CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22368Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.5.2 Patent Certification

The active ingredient, mannitol, for TRADENAME (Mannitol Bronchial Challenge Test) is a Generally Recognized as Safe (GRAS) ingredient. The formulation, composition and method of use are covered by the US Patent No. 5,817,028, which Pharmaxis has obtained all rights from the patent owner, Sydney South West Area Health Service, for the US market.

Pharmaxis Ltd certifies that Patent No. 5,817,028 covers the formulation, composition and method of use of the drug substance mannitol, which is the subject of NDA 22-368 for which approval is sought. In the opinion and to the best knowledge of the undersigned, there are no effective patents other than the method of use patent (above) that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim the current use of such drug or drugs which is the subject of this application for which approval is being sought.

Signature: _____ Date: Feb. 26, 2009
Pauliana Hall, RAC (US, EU and Canada)
US Agent/Regulatory Consultant, Pharmaxis Ltd

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
22-368

NAME OF APPLICANT/NDA HOLDER
Pharmaxis, Ltd

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Aridol

ACTIVE INGREDIENT(S)	STRENGTH(S)
D-mannitol, mannitol	0 mg, 5 mg, 10 mg, 20 mg, 40 mg

DOSAGE FORM
Dry powder capsules for oral inhalation

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,817,028	October 6, 1998	February 23, 2015

d. Name of Patent Owner		
Sydney South West Area Health Service	Address *(of Patent Owner)* Eastern Campus Liverpool Hospital	
	City/State Liverpool NSW AUSTRALIA	
	ZIP Code 2052	FAX Number *(if available)* (02) 9385 2000
	Telephone Number (02) 9385 1000	E-Mail Address *(if available)* pauliana.hall@gmail.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		
☞ Pauliana C Hall, RAC	Address *(of agent or representative named in 1.e.)* PCH Integrated Regulatory Services, 30412 Le Port,	
	City/State Laguna Niguel, CA	
	ZIP Code 92677	FAX Number *(if available)* 949-315-3757
	Telephone Number 949-249-2298	E-Mail Address *(if available)* PaulianaH@aol.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☑ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☑ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* Nos. 1, 2, 4, 5, 6, 7, 8, 9, 10 and 11	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes	☑ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* Aridol is 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

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☑ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Pauliana C. Hall	February 27, 2009

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Pauliana Hall, RAC	
Address 30412 Le Port	City/State Laguna Niguel, CA
ZIP Code 92677	Telephone Number (949) 249-2298
FAX Number *(if available)* (949) 315-3757	E-Mail Address *(if available)* Pauliana.hall@gmail.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22368 SUPPL # HFD # 570

Trade Name Aridol

Generic Name Mannitol Brochial Challenge Test

Applicant Name Pharmaxis, Ltd.

Approval Date, If Known October 5, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b) (1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 80677,16080,
20006,19603
NDA# 14738, 87409,16269

NDA# 13684,18316,83051

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Two Studies:
DPM-A-301 US Supportive Pivotal Study
DPM-A-305 US Pivotal Study

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Two Studies:
DPM-A-301 US Supportive Pivotal Study
DPM-A-305 US Pivotal Study

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # 70277 YES ☒ ! NO ☐
! Explain:

Investigation #2 ! !
IND # 70277 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Miranda Raggio
Title: Regulatory Project Manager
Date: 12-2-09 Reviewed by T. Durmowicz, M.D., 12/2/09; Reviewed by Sandy Barnes, August, 2010(resubmission)

Name of Office/Division Director signing form:
Badrul A. Chowdhury, M.D, Ph.D.
Title: Director, Division of Pulmonary and Allergy Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

MIRANDA B RAGGIO
10/05/2010

BADRUL A CHOWDHURY
10/05/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-368 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DPAP PDUFA Goal Date: 12-17-09 Stamp Date: 2/27/2009

Proprietary Name: Aridol

Established/Generic Name: mannitol bronchial challenge test

Dosage Form: dry powder capsules

Applicant/Sponsor: Pharmaxis

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients > 6 years of age with symptoms of or suggestive of asthma
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: assessment of bronchial hyper-responsiveness to aid in the diagnosis of patients > 6 years of age with symptoms of or suggestive of asthma

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

*** *Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☒ No: Please check all that apply:
  - ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed△
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. 1 mo.	6 yr. 0 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☒ Other (e.g., patients geographically dispersed): inability of children less than 6 years of age to perform test adequately

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Product Name: Mannitol bronchial challenge test

Proposed Proprietary Name: Aridol™

IND/NDA #: 70,277/22-368

Applicant: Pharmaxis Inc.

Proposed Indication: Aridol (mannitol bronchial challenge test) is 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

In accordance with 21 CFR 314.55(c)(3), Pharmaxis Inc. requests a pediatric waiver for patients <6 years old.

Rationale

The waiver is sought because clinical studies would be highly impracticable in patients <6 years old and the mannitol bronchial challenge test is unsuitable for children under the age of 6 years. As well, the clinical program for TRADENAME (mannitol bronchial challenge test) includes a total of 246 pediatric subjects, which have been evaluated in two Phase 3, well-controlled clinical trials (see Table 1). This total includes 82 subjects 6-11 years of age and 56 subjects 12-17 years old in Protocol No. DPM-A-301 (Safety Population), and 36 subjects 6-11 years of age and 72 subjects 12-17 years old in Protocol No. DPM-A-305 (Safety Population).

The diagnostic effectiveness of TRADENAME in the pediatric population in Study Nos. DPM-A-301 and DPM-A-305 is similar to the overall population (See Tables 5 and 6 in the proposed labeling, Module 1.14).

Table 1 Age Distribution of Subjects in Studies DPM-A-301 and DPM-A-305, All Enrolled Subjects

Age	DPM-A-301 N = 646 n (%)	DPM-A-305 N = 509 n (%)
6-9 years	41 (6.3%)	14 (2.8%)
10-11 years	41 (6.3%)	22 (4.3%)
12-17 years	56 (8.7%)	72 (14.1%)
18-30 years	148 (22.9%)	261 (51.3%)
31-50 years	224 (34.7%)	140 (27.5%)
51-64 years	111 (17.2%)	0
≥ 65 years	25 (3.9%)	0

Justifications

1. The dry powder mannitol bronchial challenge test is dependent on reliable repeated spirometric measures of FEV_1 throughout the dosing stages of the test. The spirometry is expected to comply with ATS standards [(i)]. Reliable spirometry, and in particular the FEV_1 measure, is not adequately achievable in this age group and in particular compliance with ATS standards is usually not achieved. The Aridol test will not lead to fruition in patients < 6 years of age. The use of Aridol in this age group will not yield reliable result compared with the current method of diagnosis.

2. Several reports [(ii-iii)] including an ATS/ERS statement [(iv)] on pulmonary function testing in pre-school children, confirm that an FEV_1 measurement is infrequently achieved under the age of six because the expiration is completed in less than one second. Repeatability of spirometry measures is also poor, end of test criteria are not met and other key measures such as the FEV_1 /FVC ratio are also frequently not attainable. Aridol is not a reliable diagnostic test for patients < 6 years of age.

3. Due to the method of administration of Aridol, i.e., using a dry powder inhaler (DPI), and consistent with the pediatric waiver granted to other DPI drug products, e.g., Pulmicort™ (budesonide inhalation powder) for asthma [(v)], study with Aridol in patients' < 6 years of age is not warranted for its intended use.

Pharmaxis Inc. hereby certifies that the information provided in the enclosed Pediatric Waiver request is truthful and accurate.

References:

i. American Thoracic Society (ATS), "Standardization of spirometry" adopted by the ATS board of directors, 2005.

ii. Crenesse D, Berlioz M, Bourrier T, Albertini M. Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuvers. Pediatr Pulmonol. 2001 Jul;32(1):56-61.

iii. Paul Aurora, Janet Stocks, Cara Oliver, Clare Saunders, Rosemary Castle, Greg Chaziparasidis, and Andrew Bush, on behalf of the London Cystic Fibrosis Collaboration. Quality Control for Spirometry in Preschool Children with and without Lung Disease. Am J Respir Crit Care Med Vol 169. pp 1152–1159, 2004.

iv. Nicole Beydon, Stephanie D. Davis, Enrico Lombardi, Julian L. Allen, Hubertus G. M. Arets, Paul Aurora, Hans Bisgaard, G. Michael Davis, Francine M. Ducharme, Howard Eigen, Monika Gappa, Claude Gaultier, Per M. Gustafsson, Graham L. Hall, Zolta´n Hantos, Michael J. R. Healy, Marcus H. Jones, Bent Klug, Karin C. Lødrup Carlsen, Sheila A. McKenzie, Franc¸ois Marchal, Oscar H. Mayer, Peter J. F. M. Merkus, Mohy G. Morris, Ellie Oostveen, J. Jane Pillow, Paul C. Seddon, Michael Silverman, Peter D. Sly, Janet Stocks, Robert S. Tepper, Daphna Vilozni, and Nicola M. Wilson, on behalf of the American Thoracic Society/ European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. An Official American Thoracic Society/European Respiratory Society Statement: Pulmonary Function Testing in Preschool Children. Am J Respir Crit Care Med Vol 175. pp 1304–1345, 2007.

v. Pulmicort™ (budesonide inhalation powder), NDA 21-949 approval letter 7/12/06.

pharmaxis

DEBARMENT CERTIFICATION

NDA Number:	**22-368**
Trade Name:	**TRADENAME (mannitol bronchial challenge test)**
Proposed Indication:	**TRADENAME is indicated for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients with symptoms of or suggestive of asthma.**

Pharmaxis hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature: Brett Charlton Date: 12 JAN 2009

Brett Charlton, MD
Medical Director
Pharmaxis Ltd.

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ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-368 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Aridol Established/Proper Name: mannitol Dosage Form: dry powder capsules (inhalation powder)		Applicant: Pharmaxis, Ltd. Agent for Applicant (if applicable):
RPM: Miranda J.Raggio		Division:

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	12-27-09(original) Resubmission: 10-7-10 August 6, 2010
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR on 12-23-09
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard (Class 2 Resubmission-6 month clock) ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	10-7-09(original)
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	CR 12-23-09(original) AP October 5, 2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	9-24-10
• Original applicant-proposed labeling	2-27-09
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	4-7-10 resubmission
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ Physician Instructions

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	4-7-10 resubmission
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	2-27-09 original 4-7-10 RS, 8-26-10, 9-24-10
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 4-10-09, 5/21/10 ☒ DMEDP 12-8-09 ☐ DRISK ☒ DDMAC 7/9/10 ☐ CSS ☒ Other reviews SEALD 12-14-09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	4-2-09
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	5-12-09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ 10-5-10
❖ Application Integrity Policy (AIP) Status and Related Documents www fda.gov/ora/compliance_ref/aip_page html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None #1667-1 Template 10-5-10
• Outgoing communications *(if located elsewhere in package, state where located)*	12-9-09
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☐ None #1667 2 & 3 Templates 10-5-10(2)

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	In Outgoing Communications Section
• Incoming submission documenting commitment	8-25-10
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	3/6/09, 5/12/09, 10/1/09, 11/20/09, 12,3/09, 12/7/09, 12/9/09, 12/10/09, 12-14-09, 12-22-09, 4/14/10, 6/17/10, 7/22/10, 8/20/10, 8/25/10, 9/20/10
❖ Internal memoranda, telecons, etc.	10/7/09
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable Not available
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 3-12-08/3-13-08
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Pre-IND mtg 7-19-04
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	11/20/09
• 48-hour alert or minutes, if available	11/20/09
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 10-5-10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7/27/10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	11/30/09, 7/27/10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	10-5-10 DD Summary Review
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 12/2/09, 12/14/09
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 12/3/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None 11/17/09
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 4-15-09, 8/6/09, 10/30/09, 11/13/09, 11/17/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 12/9/09, 8/5/10, 9/1/10
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 8/6/09, 11/18/09, 12/8/09, 12/22/09
• BLAs only: Facility information review(s) *(indicate dates)*	☒ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	10/7/09 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	

☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	In CMC review 12/9/09
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	12/21/09
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☒ Acceptable 7/30/10 ☒ Withhold recommendation 12/21/09
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

MIRANDA B RAGGIO
10/05/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: September 20, 2010

To: Valerie Waltman
Senior Regulatory Affairs Manager

Company: Pharmaxis

Phone: 610-363-5120 x103

Fax: 610-3363-5926

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 22368 Resubmission (Aridol) Labeling Comments #4

# of Pages: 17

Comments: Please call with any questions. Thanks, miranda

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NDA 22-368 Resubmission Labeling Comments #3

We are currently reviewing your April 7, 2010, NDA for Aridol, and are providing preliminary labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes shown in the attached marked up package insert and the comments listed below related to both the package insert and the instructions for use:

General Comments

1. Several grammatical or punctuation corrections were made and are shown as tracked changes, including the addition of a comma after "Aridol" in the first sentence of the Boxed Warning in the HIGHLIGHTS section.

FULL PRECRIBING INFORMATION

2. **Section 6, ADVERSE REACTIONS**, **Clinical Trials Experience, Table 3**: The number (b) (4) was rounded up to 1% to be consistent with the rest of the numbers in the table.

INSTRUCTION SHEET

3. **Step 3 in the Aridol Bronchial Challenge Test Kit Procedure description**: The last sentence should read, "The ARIDOL bronchial challenge test should not be performed in patients with an FEV1 of less than 70% predicted."

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by noon on Monday, September 27. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

Note: No additional changes were made to the Aridol carton/container or Aridol foil package.

NDA 22-368 Resubmission Labeling Comments #3

Drafted by Miranda Raggio/9-15-10
Initialed by Sandy Barnes/9/20/10
Deepika Arora/9/20/10
Prasad Peri/9-20-10
Tony Durmowicz/9-20-10
Lydia Gilbert-McClain/9/20/10

Finalized by M. Raggio/9/20/10

13 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

MIRANDA B RAGGIO
09/20/2010

MEMORANDUM

Date: 1-SEP-2010

From: Deepika Arora, Ph.D., CMC Reviewer, Branch IX/ONDQA

To: NDA 22-368, Aridol (mannitol inhalation powder)

Through: Prasad Peri, Ph.D., Branch Chief (Acting), Branch VII/ONDQA

Subject: Approval recommendation. Updated labeling (submitted review 27-AUG-2010)

In the CMC review #4, dated 15-JUN-2010, the NDA is recommended for approval. Updated labeling has been provided following Agency's labeling comments dated 20-AUG-2010. Also the applicant's US office address has been updated to the following:

One East Uwchlan Avenue, Suite 405, Exton, PA 1934
Phone: (610) 363-5120; Fascimile: (610) 363-5926

(b) (4)

[redacted]

Evaluation: Adequate.

ARIDOL Instructions Sheet

The instruction sheet has been modified to reflect the name ARIDOL refers to the entire bronchial challenge test kit.

Foil
The foil has been modified to include "Pharmaxis, Inc." per the requirements in 21 CFR 201. 10(h)(2). A revised draft ARIDOL foil is provided.

Full Prescribing Information
Tracked changes show that all labeling recommendations have been incorporated.

In conclusion, NDA 22-368 is recommended for approval from CMC perspective. All recommended labeling edits have been incorporated.

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

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/s/

DEEPIKA P ARORA
09/01/2010
Recommend approval from CMC perspective.

PRASAD PERI
09/01/2010
I concur

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 25, 2010

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 610-363-5120 x103	**Phone number:** 301-796-2109

Subject: CMC PMC Fax for Aridol™ (mannitol inhalation powder) Bronchial Challenge Kit, NDA 22-368 Resubmission

Total no. of pages including cover: 3

Comments: Please confirm receipt via email or phone call. Thanks, m

Document to be mailed: YES xNO

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NDA # 22-368 Resubmission

Your submission dated April 7, 2010, to NDA 22-368, is currently under review.

In an email from Miranda Raggio on August 23, 2010, we informed you that chemistry, manufacturing, and controls (CMC) agreements outlined in the December 23, 2009, CR letter will now be considered Post Marketing Commitments (PMCs). Below are the proposed PMCs. Respond with a letter of intent to comply with the PMCs and provide requested timelines.

1. The proposed specifications for foreign particulate matter are interim specifications. Test for foreign particulate matter in the first six U.S. commercial batches of ARIDOL and evaluate the results from this testing to either remove or finalize the foreign particulate drug product specifications. Submit this data to the Agency as a changes-being-effected (CBE) supplement.

2. The proposed specifications for the Aerodynamic Particle Size Distribution (APSD) are interim specifications. Revise the APSD specifications based on the first ten U.S. commercial batches of ARIDOL and submit the revised specifications to the Agency as a prior-approval (PA) supplement.

Your letter must include the following for each PMC:

1. Final Protocol Submission: MM/YY (if applicable)
2. Study/Trial Completion: MM/YY (if applicable)
3. Final Report Submission MM/YY

Submit your response to me via email at Miranda.Raggio@fda.hhs.gov by noon August 27, 2010. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

NDA # 22-368 Resubmission

Drafted by M. Raggio/
Initialed by Sally Seymour/8-24-10
Ladan Jafari/8-24-10
Sandy Barnes/8-24-10
Deepika Arora/8-24-10
Alan Schroeder/8-24-10
Lydia Gilbert-McClain/8-25-10
Finalized by: Miranda Raggio/8-25-10

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

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/s/

MIRANDA B RAGGIO
08/25/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: August 20, 2010

To: Valerie Waltman
Senior Regulatory Affairs Manager

Company: Pharmaxis

Phone: 610-363-5120 x103

Fax: 610-3363-5926

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 22368 Resubmission (Aridol) Labeling Comments #3

# of Pages: 17

Comments: Please call with any questions. Thanks, miranda

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NDA 22-368 Resubmission Labeling Comments #3

We are currently reviewing your April 7, 2010, NDA for Aridol, and are providing preliminary labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes shown in the attached marked up labeling and the comments listed below.

HIGHLIGHTS of PRESCRIBING INFORMATION

1. As discussed during our August 18, 2010, teleconference the wording of the Boxed Warning was changed to better reflect safety concerns and to be consistent with other approved drug products for bronchial challenge testing.

2. The Drug-Drug interaction section was deleted as there are no formal studies and therefore it is not required in the HIGHLIGHTS section.

FULL PRECRIBING INFORMATION

3. **BOXED WARNING:** Changes made per comment #1 above.

4. **Section 1, INDICATIONS AND USAGE:** Changes made to reflect that mannitol is the sugar alcohol and ARIDOL refers to the entire product.

5. **Section 6, ADVERSE REACTIONS**: Per our discussion on August 18, 2010, the text has been edited to reflect adverse reactions observed in the overall population. Tables 2 and 3 have been changed back to the previous version to reflect the overall population, Table 4 has been deleted, and the three most frequent adverse reactions observed in children and adolescents has been added as text. With regard to Table 2, re-order the list of adverse reactions based on frequency with the most common events listed first.

6. **Section 6, ADVERSE REACTIONS**: With regard to the decrease in FEV1 in children and adolescents who received the ARIDOL bronchial challenge test, the combined incidence for studies 301 and 305 of pediatric patients/subjects who had bronchial challenge testing with ARIDOL and decreases in FEV1 of ≥ 30% was 13/241 or 5.4% (see tables 2.7.4.54 and 2.7.4.56 in the Summary of Clinical Safety, Module 2.7.4).

7. **Section 8.3, USE IN SPECIFIC POPULATIONS (Nursing Mothers):** Wording has been changed to be consistent with the wording for the approved intravenous mannitol formulation.

8. **Section 8.4, USE IN SPECIFIC POPULATIONS (Pediatric Use):** Percent reduction in FEV1 values has been rounded to the nearest %.

CARTON LABELING and INSTRUCTION SHEET

9. Where appropriate, both the carton and clinician instruction sheet should be updated throughout to reflect that the name ARIDOL refers to the entire bronchial challenge test kit. For example, for the carton labeling, under the trade name ARIDOL, the following wording should be inserted:

   (mannitol inhalation powder)

   Bronchial Challenge Test Kit

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB Wednesday, July 28, 2010. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

16 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

NDA 22-368 Resubmission Labeling Comments #3

Drafted by Miranda Raggio/8-20-10
Initialed by Sandy Barnes/8-20-10
Deepika Arora/8-20-10
Alan Schroeder/8-20-10
Tony Durmowicz/8-20-10
Lydia Gilbert-McClain/8-20-10

Finalized by M. Raggio/8/20/10

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

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/s/

MIRANDA B RAGGIO
08/20/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: July 22, 2010

To: Valerie Waltman
Senior Regulatory Affairs Manager

Company: Pharmaxis

Phone: 610-363-5120 x103

Fax: 610-3363-5926

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary,Allergy,and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 22368 Resubmission (Aridol) Labeling Comments #2

# of Pages: 20

Comments: Please call with any questions. Thanks, miranda

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NDA 22-368 Resubmission Labeling Comments #2

We are currently reviewing your April 7, 2010, NDA for Aridol, and are providing preliminary labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes shown in the attached marked up labeling and the comments listed below.

HIGHLIGHTS of PRESCRIBING INFORMATION

1. In the Table of Contents, revise all indented subheadings so that are consistent.

2. The abbreviated Boxed Warning must be formatted into one box.

FULL PRECRIBING INFORMATION

3. **Section 6, ADVERSE EVENTS**: In the penultimate paragraph, insert combined incidences from studies 301 and 305 for adverse reactions of headache, pharyngolaryngeal pain, and nausea in children after the sentence which states, "There were no major differences in the types of adverse reactions observed in children 6-11 years of age compared to adolescents 12-17 years old". Submit the appropriate adverse reaction data to support the respective incidences.

4. **Section 8.4, USE IN SPECIFIC POPULATIONS, Pediatric Use**: In the second paragraph insert the mean/median maximal % reduction in FEV1 in children for both studies 301 and 305 combined after the sentence which states, "The mean and median maximum percentage reduction in FEV1 in children and adolescents 6 to 17 years of age showed no apparent difference than in the overall population". Submit the appropriate clinical trial data to support the FEV1 values.

CARTON LABELING

5. The presentation of the first letter of the proprietary name ('a') resembles the letter 'O' and the name may be read incorrectly. Revise the font to clearly present it as the capital letter "A" to diminish the potential confusion.
6. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half as large as the proprietary name letters and that it has a prominence commensurate with the prominence as the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other pointing features.

INSTRUCTION SHEET

7. **Step 3**: Remove the last line [redacted] (b) (4) and replace it with "Aridol should not be used in patients with an FEV1 of less than 70% predicted.

8. **Step 11**: Replace [redacted] (b) (4)

(b) (4)

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

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB Wednesday, July 28, 2010. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

16 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

NDA 22-368 Resubmission Labeling Comments #2

Drafted by Miranda Raggio/7-20-10
Initialed by Sandy Barnes/7-21-20
Deepika Arora/7-21-10
Prasad Peri/7-21-10
Anya Harry/7-21-10
Tony Durmowicz/7-21-10
Lydia Gilbert-McClain/7-22-10
Badrul A. Chowdhury7/22/10
Finalized by M. Raggio/7/22/10

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

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/s/

MIRANDA B RAGGIO
07/22/2010

MEMORANDUM

NDA:	22-368
Sponsor:	Pharmaxis Ltd.
Drug:	Aridol (mannitol brochial challenge test) dry powder capsules
Submission Date:	April 7, 2010
Indication:	Assessment of bronchial hyperresponsiveness
Reviewer:	Ying Fan, Ph.D.
Team Leader (Acting):	Yun Xu, Ph.D
Memo Date:	July 7, 2010

Introduction

Aridol (mannitol inhalation powder) is a single use product inhaler used in a single patient 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.

Administrative and Regulatory History

The original NDA 22-368, a 505(b) (1) application was submitted on February 27, 2009 and. The Office of Clinical Pharmacology has reviewed the application and found the submission acceptable from a clinical pharmacology perspective. The Division gave the complete response on December 23, 2009 because the office of compliance made a withhold recommendation due to violations seen in the testing sites. On April 7, 2010, the sponsor submitted the Complete Response Resubmission addressing the remaining NDA final approval issues about the Product Quality, Labeling, and Safety Update.

Clinical Pharmacology Finding:

There is one on-going new pharmacokinetics (PK) study (Study DPM-PK-102) submitted in this application. However, there is no PK data or PK report included in this submission. Therefore, there are no additional clinical pharmacology studies to be reviewed from the clinical pharmacology perspective in the submissions. The sponsor submitted this study mainly for the purpose of safety updates. The PK result of this study will not affect approvability of the product.

Labeling Recommendations:

The sponsor changed all the labeling based on our recommendation on December 10, 2009 and December 22, 2009. This submission is acceptable from a clinical pharmacology perspective.

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

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/s/

YING FAN
07/08/2010

YUN XU
07/13/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: June 17, 2010

To: Valerie Waltman
Senior Regulatory Affairs Manager

Company: Pharmaxis

Phone: 610-363-5120 x103

Fax: 610-3363-5926

From: Miranda Raggio, RN, BSN, MA
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 22368 RS (Aridol) Labeling Comments #1

# of Pages: 4

Comments: Please call with any questions. Thanks, miranda

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NDA 22368 Resubmission Labeling Comments #1

We are currently reviewing your submission to dated April 7, 2010, to NDA 22368, and are providing preliminary labeling comments. Submit revised labeling incorporating the changes noted in the comments listed below.

Highlights

1. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

2. The rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

   Refer to the "Guidance for Industry: Determining Established a Pharmacologic Class for Use in Highlights of Prescribing Information"

3. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]. Provide an email address, phone number, or company website which is dedicated to the reporting of adverse reactions.

4. The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION". [See 21 CFR 201.57(a)(14)]

5. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

6. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Table of Contents

7. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]. Indent all subsection headings, as some are not indented in the proposed label.

8. Remove the extra spaces after subsections 8.6 and 13.1 prior to the subsection heading.

Full Prescribing Information (FPI)

9. Remove the extra spaces after subsections 8.6 and 13.1 prior to the subsection heading.

10. If a Boxed Warning is included, the same title from the Boxed Warning must be inserted at the beginning of the TOC, in bold type and upper case letters.

11. Do not refer to adverse reactions as [redacted] (b) (4) Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The proposed label has "adverse event" in line # 135.

12. Section 8 USE IN SPECIFIC POPULATIONS, subsection 8.1 Pregnancy states [See Nonclinical Toxicology (13.2)]. Correct this to match the 13.2 subsection heading of Animal Toxicology and/or Pharmacology in the FPI.

13. The revision date at the end of the Highlights section replaced the revision date at the end of the labeling and should not appear in both places. Delete the revision date at the end of the FPI.

Inhaler Instructions Sheet

14. The photos on the instruction sheet in Steps 6-8 show an individual with a nose-clip in place. However, there is no mention of having the subject put on nose-clip in the instructional text. Insert this step, as appropriate.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB July 6, 2010. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

NDA 22368 Resubmission Labeling Comments #1

Drafted by Miranda Raggio/5-21-10
Initialed by Sandy Barnes/6/15/10
Anya Harry/6/16/10
Tony Durmowicz/6/16/10
Finalized by M. Raggio/6/17/10

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

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/s/

MIRANDA B RAGGIO
06/17/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:
Division of Drug Marketing, Advertising, and Communications (DDMAC
CDER-DDMAC-RPM: Roberta Szydio and Robyn Tyler

FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Pulmonary and Allergy Products: Miranda Raggio, 301-796-2109

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
5-7-10		NDA 22368	(PLEASE CHECK OFF BELOW) Class 2 Resubmission NDA

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Aridol(mannitol bronchial challenge test)	Standard 6-month clock	Respiratory	July 9, 2010

NAME OF FIRM: Pharmaxis, Ltd.

PDUFA Date: 10-7-10 BUT DPARP plans to take action on August 6, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

Resubmission, Class 2

REASON FOR LABELING CONSULT
- X INITIA/ResubmittedL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\EVSPROD\NDA022368

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: Pharmaxis submitted a Class 2 resubmission of NDA 22368. This NDA is for Aridol, to be used as a diagnositc tool for bronchial hyper-responsiveness. Please review the package insert, and test procedure instructions for physicians. Note, the procedure instructions are not for patients. Please notify Miranda of assigned reviewers so that Word versions of the label can be sent. Thank you.

Mid-Cycle Meeting: [Insert Date] None

Labeling Meetings: [Insert Dates] None

Wrap-Up Meeting: [Insert Date] None

SIGNATURE OF REQUESTER: Miranda Raggio, Senior Regulatory Project Manager 301-796-2109	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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

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/s/

MIRANDA B RAGGIO
05/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Surveillance and Epidemiology/Carolyn Volpe

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Division of Pulmonary and Allergy Products: Miranda Raggio, 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5-5-10		22-368	Class 2 Resubmission of NDA	4-7-10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aridol(mannitol bronchial challenge test)	Standard-6 month clock	Respiratory	July 9, 2010 Note: DPARP plans to take an early action on August 6, 2010

NAME OF FIRM: Pharmaxis, Ltd.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☒ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Pharmaxis submitted a Class 2 Resubmission of thier NDA for Aridol, to be used as a diagnositc tool for bronchial hyper-responsiveness. This test kit will be administered by physicians in a clinical setting. Please review the package insert and instructions for physicians for safety issues related to instruction interprepation and implementation.Please note that the instructions are not for patients. Please notify Miranda of assigned reviewers so that Word versions of the label can be sent. The EDR link is \\CDSESUB1\EVSPROD\NDA022368. Thank you.

SIGNATURE OF REQUESTOR
Miranda Raggio, RN, BSN, MA

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-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/

MIRANDA B RAGGIO
05/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22368 **ACKNOWLEDGE CLASS 2 RESPONSE**

Pharmaxis, Inc.
403 Gordon Drive
Exton, PA 19341

Attention: Valerie Waltman, MS
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

We acknowledge receipt on April 7, 2010, of your April 7, 2010, resubmission to your new drug application for Aridol (mannitol inhalation powder).

We consider this a complete, class 2 response to our December 23, 2009, action letter. Therefore, the user fee goal date is October 7, 2010.

If you have any questions contact me at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Miranda J. Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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

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/s/

MIRANDA B RAGGIO
04/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22368 **MEETING DENIED**

Pharmaxis, Inc.
403 Gordon Drive
Exton, PA 19341

Attention: Valerie Waltman, MS
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aridol™ (mannitol inhalation powder).

We also refer to your January 9, 2010, correspondence requesting a meeting to discuss the deficiencies stated in the Complete Response letter of December 23, 2009. We are denying the meeting because a meeting is not necessary at this time.

The stated purpose of the meeting you requested was to seek FDA feedback on the status of the responses you submitted to the Office of Compliance regarding manufacturing and testing facility deficiencies, the format and requirements of the safety update, and to discuss proposed draft labeling for the Aridol NDA resubmission. The review of your submitted 483 Forms is still ongoing, requirements of the safety update have been conveyed via a previous communication, and it is premature to discuss labeling issues at this time.

If you have any questions, call Miranda J. Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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

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/s/

LYDIA I GILBERT MCCLAIN
01/22/2010
Signed for Badrul Chowdhury

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-368 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Aridol Established/Proper Name: mannitol Dosage Form: dry powder capsules (inhalation powder)		Applicant: Pharmaxis, Ltd. Agent for Applicant (if applicable):
RPM: Miranda J.Raggio		Division:

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	12-27-09
❖ Actions	
• Proposed action	☐ AP ☐ TA ☐ AE ☐ NA ☒ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	10-7-09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	☐ Yes ☐ No
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	CR 12-23-09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	2-27-09
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ Physician Instructions

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	2-27-09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 4-10-09 ☒ DMEDP 12-8-09 ☐ DRISK ☐ DDMAC ☐ CSS ☒ Other reviews SEALD 12-14-09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	4-2-09
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	5-12-09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐
❖ Application Integrity Policy (AIP) Status and Related Documents www fda.gov/ora/compliance_ref/aip_page html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	12-9-09
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	3/6/09, 5/12/09, 10/1/09, 11/20/09, 12,3/09, 12/7/09, 12/9/09, 12/10/09, 12-14-09, 12-22-09
❖ Internal memoranda, telecons, etc.	10/7/09
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable Not available
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 3-12-08/3-13-08
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Pre-IND mtg 7-19-04
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	11/20/09
• 48-hour alert or minutes, if available	11/20/09
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	11/30/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 12/2/09, 12/14/09
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 12/3/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None 11/17/09
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 4-15-09, 8/6/09, 10/30/09, 11/13/09, 11/17/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 12/9/09
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 11/18/09, 12/8/09, 12/22/09
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	10/7/09 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	In CMC review 12/9/09
☐ Review & FONSI *(indicate date of review)*	

☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	12/21/09
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

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/s/

MIRANDA B RAGGIO
12/23/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: December 22, 2009

To: Valerie Waltman
Senior Regulatory Affairs Manager

Company: Pharmaxis

Phone: 610-363-5120 x103

Fax: 610-3363-5926

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 22368 (Aridol) Labeling Comments #2

# of Pages: 26

Comments: Please call with any questions. Thanks, miranda

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NDA 22-368 Labeling Comments #2

We are currently reviewing your February 27, 2009, NDA for Aridol, and are providing preliminary labeling comments. Submit revised labeling incorporating changes shown in the attached marked up labeling and the comments listed below.

1. General Labeling Comments

Numerous changes were made in the label in order to make the language more clear, to correct inaccuracies, or to remove promotional language

2. HIGHLIGHTS of PRESCRIBING INFORMATION

The Highlights section has been updated to reflect changes made in the main section of the label.

3. FULL PRECRIBING INFORMATION

a. Indications and Usage:
Section 1: The sentence stating that Aridol is not a test for asthma has been added back. This point was made at the Advisory Committee and should be reflected in the product label.

b. Adverse Reactions:
Section 6.1: The term "feeling jittery" was added back to the list of adverse reactions resulting in discontinuation (see Table 2.7.4.20, Clinical Summary of Safety).

Section 6.1: Table 3. The safety data for Aridol for both clinical trials is relevant to the physician who utilizes the test. Undoubtedly some of the patients tested will have asthma. The sources for the data were Tables 2.7.4.26 and 2.7.4.27 in the Clinical Summary of Safety. Note that Table 2.7.4.3 in the Clinical Summary of safety lists that 416 subjects were exposed to Aridol, which is not consistent with other sources or FDA determination of 419 exposed subjects. . Clarify that total should be 1046 rather than 1043.

c. Section 6.2: Updated with data from 120 day safety update.

d. Drug Interactions:
Sections 7.1 and 7.2: These sections were removed from the label. The Drug Interactions section should be limited to those drug-drug interactions that affect the metabolism of a drug not a potential difference in physiologic response because of other drugs. The information in Section 7.1 is not supported by data obtained from Studies 301 or 305. Regarding Section 7.2, the information and table presented are those for the approved drug Provocholine, not for Aridol.

e. Clinical Studies:
The results table (Table 4) was revised to include the differences in sensitivity and specificity between Aridol and methacholine.

(b) (4)

f. Aridol bronchial test instructions:
The Aridol test instructions should be updated to reflect the changes in the main body of the label (see Section 2, Dosage and Administration and Section 7, Drug Interactions).

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB Tuesday, December 22, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109. If you have questions on Friday, December 18, 2009, contact Eunice Chung, Regulatory Project Manager, at 301-796-4006 or Eunice.Chung@fda.hhs.gov

16 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

NDA 22-368 Labeling Comments #2

Drafted by Miranda Raggio/12-22-09
Initialed by Sandy Barnes/12/22/09
Tony Durmowicz/12/22/09
Finalized by M. Raggio/12/22/09

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

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/s/

MIRANDA B RAGGIO
12/22/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: December 10, 2009

To: Valerie Waltman
Senior Regulatory Affairs Manager

Company: Pharmaxis

Phone: 610-363-5120 x103

Fax: 610-3363-5926

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 22368 (Aridol) Initial Labeling Comments

# of Pages: 26

Comments: Please call with any questions. Thanks, miranda

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NDA 22-368 Labeling Comments #1

We are currently reviewing your February 27, 2009, NDA for Aridol, and are providing preliminary labeling comments. Submit revised labeling incorporating changes shown in the attached marked up labeling and the comments listed below. We will have additional comments as we continue our review.

General Labeling Comments

1. "Mannitol bronchial challenge test" is not the correct established name for this product. Additionally, "Capsule for Oral Inhalation" is not a recognized, proper designation of the dosage form. Revise the established name and dosage form throughout the labeling and instructions for use to read as follows [i.e. mannitol inhalation powder].

2. Revise the statement "Single Use Only" throughout the labeling and instructions for use to read "Single Patient Use Only".

3. Revise the graphics to include a closer view that clearly represents each individual step in the test administration process.

HIGHLIGHTS of PRESCRIBING INFORMATION

4. See attached labeling. Note that the changes recommended in the Full Prescribing Information section will need to be incorporated in the Highlights and Table of Contents sections.

FULL PRECRIBING INFORMATION

5. See attached labeling

CARTON and CONTAINER

Carton

6. Remove the red triangular logo present on the front, back and sides of the outer carton as it can be distracting.

7. Change "TRADENAME mannitol bronchial challenge test" to "**TRADENAME (Mannitol Inhalation Powder)**",

8. The front of the carton must contain the following:

    a. **TRADENAME (Mannitol Inhalation Powder)**
    b. **Do Not Swallow TRADENAME Capsules**
    c. **For Use With Enclosed Aridol Device Only**
    d. **FOR ORAL INHALATION ONLY**
    e. **Contains one Aridol device and three blister cards.**

9. The presentation of the first letter of the proprietary name ('a') resembles the letter 'O' and the name may be read incorrectly. Revise the font to clearly present it as the capital letter "A" to diminish the potential for confusion and errors.

10. The product is described as a "test kit" and will be used for diagnostic use. The description (e.g. "Diagnostic Kit") should be prominently displayed to clarify that it is only intended for diagnostic use and not for treatment.

11. Include the discard statement (e.g. Discard after single patient use) after the "For single patient use only" statement to ensure the unused capsules will not be reused.

12. Include the usual or recommended dosage statement per 21 CFR 201.100(b)(2) and 21 CFR 201.55.

Blister: Form Pack

13. 13. Add the following text:
    a. TRADENAME

    b. For Oral Inhalation Only with Aridol Device

    c. Open on other side only

Blister: Push Through Foil

14. Change "TRADENAME mannitol bronchial challenge test" to "**TRADENAME (Mannitol Inhalation Powder)**"

Device

15. It is strongly recommended that the device contain a small label identifying the product, for example, TRADENAME (Mannitol) Inhalation Powder

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB Monday, December 14, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

22 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

NDA 22-368 Labeling Comments #1

Drafted by Miranda Raggio/12-10-09
Initialed by Sandy Barnes/12-10-09

Prasad Peri 12/10/09
Ying Fan/12-10-09
Partha Roy/12-10-09
Tom Permutt/12-10-09
Luqi Pei/12-10-09
Tony Durmowicz/12-10-09
Finalized by Miranda Raggio/12-10-09

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

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/s/

MIRANDA B RAGGIO
12/10/2009

NDA # 22-368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 9, 2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-2109

Subject: PMR Fax for Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover: 3

Comments: Please confirm receipt

Document to be mailed: **YES** **xNO**

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NDA # 22-368

Your submission dated February 27, 2009, to NDA 22-368, is currently under review.

In our December 2, 2009, teleconference we informed you of the Post Marketing Requirement (PMR) which will be included in the action letter for Aridol. Review the Division's modified study description below and respond with a letter of intent to comply with this PMR.

Conduct a clinical trial with Aridol in subjects/patients older than 50 years of age who have significant co-morbidities common in an elderly population (e.g., COPD, obesity, cardiac risk factors, etc.) or reanalyze the data from completed clinical trials in which Aridol was administered to an elderly population with co-morbidities. A substantial number of the total population should be 65 years of age or greater. The trial should include the following objectives: 1) evaluate the degree of bronchoconstriction defined as a fall in FEV1 in the older subject/patient population and 2) evaluate the overall adverse event profile in subjects over 50 years of age.

Your letter must include the following:

1. Proposed patient population
2. Proposed number of study patients
3. Submission of Final Protocol date
4. Completion of Study date
5. Submission for Final Report date

Submit your response to me via email at Miranda.Raggio@fda.hhs.gov by COB Friday, December 11, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

NDA # 22-368

Drafted by M. Raggio/12-9-09
Initialed by Sandy Barnes/12-9-09
Sally Seymour/12-9-09
Finalized by: Miranda Raggio/12-9-09

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

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/s/

MIRANDA B RAGGIO
12/09/2009

NDA 22368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: 12/07/2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	Miranda Raggio **From:** Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-2109

Subject: CMC Request for Information: Aridol™, NDA 22-368

Total no. of pages including cover:3

Comments:

Document to be mailed: YES xNO

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Your response to request for CMC information dated 20 Nov 2009 for NDA 22-368 dated February 27, 2009, is currently under review. We have the following request for information:

Revise your proposed drug product specification for Uniformity of Mass /average mass (for 10, 20 and 40 mg) and for Uniformity of Content (for 5 mg) to the following:

Test and Method	Specifications
Uniformity of mass / average mass (for 10, 20 and 40 mg)	(b) (4)
Uniformity of content (for 5 mg)	

* Refer to USP<905> Uniformity of Dosage Units (Weight Variation for 10, 20 and 40 mg capsules and Content Uniformity for 5 mg capsules) for calculation of acceptance value.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB on 12-11-09.Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

Drafted by D. Arora and Prasad Peri 12/3/09
Revised by M. Raggio/12-7-09
Initialed by Sandy Barnes/12-7-09
Finalized by M. Raggio/12-7-09

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

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/s/

MIRANDA B RAGGIO
12/07/2009

NDA 22-368
Aridol

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 20, 2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Colette Jackson on behalf of Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-1230

Subject: Request for CMC Information: Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover: 3

Comments: Please confirm receipt

Document to be mailed: **YES** **xNO**

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NDA 22-368
Aridol

Please refer to your NDA submission dated February 27, 2009. We also refer to your November 3, 2009, submission which provided additional Quality information. We have the following requests for Chemistry, Manufacturing, and Controls information:

1. Based upon the data provided in your submission dated November 3, 2009, for foreign particulate testing, your proposed limit for foreign particulates (b) (4) NMT (b) (4) is too wide. Tighten your proposed drug product release specification limit for foreign particulates (b) (4) to NMT (b) (4)

2. Tighten the proposed Delivered Dose Uniformity specifications limit of (b) (4) (b) (4) The analyses of the data provided (including stability data, report RN 08-006-003) demonstrates that your proposed limit is wider than the data generated and must be tightened.

3. Include testing for capsule content (for e.g. USP<905>) as a product release specification or justify the exclusion of the testing from the product specifications. If it is being performed as an in-process control, list it in the specifications with a footnote indicating that the test is performed in-process.

4. Provide the updated drug product specifications sheet.

Submit your response via email at Miranda.Raggio@fda.hhs.gov by COB November 30, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

NDA 22-368
Aridol

Drafted by Jackson/11-20-09
Initialed by Jackson for Barnes/11-20-09
Prasad Peri/11-20-09
Finalized by: Jackson/11-20-09

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

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/s/

COLETTE C JACKSON
11/20/2009

NDA 22368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: 11/03/2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	Miranda Raggio **From:** Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 610-363-5120 ext. 103	**Phone number:** 301-796-2109

Subject: CMC Request for Information: Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover:3

Comments:

Document to be mailed: YES xNO

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Your submission dated February 27, 2009, to NDA 22-368, is currently under review. We have the following Chemistry, Manufacturing, and Controls requests for information:

1. The proposed stage groupings for the drug product specifications are inappropriate based upon the data generated from aerodynamic particle size distribution (APSD) method validation report er011. (b) (4)

   Revise the drug product specifications for APSD to replace proposed stage groupings with the following stage groupings:

   (b) (4)

   These groupings are more likely to detect any shifts in distribution that may be stability related. Based upon the analysis of stability data for the three batches (A0605, A0701 and 07-177) provided in RN 08-006-03 report, the following groupings and corresponding amount of mannitol deposited are recommended for the 5 mg and 40 mg capsules:

   (b) (4)

5 mg	
40 mg	

   Note that the above acceptance criteria have been calculated by pooling the stability data from the three batches (A0605, A0701 and 07-177, report RN08-006-03) for each recommended stage grouping, to calculate the Mean and standard deviation (SD). The upper and lower limit for the grouping is then calculated by Mean ± (3xSD), respectively. For example, (b) (4)

   Revise the product specification for APSD appropriately according to the aforementioned groupings for all strengths and update the stability data accordingly for this parameter. Justify the high wall losses seen with the APSD determination method.

2. Revise the drug product's proposed Uniformity of Delivered Dose specification to also include the theoretical cumulative dose (mg) alongside the dose (mg) and the cumulative label claim (mg).

Submit your response to Sadaf Nabavian (I am on annual leave the week of the 9th) via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov and cc me at Miranda.Raggio@fda.hhs.gov by COB on 11-10-09.Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

Reviewer Drafted by Deepika Arora 11-2-09
Initialed by Prasad Peri 11-3-09
Edited by Miranda Raggio 11-3-09
Returned to D. Arora and P.Peri for review 11-3-09
Cleared by D. Arora and P. Peri 11-3-09
Initialed by Sandy Barnes 11-3-09
Finalized by Miranda Raggio 11-3-09

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

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/s/

MIRANDA B RAGGIO
11/03/2009

NDA # 22-368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 23, 2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-2109

Subject: Request for CMC Information: Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover:3

Comments: Please confirm receipt

Document to be mailed: **YES** **xNO**

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NDA # 22-368

Your submission dated February 27, 2009, to NDA 22-368, is currently under review. We have the following requests for Chemistry, Manufacturing, and Controls information:

1. Provide validation data to support the method used for foreign particulate testing (Report RN07/020). Although it is written for foreign particulate testing in parenteral preparations, you may wish to refer to USP <788> as a resource for the method of particulate testing in the compendia.

2. Update the drug product specifications to include testing for foreign particulates with acceptance criteria [redacted] (b) (4)

Submit your response to me via email at Miranda.Raggio@fda.hhs.gov by COB October 30, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

NDA # 22-368

Drafted by M. Raggio/10-23-09
Initialed by Sandy Barnes/10-23-09
Deepika Arora/10-23-09
Prasad Peri/10-23-09
Finalized by: Miranda Raggio/10-23-09

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

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/s/

MIRANDA B RAGGIO
10/23/2009

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 7, 2009
TIME: 1:00 pm
LOCATION: Room 3376, Building 22, White Oak Campus
APPLICATION: NDA 22368
DRUG NAME: Aridol
SPONSOR: Pharmaxis
TYPE OF MEETING: Telecon

MEETING CHAIR: Dr. Badrul A. Chowdhury

MEETING RECORDER: Miranda J. Raggio

FDA ATTENDEES: Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products (DPAP)
Sally Seymour, M.D., Deputy Director for Safety, DPAP
Anthony Durmowicz, M.D, Clinical Team Leader, DPAP
Miranda Raggio, BSN, MD, Senior Regulatory Project Manager, DPAP

EXTERNAL CONSTITUENT ATTENDEES:

Brett Charlton, MD, Medical Director, Pharmaxis
Geetha Velummylum, Director of Regulatory Affairs, Pharmaxis
Valerie Waltman, Senior Manager Regulatory Affairs, Pharmaxis
Pauliana Hall, Regulatory Affairs Consultant

BACKGROUND:

The Division arranged a thirty minute teleconference with Pharmaxis to inform them of the agenda and plan for the Aridol Advisory Committee (AC) meeting scheduled for November 20, 2009.

DISCUSSION HIGHLIGHTS:

The Division began the discussion with a review of the draft agenda for the AC, making the following specific points:

1. Pharmaxis has ninety minutes on the agenda for their Aridol presentation. Pharmaxis is not required to utilize the entire ninety minutes.

2. The FDA Aridol presentation will include a reanalysis of the Pharmaxis efficacy data by the Division of Biometrics. Although, in general, it is anticipated that the FDA's

conclusions will align with those of Pharmaxis, there may be some variation in the actual numbers.

3. The Public Hearing is scheduled for 1-2pm, and this hearing must take place at the specified time per regulation. However, there is flexibility in the other agenda items, and adjustments may be made depending on how much time is required for the Pharmaxis /FDA presentations and the clarification questions and responses.

4. Pharmaxis stated that they were told at one point that they had sixty minutes to present, rather than ninety minutes. The Division informed Pharmaxis that they indeed have ninety minutes on the agenda, but that they are not required to use all of that time for their presentation.

5. Pharmaxis asked if the intent-to-treat population or the per protocol population analysis of efficacy data would be presented by the FDA. The Division responded that potentially both data sets could be presented.

6. Pharmaxis asked if the FDA's reanalyzed data would be in the briefing document. The Division responded in the affirmative.

7. Pharmaxis inquired as to the earliest time that the AC questions would be available to them. The Division stated that a preliminary version of the AC questions will be available in the briefing document, but that they are subject to change. The final questions will be posted on the public website when they are finalized.

8. The Division stated that it is anticipated that this AC will be straightforward with the sponsor's and FDA's presentations containing no new or surprising information or issues. The Division stated that the main goal of this AC is to present thorough information to the AC Committee so that they can then provide both Pharmaxis and the FDA with advice, guidance, and recommendations.

The meeting was adjourned at 1:30pm.

Drafted by M. Raggio/10-7-09
Initialed by Sally Seymour/10-7-09
Tony Durmowicz/10-7-09
Badrul A. Chowdhury/10-8-09
Finalized by M. Raggio/10-8-09

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

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/s/

MIRANDA B RAGGIO
10/08/2009

NDA # 22-368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 02, 2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-2109

Subject: CMC Request for Information: Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover: 4

Comments: Please confirm receipt

Document to be mailed: **YES** **xNO**

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NDA # 22-368

Your submission dated February 27, 2009 and amendment dated September 8, 2009, to NDA 22-368, is currently under review. We have the following requests for information:

1. Provide the appropriate intervals at which you propose to periodically re-establish the reliability and quality of the incoming batches of the drug substance from the manufacturer as per 21 CFR 211.84(d)(2).

2. Provide results of the system suitability procedure carried out for the method TM 006 (Purity, Assay, and Related Substances for Mannitol). The criteria proposed for this test is acceptable, however, no validation data has been presented confirming that these proposed criteria have been met.

3. Provide data ensuring the robustness of the analytical method TM 006, as per ICH Q2 (R1), to support the method validation.

4. Provide sample solution stability information for the analytical method TM 006 in support of the method validation.

5. Provide an agreement that the drug substance (DS) batch or any part of it, if used beyond the retest period, will be evaluated according to the DS established specifications. Retesting will only qualify that batch to be used in the manufacture of the drug product and will not recertify the DS with a new test date. Clarify if a batch will be discarded after the retest period, as well as the duration the retest period.

6. Reference is made to Study RN08-001 (Module 3, Section P2.4.2). Provide the acceptance criterion for device resistance for incoming inhaler devices from (b) (4) Also, clarify whether the inhaler resistance testing will be performed as a quality control test on the incoming batches.

7. Provide representative executed batch records for the manufacturing process of Aridol, Inhalation Powder, for all strengths of the drug product.

8. Provide validation data and/or representative IR scans for mannitol tested from samples taken from the drug product using Method TM036 (ID by FT-IR).

9. Tighten the acceptance criteria for the (b) (4) impurity to (b) (4). Based on the representative data provided (n = 3 batches) in the (b) (4) report for the pre-registration stability testing, the proposed (b) (4) limit of (b) (4) is excessive. The data for all three batches complies with the tightened (b) (4) specifications.

NDA # 22-368

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov. by COB on 10-09-09.Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

NDA # 22-368

Dratfted by Deepika Aroro/10-1-09
Initialed by Ali Al-Hakim 10-1-09
Revised by Miranda Raggio/10-1-09 and resent to Deepika Arora and Ali Al-Hakim
Changes accepted by D. Arora and Ali Al-Hakim 10-2-09
Cleared by Sandy Barnes/10-2-09
Finalized by Miranda Raggio/10-2-09

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

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/s/

MIRANDA B RAGGIO
10/02/2009

NDA # 22-368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 25, 2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-2109

Subject: Request for Information: Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover:3

Comments: Please confirm receipt

Document to be mailed: YES xNO

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Your submission dated February 27, 2009, to NDA 22-368, is currently under review. We have the following requests for statistical information:

1. Provide an analysis dataset for Study 305 with one row per subject and include the following variables:

    a. unique subject identification number
    b. center / investigator
    c. indicator variables for each of the subpopulations described in Figure 10-1 of the study report
    d. diagnosis using Aridol (positive or negative)
    e. diagnosis using Methacoline with 16 mg/mL cutoff (positive or negative)
    f. diagnosis using Methacoline with 12 mg/mL cutoff (positive or negative)
    g. diagnosis using Methacoline with 4 mg/mL cutoff (positive or negative)
    h. diagnosis using exercise challenges (positive or negative)
    i. diagnosis from blinded respiratory physician at visit 5 (on protocol specified ordinal scale: asthma is extremely likely or definite, very likely, probable, possible, unlikely but cannot be excluded, very unlikely or excluded)
    j. visit 2 FEV_1 prior to exercise challenge
    k. visit 2 FEV_1 at 5 minutes post-exercise
    l. visit 2 FEV_1 at 10 minutes post-exercise
    m. visit 2 FEV_1 at 15 minutes post-exercise
    n. visit 2 FEV_1 at 30 minutes post-exercise
    o. visit 3 FEV_1 prior to exercise challenge
    p. visit 3 FEV_1 at 5 minutes post-exercise
    q. visit 3 FEV_1 at 10 minutes post-exercise
    r. visit 3 FEV_1 at 15 minutes post-exercise
    s. visit 3 FEV_1 at 30 minutes post-exercise
    t. age
    u. gender
    v. race

    Include only observed data, not imputed data.

2. Provide a second analysis dataset for Study 305 with one row per subject by dose and treatment combination including the following variables:

    a. unique subject identification number
    b. center / investigator
    c. indicator variables for each of the subpopulations described in Figure 10-1 of the study report
    d. dose of Mannitol / dose of Methacoline
    e. baseline FEV_1
    f. FEV_1
    g. percent change from baseline in FEV_1

h. diagnosis using exercise challenges (positive or negative)
i. diagnosis from blinded respiratory physician at visit 5 (on protocol specified ordinal scale: asthma is extremely likely or definite, very likely, probable, possible, unlikely but cannot be excluded, very unlikely or excluded)
j. age
k. gender
l. race

Include only observed data, not imputed data.

Submit your response to me via email at Miranda.Raggio@fda.hhs.gov. by COB on September 2, 2009.Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

Drafted by M. Raggio/8-20-09
Initialed by Sandy Barnes/8-25-09
Ruthi Davi/8-25-09
Qian Li/8-25-09
Finalized by: Miranda Raggio/8-25-09

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/s/

MIRANDA B RAGGIO
08/25/2009

NDA # 22-368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 08, 2009

To: Valerie Waltman, MS Senior Manager, Regulatory Affairs	**From:** Miranda Raggio Senior Regulatory Project Manager
Company: Pharmaxis, Inc., Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 610-363-5926	**Fax number:** 301-796-9728
Phone number: 61363- x103	**Phone number:** 301-796-2109

Subject: Request for Information: Aridol™ (mannitol bronchial challenge test), NDA 22-368

Total no. of pages including cover:3

Comments: Please confirm receipt

Document to be mailed: YES xNO

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Your submission dated February 27, 2009, to NDA 22-368, is currently under review. We have the following requests for information:

1. Provide Attachments 1, 2 and3 for Study RN07-23 (Aridol Product Characterization Report – Effects of Different Flow Rates and Volumes on Particle Size Distribution).

2. Submit detailed analytical information of (b) (4) concentrations in the Mannitol used in the six-month inhalation toxicity study (Study Report 667108).

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov. by COB on July 22, 2009.Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109.

Fax prepared by D. Arora/7-8-09
Revised by M. Raggio/7-8-09
Sent to D. Arora, P. Peri, A. Al-Hakim(CMC) and Sandy Barnes(CPMS)/7-8-09
Finalized by M. Raggio/7-8-09

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/s/

Miranda Raggio
7/8/2009 02:58:13 PM
CSO

-DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**
TO *(Division/Office)*: Division Microbial Review Team David Hussong Ph.D., James McVey, Ph.D., and Ms. Sylvia Gantt New Drug Microbiology Staff (OPS)		FROM: Miranda Raggio, OND, Senior Regulatory Project Manager/6-2109	
DATE Jun 16, 2009	NDAs 22-368	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT Feb, 27, 2009
NAME OF DRUG Aridol (Mannitol) Inhalation Powder	PRIORITY CONSIDERATION: Standard Review	CLASSIFICATION OF DRUG: 1	DESIRED COMPLETION DATE July 25th, 2009
NAME OF FIRM: Pharmaxis Inc.			

REASON FOR REQUEST:

The following assessments are requested from the microbiology staff:

1. Please evaluate, from the microbiological perspective, the adequacy of the Microbial Limits test acceptance criteria (see 3.2.S.4.1) and the [redacted] (b) (4) **(see 3.2.S.4.2).**

2. Please evaluate the proposed acceptance criteria for microbial limits in drug product (see 3.2.P.5.1)

The application is on the EDR. The link is: \\CDSESUB1\EVSPROD\NDA022368\0000. The PM for all the applications in DPAP is Miranda Raggio, 301-796-2109

COMMENTS/SPECIAL INSTRUCTIONS: None. See attached specifications.

[redacted] (b) (4)

(b) (4)

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/s/

Miranda Raggio
6/16/2009 09:13:45 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM:
PharmTox Review Team **(Dr. Luqi Pei/Dr. Molly Shea)**	**Deepika Arora, Ph.D., Prasad Peri, Ph.D and Ali Al Hakim Ph.D.,** **ONDQA/DPA1/Branch 2**

DATE:	NDA:	TYPE OF DOCUMENT:	DATE OF DOCUMENT
June 4, 2009	**22-368**	**NDA**	**27-Feb-2009**

NAME OF DRUG	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Mannitol	**S**	**3**	**July 20, 2009**

NAME OF FIRM: **Pharmaxis**

REASON FOR REQUEST:

Please evaluate the levels of Impurities in Drug Substance and Drug product
The sponsor proposes levels of (b) (4) for (b) (4) as the acceptance criteria for DS and DP, although the highest levels seen are about (b) (4)
In addition, there are reports in the M3 module of Pharmaceutical development (3.2.P.2) that pertain to ISO 10993 which need to be evaluated for safety.

(b) (4)

Drug Substance related impurities

Related substances	As per TM 006	(b) (4)

Drug Product related impurities

The release and shelf-life specifications for Aridol™ inhalation powder are summarised below:

Table 3.2.P.5.1a Aridol Specifications (Aridol, Inhalation Powder)

TEST and METHOD	SAMPLE SIZE	SPECIFICATION	
		RELEASE	SHELF-LIFE
Purity by HPLC[1] TM 006 / TM 010 (adapted from USP/Ph. Eur.)	(b) (4)	(b) (4)	
Related substances[1] TM 006 / TM 010 (adapted from USP/Ph. Eur.)			

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 /s/
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Ali Al-Hakim
6/4/2009 06:29:46 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-368

Pharmaxis, Inc.
403 Gordon Drive
Exton, PA 19341

Attention: Valerie Waltman, MS
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

Please refer to your new drug application (NDA) dated February 27, 2009, received February 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Aridol.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 27, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 30, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have the following requests for information:

Chemistry, Manufacturing, and Controls

1. Provide qualification data for the impurity (b) (4) in your drug substance as per ICH Q3A document. Reference to a compendial limit is not considered sufficient evidence of safety.

2. Provide safety qualification of drug degradation products according to the ICH Guidance Q3B.

3. Provide safety qualification of any extractable/leachables from the device.

4. The capsule sizes for the proposed RS01 Model 7 device are similar to the capsule sizes of other commercial marketed inhalation products. Provide available in vitro performance data for your mannitol capsules being delivered in other devices (b) (4) and for other commercial capsules being delivered by you device to see if interchanging the devices and capsules provides comparable in vitro performance results.

5. Provide dose proportionality results for APSD and DDU of the drug product for all the proposed doses using the proposed analytical methods.

6. Revise the proposed DDU specifications to be reflective of the proposal in the Draft MDI/DPI guidance. Refer to the comments sent in the communication dated May 29, 2008, on DDU methods provided at the pre-NDA meeting with reference to using the 0 mg capsule. Regarding the test method for measuring Delivered Dose of Mannitol from Capsules (TM032), clarify the differences between the DDU measured in Capsule set # 7, Capsule set #8, and Capsule set # 9 since all three use 4 x 40 mg capsules.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D, Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
5/12/2009 02:49:01 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising, and Communications (DDMAC)	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Pulmonary and Allergy Products: Miranda Raggio, 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3-17-09		22-368	original NDA	2-27-09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aridol(mannitol bronchial challenge test)	Standard	Respiratory	October, 2009

NAME OF FIRM: (b) (4)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Pharmaxis submitted a new NDA for Aridol to be used as a diagnositc tool for bronchial hyper-responsiveness. Please review the package insert, carton and container label, and instructions for physicians. The EDR link is \\CDSESUB1\EVSPROD\NDA022368\0000. Thank you.

SIGNATURE OF REQUESTOR Miranda Raggio, RN, BSN, MA	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Miranda Raggio
3/20/2009 04:37:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-368

NDA ACKNOWLEDGMENT

Pharmaxis, Inc.
403 Gordon Drive
Exton, PA 19341

Attention: Valerie Waltman, MS
Senior Manager, Regulatory Affairs

Dear Ms. Waltman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Aridol (mannitol dry powder capsules)

Date of Application: February 26, 2009

Date of Receipt: February 27, 2009

Our Reference Number: NDA 22-368

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2009,in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Miranda Raggio
Senior Regulatory Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Miranda Raggio
3/6/2009 12:44:10 PM

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 13, 2008, 3-4:30pm
Meeting Location:	White Oak Building, Room 1415
Application Number:	70277
Product Name:	Aridol
Received Briefing Package	February 15, 2008
Sponsor Name:	Pharmaxis, Ltd.
Meeting Requestor:	Pauliana Hall, President, PCH Integrated Regulatory Services, Inc.
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D., Division Director
Meeting Recorder:	Miranda J. Raggio, RN, BSN, MA, RPM
Meeting Attendees:	
FDA Attendees:	Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products Lydia Gilbert-McClain, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products Carol Bosken, M.D., Medical Reviewer, Division of Allergy and Pulmonary Products Prasad Peri, Ph.D., Pharmaceutical Assessment Lead Division of Pre-Marketing Assessment I, Branch II Craig Bertha, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment I, Branch II Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products
Sponsor Attendees:	Pauliana Hall, RAC, US Agent and Regulatory Consultant for Pharmaxis, Ltd., President, PCH Integrated Regulatory Services, Inc.

Shane Johnston, PhD, Quality Assurance Manager, Pharmaxis Ltd.

Eddie Vaiciurgis, MSc, Quality Control Supervisor, Pharmaxis, Ltd.

John Crapper, BSc, MBA, Chief Operations Manager, Pharmaxis Ltd. (telephone)

Ron Sinani, BPharm, Regulatory Affairs Manager, Pharmaxis Ltd.

Carina Floden, Ph.D., Product Development Coordinator, Pharmaxis Ltd. (telephone)

Clare Mosedale, MSc, Regulatory Affairs Chemist, Pharmaxis Ltd.

Background

PCH Integrated Regulatory Services, Inc. (PCH), on behalf of Pharmaxis Ltd, requested a Type B, Pre-NDA meeting in a correspondence dated January 16, 2008, received January 17, 2008. The purpose of this meeting was to discuss the necessary CMC data to support the NDA filing and ensure all the CMC issues are addressed in the NDA. The meeting briefing package was submitted to the Division on February 15, 2008. Upon review of the briefing package, the Division provided responses to PCH for Pharmaxis, Ltd. via a telephone facsimile on March 8, 2008. The content of telephone facsimile is printed below, with the Division's responses (in ***bold italics***) to the Pharmaxis questions. On March 12, 2008, Pauliana Hall, on behalf of Pharmaxis, Ltd, let the Division know that they would like to discuss the CMC questions 4, 5, 7, and 8 at the meeting. Summary comments of the meeting discussion related to these questions are found in *italics* at the end of this document. A PowerPoint presentation document presented and distributed to the meeting attendees by Pharmaxis, Ltd. is attached.

Questions and Responses

Question 1. The active pharmaceutical ingredient (API) mannitol is supplied by a well-established cGMP API manufacturer, (b) (4) The Aridol NDA will reference (b) (4), DMF for mannitol. Therefore, we will not have any drug substance information for NDA/CTD Section 3.2.S except Pharmaxis release testing information presented in Section 3.2.P.2.

Does the Agency agree with our proposal for drug substance documentation?

Division Response: ***We do not agree. Include the Pharmaxis acceptance specification applied to the API upon acceptance from the supplier (i.e., your table 4.1 on p. 16 of the meeting package). Also refer to 21 CFR 211.84(d) (2) and include in the NDA any methods that are not compendial, along with the associated validation data.***

Discussion: No further discussion occurred.

Question 2. Pharmaxis intends to submit extractables data on the capsules and blister packaging. However, as Aridol is a (b) (4), pre-metered, dry powder inhalation product, exposure of the mannitol powder to the inhalation device (b) (4) will be very limited. Therefore, we do not think it is necessary to fully characterize the extractables profile on the device. Pharmaxis has provided extractable and biological reactivity data (submitted with CMC information amendment S-0043 and, for reviewer's convenience, provided in this submission as Appendix 5.3) on the 'Dry Powder Inhaler (b) (4)' manufactured by the same manufacturer from the same materials as the (b) (4), and having a very similar design and dimensions. All device components in contact with the drug and patient's mouth comply with the Agency's food additive regulations. Samples of both devices have been provided for inspection. These were sent via courier to the Division on February 11, 2008 and received on February 13, 2008. The LOAs for these two models' DMFs and technical drawings are provided in Appendices 5.4 and 5.5.

Does the Agency concur that the extractables and biological reactivity data on Dry Powder Inhaler (b) (4); are acceptable to support the (b) (4)

Division Response: ***We agree, particularly since you confirm that the two versions of the inhaler are manufactured by the same manufacturer and from the same materials (i.e., same resins, colorants, additives in the same quantities). However, this assumes that the manufacturing conditions of the injection molding are also comparable (e.g., use of virgin resin only, molding temperatures and pressures) and that similar specifications are applied to the components and finished devices.***

Discussion: No further discussion occurred.

Question 3. (b) (4) is used for critical components of the inhalers. (b) (4) was used in the pivotal clinical trial (Study No. DPM-A-305); however, the proposed Aridol commercial product will use inhalers manufactured from (b) (4) (b) (4) Comparative DDU and APSD testing for the two materials has been performed for a number of batches including one NDA stability batch (up to 12 months storage) with no significant difference found between the two materials. In addition, the (b) (4) inhalers are being used in the CF and Bronchiectasis clinical studies and no device related safety issues have ever been reported. It should, therefore, be acceptable to change the device material supplier. Data from comparative testing between inhaler materials is supplied (Appendix 5.6). (See also Section 4.3.1.)

Does the Agency accept the use of (b) (4) inhalers for commercial product?

Division Response: ***Based on our preliminary review of the comparative Delivered Dose Uniformity (DDU) and Aerodynamic Particle Size Distribution (APSD) data provided in appendix 5.6, it will be acceptable to use the (b) (4) inhalers for the commercial product. However, this assumes that all other supportive information for the (b) (4) (b) (4) material, as manufactured into inhaler components, is acceptable from a safety and quality control perspective (e.g., composition, references to food contact regulations, USP biological reactivity test results, specifications).***

Discussion: No further discussion occurred.

Question 4. The methods for determination of DDU and APSD involve [redacted] (b) (4) This "challenge" type testing is more representative of the way the product is administered to patients that the previously used standard type testing where capsules of a single dose are each discharged through a separate device and individually recovered and analyzed. Comparative testing performed on several batches, including one batch used in the DPM-A-305 clinical trial, has shown the "challenge" type method provides equivalent results to the standard method and that both methods are equally capable of demonstrating batch-to-batch variation and stability trends (Appendices 5.7 and 5.8). Pharmaxis believes the challenge type method is the most suitable one to ensure product effectiveness and consistency and better complies with the Draft Guidance for Industry: Metered dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing, and Controls Documentation, dated October 1998. (See also Section 4.3.1.)

Does the Agency concur that the "challenge" type method can be considered for Aridol?

Division Response: ***We assume you are collecting doses*** (b) (4) ***(5, 10, 20, and 40 mg) for the APSD challenge testing,*** [redacted] (b) (4) ***Also, for the DDU challenge testing, we assume you meant to state that doses*** (b) (4) ***are separately collected and quantified.*** [redacted] (b) (4)

For the Aridol product, the separate collection of doses (b) (4) [redacted] ***for DDU testing is acceptable. Based on tables 5.1 and 6.1 in appendix 5.7, it is our understanding that this challenge DDU testing will be done for each of ten separate devices, for a total of 60 doses (5, 10, 20, 40, 160, 160 mg from 10 devices).***

The separate collection of doses (b) (4) ***for APSD with the same device (n = 6 devices) is acceptable (APSD challenge test). Based on tables 5.a and 5.1c in appendix 5.8, it is our understanding that this testing would result in*** [redacted] (b) (4) ***The acceptance of the ACI challenge method for future determinations of APSD is dependent on your provision in the NDA of comparative APSD data and a summary of these data which will demonstrate that in terms of the in vitro APSD, the clinical batches behave in a comparable manner when compared to those batches representative of what you plan to market.***

Discussion: Pharmaxis presented the following slide, requesting further clarification on the response to Question 4.

(b) (4)

The Division responded that the dosing for (b) (4) (b) (4) *than the dosing for Aridol, therefore, the same schema would not apply.*

Question 5. A method for the analysis of Spray Dried Mannitol polymorph content has been developed and validated by an external testing facility (b) (4) The body of the development report (SR-20070548.01, pages 1-41) is included to facilitate the review (Appendix 5.9). Pharmaxis believes this method is suitable to control and adequate to monitor the polymorph content of in the Aridol capsules.

Does the Agency agree with our approach?

Division Response: ***We agree with your approach of having a validated method for the control of the polymorphic form(s) of the mannitol in the capsules. The adequacy of the method and the associated acceptance criteria will be evaluated during the review of the NDA.***

Discussion: Pharmaxis provided further clarification in the slide presented below.

(b) (4)

The FDA responded that Pharmaxis should follow the Q6A approach towards looking at polymorphs.

Question 6. The Agency has previously requested both the mean and individual stability data as well as graphs for some parameters. As reporting of some parameters (particularly APSD and DDU) will be quite complex, we have included a proposed stability data-reporting format in Appendix 5.10. Please note that stability data in the NDA will also be presented in SAS format.

Is the proposed format for submitting the drug product stability data in the eCTD acceptable to the Agency?

Division Response: *Yes, for the most part.* ***However, we recommend that for the presentation of the tabular DDU Challenge results you include the standard deviation for the calculated means and also include the proposed acceptance criteria for each of the doses quantified. More important will be your use and presentation of the stability data in the sections of the application where you summarize the stability of the drug product, propose an expiry, and justify your proposed specification acceptance criteria. Both the summary of the stability data and the section justifying the acceptance criteria should be presented on a parameter-by-parameter basis and should refer specifically to data supporting your proposals. Graphical presentations are encouraged.***

Discussion: No further discussion occurred.

Question 7. The Aridol kit consists of a carton with one (b) (4) device and foil-blistered mannitol capsules (one each of 0 mg, 5 mg, 10 mg, and 20 mg capsules, plus fifteen 40 mg capsules). A full-color mock-up of the proposed carton is presented in Appendix 5.11. The proposed blister labeling is presented in Appendix 5.12.

Does the Agency have any comments on the layout and information proposed in the carton and foil blister packaging labels?

Division Response: Labeling will need to be reviewed in the full context of the application and in consultation with other groups within the Agency. However, based on a preliminary review, it is unclear how physicians/healthcare providers who perform the bronchial challenge using Aridol will obtain the Aridol. (b) (4) ***Clarify how you intend to market the Aridol Kit.***

Discussion: At this point in the meeting a sample of the Aridol Kit device, capsules, and carton was passed around for the FDA attendees to view. A ten minute training video for health care professionals was shown by Pharmaxis. The following slides related to Question 7 were discussed. (The entire Pharmaxis Pre-NDA Meeting (CMC) slide presentation is attached at the end of this document).

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(b) (4)

[redacted]

Highlights of this discussion are found below:

1. *The Division clarified that the adequacy of the statement "For Single Patient Use Only" on the outer packaging would be a review issue.*
2. *Pharmaxis reiterated that the Aridol Kit will not be marketed to pharmacies, but rather distributed to physician offices.*
3. *The Division informed Pharmaxis that justification for study subjects getting a 160mg dose three times at the end of the Aridol kit test would need to be provided in the NDA. They noted that the rationale for this approach must be data driven, and not convenience driven.*
4. *The Division informed Pharmaxis that due to the fact that mannitol can cause bronchospasm, the label for the Aridol kit and the label for all mannitol products require a Boxed Warning. The Division advised Pharmaxis to consider the language in the Boxed Warning for Provocholine® when drafting the language for the Aridol label.*
5. *The Division asked how long it takes to perform a complete Aridol kit test. Pharmaxis responded that it takes approximately 10 minutes for a positive test, and approximately 20 minutes for a negative test.*
6. *The Division informed Pharmaxis that justification for the use of a spacer at the end of the Aridol kit test would need to be provided in the NDA. The Division also commented that if the label specified the use of a specific* [redacted] (b) (4)*, then the data for that product must also be submitted for review.*
7. *The Division encouraged Pharmaxis to consider various options for product packaging and distribution which would decrease the risk of unused capsules being taken inappropriately and of the device being used multiple times on multiple patients.*

Question 8. Pharmaxis is planning to submit the Aridol NDA in 2/3Q 2008. The NDA submission will be in e-CTD format, a categorical exclusion from the EA requirement will be requested, and the method validation package and sample executed batch record will be included in Module 3R, Regional Information. The executed batch record will be for a clinical or stability drug product

batch (batch to be determined). Pharmaxis is not planning to submit a separate Certified Field Copy for the method validation package.

Are these proposals acceptable?

***Division Response:* We recommend that you inform the Field when you submit the application electronically.**

Discussion: In following slide Pharmaxis asked for clarification on which field office should be informed when the electronic NDA is submitted. The Division stated that they would get back to Pharmaxis with a response to this question. In a post-meeting email sent to Pharmaxis on March 19, 2008, the Division provided the following answer:

> *"If the manufacturing of the drug product is in a foreign country, and if the sponsor has headquarters in the US, the location of the headquarters would dictate the appropriate district office. Barring the headquarters being located in the US, then the location of the US agent would dictate the district office that should be associated with the application. Pauliana Hall is acting as the US agent for the firm. Assuming Pharmaxis does not manufacture the product in the US, and their headquarters is also not in the US, then the appropriate district office would be determined from the location of their US agent."*

(b) (4)

[redacted]

A subsequent post-meeting email was received from Pharmaxis on March 19, 2008, with the following question:

> "Will it make a difference if the company has a US Operation for Marketing and Sales?"

After consultation with Susan Laska (Consumer Safety Officer of OC/DMPQ/MAPCB), the Division responded in an email to Pharmaxis on March 20, 2008, as below:

> *"Your district office will be either San Francisco or Los Angeles, whichever is closest to you. You should contact them when you submit your eNDA".*

Question 9. All of the drug substance and drug product manufacturers for Aridol are located outside the USA.

(a) Does the Agency wish to have a list of holidays and facility locked-down dates for these manufacturer included in the NDA submission to facilitate in the PAIs scheduling?

Division Response: ***That is not necessary.***

Discussion: No further discussion occurred.

(b) Does the Agency have any other requirements for PAIs in foreign countries?

Division Response: We request that you include the name and phone number of the contact person for each site.

Discussion: No further discussion occurred.

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Linked Applications	Sponsor Name	Drug Name
IND 70277	PHARMAXIS LIMITED	ARIDOL

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

/s/

MIRANDA B RAGGIO
03/24/2008

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 12, 2008, 2-3:30pm
Meeting Location:	White Oak Building, Room 1415
Application Number:	70277
Product Name:	Aridol
Received Briefing Package	February 14, 2008
Sponsor Name:	Pharmaxis Ltd.
Meeting Requestor:	Pauliana Hall, President, PCH Integrated Regulatory Services, Inc.
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D., Division Director
Meeting Recorder:	Miranda J. Raggio, RN, BSN, MA, RPM
Meeting Attendees:	
FDA Attendees:	Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products
	Lydia Gilbert-McClain, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products
	Carol Bosken, M.D., Medical Reviewer, Division of Pulmonary and Allergy Products
	Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products
	Wei Qiu, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
	Qian Li, Sc.D., Biostatistics Team Leader, Division of Biometrics II
	Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees: Pauliana Hall, RAC, US Agent and Regulatory Consultant for Pharmaxis, Ltd., President, PCH Integrated Regulatory Services, Inc.

Brett Charlton, M.D., Ph.D., Medical Director, Pharmaxis, Ltd.

Ron Sinani, BPharm, Regulatory Affairs Manager, Pharmaxis, Ltd.

(b) (4)

Background

PCH Integrated Regulatory Services, Inc. (PCH), on behalf of Pharmaxis Ltd, requested a Type B, Pre-NDA meeting in a correspondence dated January 16, 2008, received January 17, 2008. The purpose of this meeting was to discuss the necessary clinical/nonclinical data to support the NDA filing and ensure all the clinical issues are addressed in the NDA. The meeting briefing package was submitted to the Division on February 14, 2008. Upon review of the briefing package, the Division provided responses to PCH for Pharmaxis, Ltd. via a telephone facsimile on March 6. 2008. The content of telephone facsimile is printed below, with the Division's responses (in ***bold italics***) to the Pharmaxis questions. On March 11, 2008, Pauliana Hall, on behalf of Pharmaxis, Ltd, let the Division know that they would like to discuss the clinical/nonclinical 2, 8, and 10 at the meeting. Summary comments of the meeting discussion related to these questions are found in *italics* at the end of this document. A powerpoint presentation document which was presented and distributed to the meeting attendees by Pharmaxis, Ltd. is attached.

Questions and Responses

Question 1. The Agency informed Pharmaxis at the pre-IND meeting (held July 19, 2004) that a PK study was required to demonstrate that inhaled mannitol was not accumulating in the airways. A bioavailability study was conducted following further discussion on the design and conduct of such a study (Bronchiectasis Type B meeting) and submission of the study protocol to the Agency for review.

Based on the data presented in this Pre-NDA Clinical/Nonclinical Meeting Package, does the Agency agree that the biopharmaceutical aspects of Aridol have now been satisfactorily addressed?

Division Response: ***The Bioavailability study (DPM-A-101) synopsis included in this submission is acceptable for NDA review. Whether biopharmaceutical aspects of Aridol have been satisfactorily addressed or not is a review issue.***

Discussion: No further discussion occurred.

Question 2. The Agency informed Pharmaxis at the pre-IND meeting (held July 19, 2004) that the Phase 3 clinical trial that was ongoing outside the United States (Australia) at the time (Study DPM-A-301) was not sufficient to establish the efficacy of Aridol in the proposed indication. Therefore, a second Phase 3 clinical trial was conducted in the United States (Study DPM-A-305) following the Agency's recommendations, investigated Aridol's use in subjects with suspected asthma rather than subjects with known asthma and healthy volunteers (study population for Study DPM-A-301). Although the second Phase 3 trial (Protocol No. DPM-A-305) investigated the "target" population, Pharmaxis contends that true sensitivity and specificity cannot be measured in such a population and therefore requests the Agency to consider both trials as pivotal clinical trials to support the proposed indication for Aridol.

Does the Division agree that substantial clinical evidence for safety and efficacy can be established based on the results from Protocol Nos. DPM-A-301 and DPM-A-305?

Division Response: ***We are uncertain if substantial evidence of efficacy can be established based on the results from Protocol DPM-A-301 and DPM-A-305 for the proposed indication of detection of bronchial hyperresponsiveness. The deficiencies of the development program of Aridol as a bronchoprovoactive agent have been previously discussed in various communications (see minutes of the July 19, 2004 pre-IND Meeting; FDA comments dated April 25, 2005). The design of your studies DPM-A-301 and DPM-A-305 do not address:***

(a) Sensitivity and specificity of Aridol in a random population of patients with hyperresponsiveness (refer to comment # 16 of FDA comments dated April 25, 2005). Since the most common clinical indication for a bronchial challenge is to evaluate the likelihood of asthma in patients in whom the diagnosis is suggested by current symptoms but is not obvious, it is important to test your product in patients who are likely to be subjected to the test, such as patients with non-asthmatic conditions that are also associated with hyperresponsiveness, and subjects who are relatively healthy.

(b) Comparison of subjects with a known range of sensitivity to methacholine to their responsiveness to mannitol. This would require complete characterization of the bronchial response curves (sensitivity and specificity) to mannitol and methacholine and not just the qualitative analysis.

To define sensitivity and specificity of the test you may also need to test the performance of the Aridol test in a normal population (i.e. patients with normal spirometry, non-smokers, with no history or symptoms of asthma or any other lung disease, no family history of asthma, and no symptoms of allergy). Although protocol DPM-A-301 was conducted in asthmatic (n =557) and "non-asthmatic" (n =97) subjects, it is not clear what population constitutes the "non-asthmatics."

For a diagnostic test you will need to target for an acceptable level of sensitivity and specificity of the test. The thresholds generally expected will be above 85%. If your product has a lower threshold of sensitivity and specificity you will need to justify the lower thresholds.

You state in your briefing package (page 69) that in the pivotal study DPM-A-305, some subjects enrolled in this study likely had other diagnoses such as de-conditioning. Both studies DPM-A-301 and 305 contain ambiguities in the patient population that would need to be sorted out in order for these studies to be reviewed in support of your proposed indication. The final study report for both studies must include the following detailed information on the patient population:

1) ***Methods used for screening the patients for enrollment,***
2) ***Description of specific signs and symptoms considered to be suggestive of asthma,***
3) ***Pulmonary function test results,***
4) ***Response to beta agonists if reversibility testing was performed,***
5) ***Asthma diagnostic standards used for patients diagnosed with asthma,***
6) ***Characterization of severity for patients diagnosed with asthma,***
7) ***Listing of concomitant medications for each patient and a summary of concomitant medications for the study population, and***
8) ***The diagnosis of each patient with a negative mannitol bronchoprovocation test.***

Regarding safety, we concur that there is enough safety information to support an NDA for the proposed indication of diagnosis of bronchial hyperresponsiveness.

(b) (4)

[redacted]

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Highlights of this discussion are provided below:

1. *The FDA stated that pivotal trials require a greater variety in the patient population selected than Pharmaxis has selected. Studies must look across a group of patients with a diagnosis associated with hyperresponsiveness, not just those with asthma, and should include healthy subjects.*
2. *The FDA stated that tests performed on these study subjects must be able to discriminate between those patients with asthma and those with other diseases which present in a similar manner.*
3. *The FDA noted that it is vital that at the end of the trial study investigators are able to make a determination as to which patients definitively have asthma, without unblinding the study population.*
4. *The FDA asked Pharmaxis for a clarification as to what constitutes a healthy volunteer in study A-301. Pharmaxis responded that the healthy volunteer group is comprised of patients with no history of smoking, no family history of diseases which cause bronchial hyperresponsiveness, and no clinical signs or symptoms of hyperresponsive reactions. Pharmaxis further clarified that their criteria for non-asthmatics includes those patients who have never had a clinical diagnosis of asthma nor experienced signs and symptoms suggestive of asthma.*
5. *Pharmaxis stated that the Aridol kit is not meant to be used as a definitive diagnostic procedure for asthma. They described the distinctions between an indirect challenge test and a direct challenge test with regards to lower thresholds for sensitivity and specificity and the justification for these thresholds.*
6. *The FDA and Pharmaxis discussed the concept of bronchoprovacation tests, including the methachloline challenge. Pharmaxis stated that the methacholine challenge was too sensitive for the purpose of excluding subjects from the military and other activities because it identified individuals as abnormal who will never develop asthma. Pharmaxis wants to develop a test that when positive one could be sure that the subject had asthma.* (b) (4) [redacted] *The FDA also noted that some of the differences in test performance were related to the cutoffs that were chosen to distinguish between normal and abnormal. In order to evaluate the usefulness of the mannitol challenge test the reviewers will require enough data to assess the entire range of mannitol and comparator reactivity.*
7. *The FDA stated that in the NDA Pharmaxis must present clear justification for the cut-offs and thresholds. Pharmaxis confirmed that this data would be in the NDA submission.*
8. *The FDA recommended that Pharmaxis look at the differences in the clinical tests performed and the outcomes of these tests with regard to the various diseases studied.*
9. *Pharmaxis confirmed that they would submit all study data, not just summary data, with the NDA so that the FDA can perform an independent analysis.*

Question 3. Considering the indication for use, the benign safety profile and low potential risk associated with the mannitol dry powder inhaler, does the Division agree that postmarketing pharmacovigilance activities will be adequate to minimize the potential risk associated with the use of Aridol (mannitol) dry powder inhaler for detection of bronchial hyperresponsiveness in patients with suspected asthma?

Division Response: This is a review issue.

Discussion: No further discussion occurred.

Question 4. The safety of mannitol has been well established through its use as a food ingredient and a pharmaceutical excipient. During the Pre-IND Meeting on July 19, 2004, the Agency requested that Pharmaxis conduct a further nonclinical toxicology study in non-rodents in addition to the studies completed in rats. Pharmaxis has completed a (b) (4), a 3-month study in rats, and a 6-month study in dogs, (b) (4) The Agency has confirmed that the current nonclinical safety data package is adequate to support the Phase 3 clinical studies for the 30 pages has been Pharmaxis is not planning to do any additional nonclinical inhalation toxicology study to support the Aridol NDA submission.

Does the Division agree that no additional toxicology study is required to support the Aridol NDA filing?

Division Response: Yes, we agree.

Discussion: No further discussion occurred.

Question 5. Pharmaxis plans to combine the safety data from Study Nos, DPM-A-301 and DPM-A-305 for the purpose of an integrated safety analysis. The full details of the safety data from the supportive, published clinical trials are not available to Pharmaxis. The NDA will contain a summary of the safety results reported in the publications for these supportive trials, but this will not be included in the formal ISS. In addition, the NDA will contain any relevant safety information from multiple-dose Phase 2 and 3 studies being run for separate uses of inhaled mannitol in the management of bronchiectasis and cystic fibrosis. However, it will not be formally analyzed as part of the ISS. Some proposed mock-up tables for the ISS are provided in Appendix 8.7. Potential additional safety factors to tabulate include maximum fall in FEV_1 and recovery time after challenge.

Does the Division concur that the Integrated Summary of Safety will include only safety data from DPM-A-301 and DPM-A-305, and that the supportive safety data from other sources will be presented as narrative summaries?

Division Response: This is acceptable. However, see our response to Question 2.

Discussion: No further discussion occurred.

Question 6. Does the Agency agree that the Integrated Summary of Efficacy will include an **integrated analysis** of the effectiveness data, i.e., test sensitivity and specificity, from the two pivotal trials (Studies Nos, DPM-A-301 and DPM-A-305)? (emphasis added)

Division Response: ***No, we do not agree. The data should be presented separately. See our response to Question 2.***

Discussion: No further discussion occurred.

Question 7. Pharmaxis is planning to submit the Aridol NDA as an eCTD. The planned publisher of the eCTD has previously published eCTDs which have been submitted to the FDA. Does the Division wish to obtain a sample eCTD?

Division Response: We do not need to see a sample eCTD.

Discussion: No further discussion occurred.

Question 8. The proposed PI for Aridol is presented in Appendix 8.9. The content of the Aridol proposed PI is based on the Australian PI for Aridol (March 22, 2006). The format is based on FDA's "Requirements on Content and Format of Labeling for Human Prescribing Drug and Biological Products; Final Rule and Draft Guidance," published January 26, 2006.

In general, does the Division agree with our approach to the Aridol labeling?

Division Response: We note that your label does not entirely conform to the Physician's Labeling Rule (PLR) format. The label must conform to all the requirements of the Final Rule. Be advised that any agent approved for bronchoprovocation testing will have a boxed warning similar to the current boxed warning for Provocholine®. You may use the currently approved Provocholine® label as a guide in drafting a boxed Warning for Aridol. We note that section 14 (Clinical Studies) lacks patient population information that must be included to comply with the Physician Labeling Rule. Refer to the draft "Guidance for Industry on the Clinical Studies Section of the Label" for further guidance in completing this section of the label. Refer to CMC response to Question 7 for additional comments on Aridol labeling.

Discussion: It was decided that Question 8 would be discussed at the CMC meeting on March 13, 2008.

Question 9: The clinical study report for the pivotal clinical study (Protocol No, DPM-A-305) will be written according to the ICH E3 Guidance, with all appendices included in the NDA submission. A draft table of contents is provided in Appendix 8.10,

Does the Division have any comments on the structure of the pivotal clinical study report (Protocol No. DPM-A-305) outlined in the study report TOC (Appendix

8.10)?

Division Response: The outline of the structure of the study report TOC is acceptable. However, see our response to Question 2 for additional information that must be included in the content of the study report.

Discussion: No further discussion occurred.

Question 10: We will have clinical studies in cystic fibrosis and bronchiectasis patients in progress during the Aridol NDA review. We propose excluding these studies from the NDA Safety Update because they are for different indications, with very different dosages - (b) (4) (same active ingredient) (b) (4) whereas Aridol is indicated only for a single use for diagnostic purposes.

Does the Division agree with our proposed NDA Safety Update plan?

Division Response: No, we do not agree. Summary tables of adverse events reported in patients treated with mannitol for other indications should be included.

(b) (4)

Question 11. Pharmaxis is an Australian company with an operation in the United States. We are currently employing fewer than 500 full-time-equivalent employees and have no marketed products in the United States. Aridol is our first NDA submission to the FDA. We are planning to submit a request to waive the User Fees 3 months before the NDA submission.

Does the Agency agree that we are eligible for the User Fees Waiver?

Division Response: The Division does not make the decision about user fees. Contact the Office of Regulatory Policy for further information.

Discussion: No further discussion occurred.

Question 12. Does the Agency agree that our current clinical data package can be considered for the Pediatric Research Equity Act of 2007 (PREA) requirements and no additional Phase 4 pediatric effectiveness and safety study should be required?

Division Response: A request and justification for a waiver should be included in the NDA, and a decision will be made during the review.

Discussion: *No further discussion occurred.*

ADDITIONAL COMMENTS

Pharmacology/Toxicology

1. ***Address the safety qualification of drug impurities and degradation products according to the ICH Guidances Q3A and Q3B.***

2. ***Address the safety qualification of any extractable/leachables from the device.***

Discussion: *No further discussion occurred.*

Clinical

1. ***In the summary for protocol DPM-A-305 305 a positive response to mannitol is defined in two ways: When the FEV_1 falls 15% from baseline OR 10% from the previous FEV_1. However, in the proposed Aridol label, a positive test is defined as a 15% fall in FEV_1 from baseline. In order to support the label, the definition of a positive test used in the study must be the same as that proposed for the label.***

2. ***Throughout your briefing package, multiple inconsistencies are noted, leading to assumptions about the meaning of many statements. Such inconsistencies in an NDA submission could result in numerous information requests for clarification which may hinder the efficiency of the review process. Please ensure that your NDA submission is carefully edited. Refer to the "Guidance for Review Staff and Industry - Good Review Management Principles and Practices for PDUFA Products."***

Discussion: *No further discussion occurred.*

30 pages has been withheld in full as B(4) CCI/TS immediately following this page

Linked Applications	Sponsor Name	Drug Name
IND 70277	PHARMAXIS LIMITED	ARIDOL

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

/s/

MIRANDA B RAGGIO
03/19/2008