ± (b)(4) %) with a precision of 2.6% (acceptance criterion ≤(b)(4) %). Following a 100-fold dilution of a 200000 ng/mL sample, dilution accuracy was found to be 92.5% (acceptance criterion 100 ± (b)(4) %) with a precision of 1.7% (acceptance criterion ≤(b)(4) %). The dilution accuracy of Mannitol in human urine following a 10-fold dilution of a 250000 ng/mL sample was found to be 97.6% (acceptance criterion 100 ± (b)(4) %) with a precision of 3.9% (acceptance criterion ≤(b)(4) %). Following a 100-fold dilution of a 250000 ng/mL sample, dilution accuracy was found to be 112.8% (acceptance criterion 100 ± (b)(4) %) with a precision of 6.4% (acceptance criterion ≤(b)(4) %). These results showed that 10-fold and 100-fold dilution of samples containing Mannitol in human serum and urine had no effect on the accuracy and precision.

The Stability of mannitol in serum and urine was demonstrated through three freeze/thaw cycles at both -20 °C and -80 °C, up to 24 hours at room temperature, at least 10 hours at ambient temperature, at least 17 hours at 4 °C.

3. LABELING COMMENTS

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 CPB Filing/Review Form

Office of Clinical Pharmacology			
New Drug Application Filing Form			
General Information About the Submission			
	Information		Information
NDA Number	**22-368**	**Brand Name**	**Arildol**
OCP Division	**DCP2**	**Generic Name**	**Mannitol bronchial challenge test**
Medical Division	**DPAP (OND-570)**	**Drug Class**	
OCP Reviewer	**Ying Fan**	**Proposed Indication(s)**	**Assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma**
OCP Team Leader	**Sally Choe**	**Dosage Form**	**Dry powder capsules**
		Dosing Regimen	**See details in the introduction**
Date of Submission	**27 February 2009**	**Route of Administration**	**Oral inhalation**
Estimated Due Date of OCP Review	**12 Octorber 2009**	**Sponsor**	**Pharmaxis Ltd**
PDUFA Due Date	**27 December 2009**	**Priority Classification**	**Standard**
Division Due Date	**27 October 2009**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		**Study DPM-PK-101**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		**There are no comments for sponsor at this time.**
QBR questions (key issues to be considered)	**1. What is the pharmacokinetics of mannitol after the inhale administration?** **2. What is the bioavailability of mannitol after the inhale administration compared with the intravenous administration and oral administration?**	

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

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

/s/

YING FAN
11/17/2009

PARTHA ROY
11/17/2009