

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-222Orig1s000

**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: March 23, 2010

To: Donna Griebel, MD Director
Division of Gastroenterology Products (DGP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)
Sharon Mills, RN, BSN, CCRP
Acting Team Leader
Division of Risk Management (DRISK)

From: Jessica Diaz, RN, BSN
Patient Labeling Reviewer
Division of Risk Management (DRISK)
Jodi Duckhorn, MA
Senior Social Science Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide) and
Proposed Risk Evaluation and Mitigation Strategy (REMS)
TRADENAME (pancrelipase) Delayed-Release Capsules

Drug Name(s):

Application Type/Number: NDA 22-222

Applicant/sponsor: Axcan Pharma, Inc

OSE RCM #: 2009-1000

1 INTRODUCTION

This memorandum is in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Medication Guide and the proposed Risk Evaluation and Mitigation Strategy (REMS) for TRADENAME (pancrelipase).

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.

2 BACKGROUND

On September 28, 2007, Axcan Pharma, Inc submitted New Drug Application (NDA) 22-222 for the treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis (CF) and chronic pancreatitis. FDA issued a complete response on July 1, 2008.

On April 7, 2009 NDA 22-222 was resubmitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA). On May 20, 2009, the DGP sent a REMS Notification Letter to Axcan Pharma, Inc because DGP determined that a REMS is necessary for NDA 22-222 TRADENAME (pancrelipase) capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

The letter stated that the REMS must include a Medication Guide and a Timetable for Submission of Assessments. On September 9, 2009 the Agency issued another complete response letter citing a number of deficiencies including product quality, REMS, labeling, and facility inspection deficiencies. Axcan Pharma, Inc submitted the complete response addressing the product quality and facility inspection deficiencies. The REMS submission that is the subject of this review was submitted on June 2, 2009 (prior to the complete response action).

2 MATERIAL REVIEWED

- Draft TRADENAME (pancrelipase) Delayed Release Capsules Prescribing Information (PI) submitted July 14, 2009, revised by the review division throughout the review cycle, and provided to DRISK on March 2, 2010
- Draft TRADENAME (pancrelipase) Delayed Release Capsules Medication Guide submitted July 14, 2009 and revised by the review division throughout the review cycle
- TRADENAME (pancrelipase) Delayed Release Capsules Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated May 20, 2009
- Proposed TRADENAME (pancrelipase) Delayed Release Capsules Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on June 2, 2009

3 RESULTS OF REVIEW

3.1 In our review of the Medication Guide, we have:

- Simplified wording and clarified concepts where possible
- Ensured that the MG is consistent with the PI
- Removed unnecessary or redundant information
- Ensured that the MG meets the Regulations as specified in 21 CFR 208.24
- Ensured that the MG meets the criteria as specified in FDA's Guidance Useful Written Consumer Medication Information (published July 2006)

3.2 In our review of the proposed REMS and REMS Supporting Document, we have:

- Ensured it includes the elements outlined in the REMS Notification Letter
- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.
- Reviewed the survey methodology for acceptability in assessing the goal of the REMS

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

We have the following comments and recommendations for the DGP and Applicant with regard to the MG, the proposed REMS and the REMS Assessment methodology.

Comments to DGP:

Our annotated MG is appended to this memo (Appendix A Marked Copy, Appendix B Clean Copy). Any additional revisions to the PI should be reflected in the MG.

Comments to Axcan Pharma, Inc:

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

a. GOAL

Your proposed goal is acceptable.

- b. It is not clear if your Medication Guide distribution plan is acceptable. Under 21 CFR 208.24 (b), 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. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

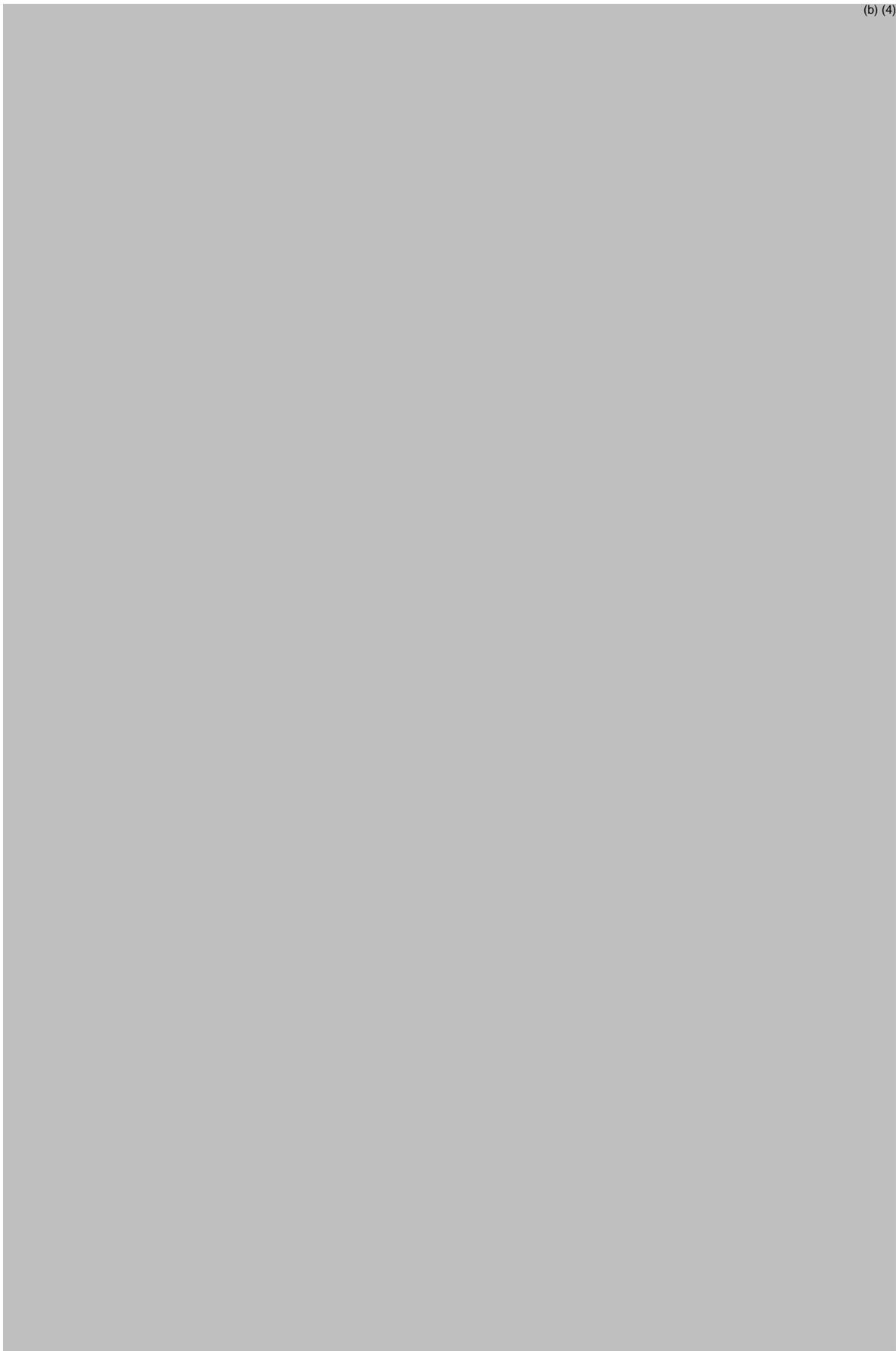
- A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
 - A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
- c. We acknowledge your inclusion of “an instruction alerting the pharmacist to provide a Medication Guide to each patient.” We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
- “Dispense the enclosed Medication Guide to each patient.” Or
 - “Dispense the accompanying Medication Guide to each patient.”
- d. Your proposed timetable for submission of assessments 18 months, 3 years, and 7 years is acceptable].

We have some editorial comments in this section of the proposed REMS.

- e. The submitted methodology lacks sufficient detail to complete a review.

(b) (4)









Please let us know if you have any questions.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

JESSICA M DIAZ
03/23/2010

CLAUDIA B KARWOSKI
03/23/2010
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: August 3, 2009

To: Donna Griebel, MD, Director
Division of Gastrointestinal Products

Through: Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: Robin Duer, RN, MBA
Patient Product Information Reviewer
Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
Division of Risk Management

Subject: Memo to File re: Review of Patient Labeling (Medication Guide) and Risk Evaluation Mitigation Strategy (REMS)

Drug Name(s): Ultrase (pancrelipase) Capsules

Application Type/Number: NDA 22-222

Applicant/sponsor: Axcan Pharma

OSE RCM #: 2009-1000

The Division of Gastrointestinal Products (DGP) requested that the Division of Risk Management (DRISK) review the proposed patient labeling and Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA) 22-222 submitted by Axcan Pharma for Ultrase (pancrelipase) Capsules.

DGP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide-only REMS until such time as the review division plans to address labeling. Please send us a new consult at that time. This memo serves to close-out the consult request for Ultrase (pancrelipase) Capsules.

Please let us know if you have any questions.

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

/s/

ROBIN E DUER
08/06/2009

JODI M DUCKHORN
08/06/2009

Risk Evaluation and Mitigation Strategy (REMS) Memorandum Porcine-Derived Pancreatic Enzyme Products

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III

NDA: 22-222
Products: Ultrase (pancrelipase) MT12, MT18, MT20 Capsules
SPONSOR: Axcan Pharma US, Inc.

FROM: Julie Beitz, MD
DATE: May 20, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Ultrase (pancrelipase) Capsules to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with high doses of pancreatic enzyme products (PEPs), and the theoretical risk of transmission of viral disease to patients.

In reaching this determination, we considered the following:

- A. The estimated size of the population likely to use the drug involved:

The estimated number of patients in the United States with maldigestion due to exocrine pancreatic insufficiency (EPI) is over 200,000.^{1,2} This figure is based on estimates of the

¹ Cystic Fibrosis Foundation Patient Registry 2006. Annual Data Report to the Center Directors, Bethesda, MD. www.cff.org

² Russo MW, Wei JT, Thiny MT, et al. Digestive and liver disease statistics, 2004. *Gastroenterology* 2004;126:1448–1453.

number of patients with cystic fibrosis (30,000), various forms of pancreatitis (over 200,000), and other disorders such as pancreatectomy, all of which feature EPI.

B. The seriousness of the disease or condition that is to be treated with the drug:

Exocrine pancreatic insufficiency in patients with cystic fibrosis is associated with fat malabsorption and macro- and micronutrient malabsorption, and can lead to serious clinical conditions that include growth failure and impaired pulmonary function, which contribute to premature death. EPI due to, for example, chronic pancreatitis or pancreatectomy, is also associated with fat malabsorption and macro- and micronutrient malabsorption. These deficiencies can lead to serious clinical conditions that include wasting, vitamin K deficiency and coagulation abnormalities.

C. The expected benefit of the drug with respect to such disease or condition:

Patients with EPI due to cystic fibrosis will have improved growth, pulmonary function, and long-term survival. It is also standard medical practice to treat patients with EPI due to chronic pancreatitis, pancreatectomy, and other disorders because it is considered that PEP replacement will lead to clinical benefits including improved nutrition and decreased co-morbidities.

D. The expected or actual duration of treatment with the drug:

The expected duration of treatment with PEPs in patients with EPI is for the life of the patient.

E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug:

PEPs have been reported to cause fibrosing colonopathy, a serious condition that may lead to colonic stricture. Doses greater than 6,000 lipase units/kg of body weight (kg)/per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age.^{3,4} The background incidence of such events is unknown. The Cystic Fibrosis Foundation (in conjunction with FDA) has established dosing guidelines that recommend that dosing not exceed 2,500 lipase units/kg of body weight (kg)/meal (or 10,000 lipase units/kg/day), or 4,000 lipase units/grams of fat ingested per day. Doses greater than 2,500 lipase units/kg/meal (or greater than 10,000 lipase units/kg/day) should only be used with caution and only if they are documented by laboratory testing that demonstrates improved fat absorption. Patients currently receiving higher doses than 6,000 lipase units/kg/meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

³ Borowitz DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr* 1995; 127: 681-684.

⁴ FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, et. al. High-Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis. *N Eng J Med* 1997; 336:1283-9.

In addition to the known risk of fibrosing colonopathy, there is a theoretical risk for transmission of viral disease associated with treatment with porcine-derived PEPs. However, the risk of transmission of viruses that may be pathogenic to humans has not yet been determined, as no case of viral transmission in human has been documented.

F. Whether the drug is a new molecular entity (NME):

Ultrase (pancrelipase) Capsules is a new chemical entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that porcine-derived PEPs, of which Ultrase (pancrelipase) Capsules is a member of the class, pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of porcine-derived PEPs. FDA has determined that porcine-derived PEPs are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use porcine-derived PEPs. FDA has determined that porcine-derived PEPs are products that are important to health and patient adherence to directions for use is crucial to the drugs' effectiveness. FDA has also determined that porcine-derived PEPs are products for which patient labeling could help prevent serious adverse events.

The elements of the REMS for porcine-derived PEPs will be a Medication Guide and a timetable for submission of assessments of the REMS.

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

/s/

Kristen Everett
5/20/2009 10:12:52 AM
CSO

Julie Beitz
5/20/2009 10:17:12 AM
DIRECTOR