

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22368Orig1s000**

**OTHER ACTION LETTER(s)**



NDA 22368

**COMPLETE RESPONSE**

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 26, 2009, received February 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aridol (mannitol inhalation powder).

We acknowledge receipt of your amendments dated June 11, July 17, August 31, September 4 and 8, October 15, 22, and 30, November 3 and 13, December 4, 15, 17, 18, 21, 22, and 23, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

### **PRODUCT QUALITY**

During recent inspections of the following manufacturing and testing facilities our field investigators conveyed deficiencies to the respective representative of each facility.

(b) (4)

Satisfactory resolution of these deficiencies is required before this application may be approved.

## **LABELING**

Submit draft labeling that incorporates the revisions in the attached labeling, and the enlarged graphics submitted on December 22, 2009. Revise the instruction sheet to reflect all changes made in the package insert. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. There may be additional revisions to the label.

Please submit draft carton and container labeling revised per your submission of December 18, 2009.

## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

## **POSTMARKETING REQUIREMENTS UNDER 505(0)**

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify any unexpected serious risks in patients > 50 years of age with co-morbid conditions common in older populations.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this potential serious risk(s).

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify any unexpected serious risks in patients > 50 years of age with co-morbid conditions common in older populations.

Therefore, based on appropriate scientific data, FDA has determined that you will be required, to conduct the following if your application is approved:

A clinical trial with Aridol (mannitol inhalation powder) 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 (mannitol inhalation powder) 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.

Any additional specific details of this required postmarketing trial, including the schedule of milestones, will be described more fully in the approval letter for this application, if it is approved.

If you plan to reanalyze data from completed clinical trials with Aridol (mannitol inhalation powder) to address this requirement, you may submit this reanalysis in your Complete Response submission to facilitate review of the information.

## **OTHER**

You have not fully characterized foreign particulate matter and aerodynamic particle size distribution to set final release specifications. The agency acknowledges agreements in your submissions received November 13, and December 4, 2009, to revise these specifications when more data become available (i.e., first six batches for foreign particulate matter and first ten batches for APSD).

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:Labeling 12-23-09

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

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/

BADRUL A CHOWDHURY  
12/23/2009