CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022522Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022522

COMPLETE RESPONSE

Forest Research Institute, Inc.
Harborside Financial Center
Plaza Five, Suite 1900
Jersey City, NJ 07311

Attention: Lisa L. Travis, M.S., RAC
Director, Regulatory Affairs

Dear Ms. Travis:

Please refer to your July 15, 2009, New Drug Application (NDA), received July 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daxas (roflumilast) Tablets, 500 mcg.

We acknowledge receipt of your amendments dated August 10 and 24, September 11, October 13, November 17, and December 2, 4, 21, and 22, 2009, and January 19, 22, and 29, February 8, 12, 23, and 26, March 1, 8, 10, 18, and 26, and April 5, 6, 16, 19, and 23, 2010.

We also acknowledge receipt of your submission dated April 14, 2010, which included a proposed risk evaluation and mitigation strategy (REMS) for Daxas (roflumilast) Tablets. This amendment was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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.

CLINICAL

1. The submitted data do not provide substantial evidence of safety to support the use of roflumilast in patients with chronic obstructive pulmonary disease (COPD). Specifically, the safety signal of suicides and the psychiatric adverse reactions with roflumilast have not been fully assessed to understand the strength of the signal and its impact on the risk-benefit assessment for the treatment of patients with COPD.

   To support the safety of roflumilast regarding suicides and psychiatric adverse reactions, submit a comprehensive review and evaluation of all roflumilast safety data utilizing an acceptable method, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The assessment should include data from all COPD studies, as

well as studies conducted with roflumilast for other indications. Such an assessment is essential to fully explore the safety signal of suicides and the psychiatric adverse reactions and their impact on the risk-benefit assessment.

(b) (4)

3. The proposed dose of 500 mcg of roflumilast once daily is the maximal tolerated chronic dose of the drug. Because roflumilast has significant dose-related adverse reactions, the increased exposure to roflumilast, if it is a P-glycoprotein (P-gp) substrate, when taken concomitantly with other drugs that are P-gp inhibitors (e.g. ketoconazole) is a safety concern. Therefore, conduct an in vitro evaluation of the potential of roflumilast as a substrate for P-gp.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 214.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

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, Allergy, and Rheumatology products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

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.

Prominently identify submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022522
PROPOSED REMS - AMENDMENT

If you do not submit electronically, please send five copies of your REMS-related submissions.

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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

You may also request a post-action feedback meeting to discuss the quality of the application and to evaluate the communication process. The completed Quality Assessment form will be used as the reference for issues that are pertinent to the discussion. This meeting is not considered a PDUFA meeting and minutes will not be generated by FDA.

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 Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

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

/s/

CURTIS J ROSEBRAUGH
05/17/2010