CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022522Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	February 04, 2011
To:	Badrul Chowdhury, MD, Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	Claudia Karwoski PharmD, Director **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	roflumilast Tablets
Application Type/Number:	NDA 22-522
Applicant/sponsor:	Forest Research Institute Inc.
OSE RCM #:	2010-1979

1. INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for roflumilast tablets.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

The DRISK review of the Medication Guide will be provided under a separate cover. The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

2. BACKGROUND

Forest Laboratories Inc., submitted a New Drug Application (NDA) for roflumilast tablets as a maintenance treatment to reduce the risk of COPD exacerbations in patients with severe COPD. The Applicant submitted a voluntary REMS as part of this submission. The goal of the REMS is to mitigate the serious risks associated with the use of roflumilast tablets, specifically the risk of suicidal thinking and behavior. DPARP concurred with the applicant that a Medication Guide REMS was necessary for this submission to ensure that the benefits of the drug outweigh the risks.

3. MATERIAL REVIEWED

- Proposed roflumilast tablets Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on April 23, 2010, and received by DRISK on January 25, 2011.

4. RESULTS OF REVIEW

In our review of the proposed REMS, we have:

- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the proposed REMS.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to Forest Laboratories Inc.:

See the appended roflumilast REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

a. **GOAL**

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of roflumilast tablets.

b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document. See our editorial comments on this section of the proposed REMS (see Appendix A)

- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. You state that you plan to make tear pads containing the Medication Guide available to pharmacies for direct distribution to patients. We find this distribution plan acceptable.
- We remind you that under 21 CFR 208.24, you are responsible for ensuring that the roflumilast tablet carton or container label contains a prominent statement that the Medication Guide should be dispensed to each patient. We suggest the following language if the product is enclosed in the carton. "Dispense accompanying Medication Guide to each patient."

c. Your proposed timetable for submission of assessments (18 months, 3 years and 7 years) is acceptable.

We have some editorial comments on this section of the REMS.

d. Regarding your REMS Assessment Plan

The submitted methodology lacks sufficient detail to complete a review.

1. Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of [Tradename]. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." If the plan is to conduct the required assessment using a survey, the submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of [Tradename].
2. We encourage you to recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
   Explain how often non-respondent follow-up or reminders will be completed.
   Explain how an incentive or honorarium will be offered, and the intended amount.
   Explain how recruitment sites will be selected.
   Submit for review any recruitment advertisements.
3. Define the sample size and confidence intervals associated with that sample size.

4. Define the expected number of patients to be surveyed to obtain the final proposed sample size, and how the sample will be determined (selection criteria)
5. The patient sample should be demographically representative of the patients who use [Tradename].
   If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.
6. Explain the inclusion criteria; that is, who is an eligible respondent. For example, *patient* respondents might be:
   - Age 18 or older
   - Currently taking [Tradename] or have taken in past 3 months
   - Not currently participating in a clinical trial involving [Tradename]
   - Not a healthcare provider

   Submit any screener instruments, and describe if any quotas of sub-populations will be used.
7. Explain how surveys will be administered, and the intended frequency.
   We encourage you to offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person.
   Explain how surveyors will be trained.
8. Explain controls used to compensate for the limitations or bias associated with the methodology.
9. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
   Potential respondents should be told that their answers will not affect their ability to receive or take [Tradename], and that their answers and personal information will be kept confidential and anonymous.
10. Respondents should not be eligible for more than one wave of the survey.
11. The assessment is to evaluate the effectiveness of the REMS in achieving the REMS goal by evaluating patients' knowledge of the serious risks associated with use of [Tradename]. The assessment is not to evaluate consumer comprehension of the Medication Guide.
    Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
13. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.

Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about [Tradename]?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs.
The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
The order of the multiple choice responses should be randomized on each survey.

14. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.
    Respondents should not have the opportunity or ability to go back to previous questions in the survey.
    Explain if and when any education will be offered for incorrect responses.
15. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
16. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,
    Now we are going to ask you some questions about the Medication Guide you may have received with [Tradename]. The Medication Guide is a paper handout that contains important information about the risks associated with use of [Tradename] and how to use [Tradename] safely. Medication Guides always include the title "Medication Guide" followed by the word [Tradename] and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about [Tradename]," "What is [Tradename]," and "Who should not take [Tradename]."
17. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

    - Who gave you the Medication Guide for [Tradename]? (Select all that apply)
        a) My doctor or someone in my doctor's office
        b) My pharmacist or someone at the pharmacy
        c) Someone else - please explain: _____
        d) I did not get a Medication Guide for [Tradename]

    - Did you read the Medication Guide?
        - All,
        - Most,
        - Some,
        - None

    - Did you understand what you read in the Medication Guide?
        - All,
        - Most,
        - Some,

- None

- Did someone offer to explain to you the information in the Medication Guide?
  - Yes, my doctor or someone in my doctor's office
  - Yes, my pharmacist or someone at the pharmacy
  - Yes, someone else – please explain:
    _____
  - No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
  - All,
  - Most,
  - Some,
  - None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

18. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
19. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

3 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHAWNA L HUTCHINS
02/04/2011

CLAUDIA B KARWOSKI
02/08/2011
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 26, 2010
To:	Badrul Chowdhury, MD , Director Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN, Patient Product Information Reviewer Acting TL, Division of Risk Management (DRISK)
From:	Mary Dempsey, BS, Risk Management Programs Coordinator, DRISK
Subject:	Deferral Memo
Drug Name(s):	Daxas (roflumilast)
Application Type/Number:	NDA 022522
Applicant/sponsor:	Forest Research Institute
OSE RCM #:	2010-839

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Risk Management (DRISK) review the proposed patient labeling and Risk Evaluation Mitigation Strategy (REMS) for New Drug Application 022522 submitted by Forest Research Institute for Daxas (roflumilast).

DPARP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide and REMS review until such time as the review division plans to address labeling.

Please send us a new consult request at that time. This memo serves to close-out the consult request for Daxas (roflumilast) NDA 022522.

Please let us know if you have any questions.

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/

MARY J DEMPSEY
04/27/2010

LASHAWN M GRIFFITHS
04/27/2010
I concur