CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022523Orig1s000

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 24, 2010
To:	Donna Griebel, MD, Director **Division of Gastroenterology Products (DGP)**
Through:	Claudia Karwoski, PharmD, Director **Division of Risk Management (DRISK)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Steve L. Morin, RN, BSN Patient Labeling Reviewer **Division of Risk Management (DRISK)** Jodi M. Duckhorn, MA Senior Social Science Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide), Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification, and Proposed Methodology and Survey Instruments for REMS Assessments
Drug Name(s):	PANCREAZE (pancrelipase) Delayed Released Capsules
Application Type/Number:	NDA 22-523
Applicant/sponsor:	Ortho-McNeil-Janssen Pharmaceuticals, Inc
OSE RCM #:	2010-163

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 proposed Medication Guide (MG), proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS supporting documents for PANCREAZE (pancrelipase) Delayed Released Capsules.

On June 23, 2009 Johnson and Johnson Pharmaceutical Research & development, LLC on behalf of McNeil Pediatrics, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., submitted New Drug Application (NDA) 22-523 for PANCREAZE (pancrelipase) Delayed Released Capsules.

PANCREAZE (pancrelipase) Delayed Released Capsules has been marketed in the US since 1988 without a requirement to have an approved NDA. The company submitted an original NDA to fulfill the FDA requirement under 69 Federal Register [FR] 23410, 72 Federal Register [FR] 60860 that all pancreatic enzyme products are new drugs for which an NDA must be approved by April 28, 2010.

Additional reference is made to the FDA letter from October 01, 2009 which outlined the FDA's requirement that a REMS is necessary for PANCREAZE (pancrelipase) Delayed Released Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefit 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.

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 MATERIAL REVIEWED

- Draft PANCREAZE (pancrelipase) Delayed Released Capsules Prescribing Information (PI) submitted October 28, 2009 and revised by the review division throughout the review cycle.
- Draft PANCREAZE (pancrelipase) Delayed Released Capsules substantially complete PI dated March 3, 2010, provided to DRISK on March 8, 2010
- Draft PANCREAZE (pancrelipase) Delayed Released Capsules Medication Guide dated October 28, 2009 and revised by the review division throughout the review cycle
- PANCREAZE (pancrelipase) Delayed Released Capsules Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated September 14, 2009
- Proposed PANCREAZE (pancrelipase) Delayed Released Capsules Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on October 19, 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 208.20
- 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 Review Division and Applicant with regard to the MG, the proposed REMS and the REMS Assessment methodology.

Comments to Review Division:

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 Applicant:

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

a. GOAL

   Your goal is acceptable.

b. We remind you of your responsibility to comply with 21 CFR 208.24, for ensuring that sufficient numbers of Medication Guides are provided with the product. We acknowledge you will provide an FPI with each bottle of PANCREAZE. However, please clarify each packaging configuration. 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.

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

The submitted methodology lacks sufficient detail to complete a review.

Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of Pancreaze. 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 Pancreaze.

1. 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.

2. Define the sample size and confidence intervals associated with that sample size.

3. Define the expected number of patients to be surveyed, and how the sample will be determined (selection criteria)

4. Explain the inclusion criteria; that is, who is an eligible respondent. For example, patient respondents might be:
    - Age 18 or older
    - Currently taking Pancreaze or have taken in past 3 months
    - Not currently participating in a clinical trial involving Pancreaze

- Not a healthcare provider

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

5. Explain how surveys will be administered, and the intended frequency.

   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.

6. Explain controls used to compensate for the limitations or bias associated with the methodology.

7. The patient sample should be demographically representative of the patients who use Pancreaze.

   If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.

8. 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 Pancreaze, and that their answers and personal information will be kept confidential and anonymous.

9. Respondents should not be eligible for more than one wave of the survey.

10. 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 Pancreaze. 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.

11. 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.

12. 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 Pancreaze?" 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.

13. 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.

14. 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.

15. 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 Pancreaze. The Medication Guide is a paper handout that contains important information about the risks associated with use of Pancreaze and how to use Pancreaze safely. Medication Guides always include the title "Medication Guide".

16. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

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

17. 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).
18. 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.

f. Please let us know if you have any questions.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22523	ORIG-1	JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH & DEVELOPMENT LLC	Pancrelipase Microtablets

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

/s/

STEVE L MORIN
03/24/2010

CLAUDIA B KARWOSKI
03/24/2010
concur

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Risk Evaluation and Mitigation Strategy (REMS) Supporting Document

Application Number:	**NDA 22-523 TRADENAME**
TRADENAME (generic name)	**TRADENAME (pancrelipase enteric-coated microtablets)**
Applicant Name and Address:	McNeil Pediatrics, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Route 202, PO Box 300 Raritan, NJ 08869-0602
Contact Information:	Ilona Scott Director, Global Regulatory Affairs 908-927-3223

Issue/Report Date: 12 October 2009
Prepared by: Johnson & Johnson Pharmaceutical Research & Development
Document No.: EDMS-USRA-11342036:2.0

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TABLE OF CONTENTS

1. BACKGROUND

TRADENAME (pancrelipase) is a pancreatic enzyme product (PEP) that contains enteric-coated delayed-release microtablets (MT) of porcine pancreatic enzyme concentrate, predominantly lipase, amylase, and protease. TRADENAME is indicated for use in diseases and procedures that result in significant reduction of exocrine pancreatic enzyme secretions, such as cystic fibrosis, chronic pancreatitis, post-pancreatectomy, post-gastro-intestinal bypass surgery, or ductal obstruction due to neoplasm, which disrupts the normal digestion of nutrients.

Delayed-release enteric-coated microtablets were introduced in the United States under the name PANCREASE MT in June 1988 without an NDA, and have been available by prescription since then.

To ensure that the benefits of TRADENAME continue to outweigh the risks, a Medication Guide describing the possible side effects of TRADENAME will be provided to patients prescribed TRADENAME.

This Risk Evaluation and Mitigation Strategy (REMS) Supporting Document provides the rationale for, and supporting information about, the proposed TRADENAME REMS.

2. GOAL

The goal of the TRADENAME REMS is to maintain a positive benefit/risk balance by informing patients and their caregivers of the risk of fibrosing colonopathy and the theoretical risk of transmission of viral disease.

3. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

3.1. Medication Guide

The TRADENAME medication guide (Appendix 1) has been designed to increase patient awareness of the serious risks associated with the use of TRADENAME, thereby improving the patients' safe and effective use. The Medication Guide provides important information that every patient should know about TRADENAME, including but not limited to the following:

- Side effects that may be serious or cause death (e.g., fibrosing colonopathy), allergic reaction (in patients with a known allergy to porcine products), or the theoretical risk for transmission of viral disease

- Known risk factors for developing a serious adverse reaction to TRADENAME (e.g., doses in excess of the recommended 10,000 lipase Units/kg/day; patients with gout, renal impairment, or hyperuricemia; and patients with an allergy to porcine products)
- Recognizing the signs and symptoms of the serious risks associated with the use of TRADENAME (e.g., abdominal distension, constipation, and signs of intestinal obstruction; severe allergic reactions, including anaphlyaxis, asthma, hives, and pruritus)
- Action(s) for the patient to take in response to signs or symptoms of serious side effects of TRADENAME (e.g., call your healthcare provider right away)
- A description of what TRADENAME is/is not (TRADENAME is a porcine-derived pancreatic enzyme concentrate (pancrelipase) containing the enzymes lipase, amylase, and protease, which is used in infants, children, and adults in the treatment of exocrine pancreatic insufficiency)
- How to obtain more information about TRADENAME (e.g., talk with your pharmacist or healthcare provider; go to www.RxforSafety.com or call 1-800-526-7736)

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., on behalf of McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., will include a supply of package inserts that include the Medication Guide to the wholesaler with each shipment of TRADENAME, in accordance with 21 CFR 208.24.

3.2. Timetable for Submission of Assessments of the REMS

REMS assessments (see Section 4 for content) will be submitted to the FDA in accordance with the following schedule:

- Assessment 1 (XX Month YYYY through XX Month YYYY) 18 months after NDA approval
- Assessment 2 (XX Month YYYY through XX Month YYYY) 3 years after NDA approval
- Assessment 3 (XX Month YYYY through XX Month YYYY) 7 years after NDA approval

4. REMS ASSESSMENT PLAN

The effectiveness of the Medication Guide will be assessed by conducting a survey in random samples of patients prescribed TRADENAME (or their caregivers in the case of children <18 years old). The survey is designed to

assess patient/caregiver understanding of the important risks (e.g., fibrosing colonopathy, allergic reaction, or the theoretical risk for transmission of viral disease) potentially associated with the use of TRADENAME.

The TRADENAME REMS assessment will include the result of 200 Patient/Caregiver Surveys, provided in Appendix 2. The effectiveness of the TRADENAME will be evaluated by the following:

Summary of the TRADENAME Evaluation of Patient/Caregiver Survey

Data Source	Risk	Targeted Value	Timeframe[a]	Contingency
Surveys of 200 patients/ caregivers	Lack of knowledge about the major risks associated with TRADENAME	80% understanding	Within 18 months	Re-evaluate educational materials and revise as appropriate

Footnotes:
[a] Timeframe for achieving targeted value.

APPENDICES

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TRADENAME

PATIENT/CAREGIVER SURVEY

We are conducting a survey of patients/caregivers to understand better how you receive information about the benefits and risks of pancreatic enzyme products that you take, including TRADENAME, *as well as your understanding of the potentially serious side effects associated with the use of* TRADENAME**.**
If you would like to participate in this survey (logon directions to be determined).

1. **Did you receive a TRADENAME prescription?** (please select appropriate response)

   ☐ Yes ☐ No

(Note: if the patient selects "No," the survey will automatically re-direct away from the rest of the survey).

2. **Who prescribed TRADENAME to you?** (please select appropriate response)

   ☐ Physician

   ☐ Physician Assistant

   ☐ Nurse Practitioner

3. **Did you fill your TRADENAME prescription?** (please select appropriate response)

   ☐ Yes ☐ No

(Note: if the patient/caregiver selects "No," the survey will automatically re-direct away from the rest of the survey).

4. **When did you fill your TRADENAME prescription?** (please select appropriate response)

   ☐ Today

   ☐ Within the last week

   ☐ 1 to 2 weeks ago

   ☐ 3 to 4 weeks ago

   ☐ More than a month ago

TRADENAME

PATIENT/CAREGIVER SURVEY

(Note: if the patient/caregiver received the prescription more than 2 weeks ago, the survey will automatically re-direct away from the rest of the survey).

5. **Did your physician/healthcare provider discuss the possible side effects of TRADENAME with you?** (please select appropriate response)

   ☐ Yes ☐ No

6. **Did your physician/healthcare provider discuss the benefits of TRADENAME with you?** (please select appropriate response)

   ☐ Yes ☐ No

7. **When you received you TRADENAME prescription:**

   Did you receive a "Medication Guide?" ☐ Yes ☐ No ☐ Don't know

   Did you read the "Medication Guide?" ☐ Yes ☐ No ☐ Don't know

8. **These questions ask about the potential side effects of taking TRADENAME.** (Please answer these true or false answers as best you can.)

TRADENAME is a product containing enzymes including amylase, lipase and proteases to help with digestion and malabsorption.	☐ True	☐ False
TRADENAME does not cause allergic reactions.	☐ True	☐ False
Fibrosing colonopathy, a rare but serious adverse reaction has been reported following treatment with pancreatic enyzyme products in doses greater than 10,000 Units lipase/kg/day	☐ True	☐ False
Discontinue taking TRADENAME when experiencing hives, trouble breathing or swallowing, swelling of the face, or other allergic responses.	☐ True	☐ False
Human beings have been infected with pig viruses from pancreatic enzyme products.	☐ True	☐ False
TRADENAME carries a theoretical and potential risk of transmitting pig associated viral illnesses.	☐ True	☐ False

TRADENAME

PATIENT/CAREGIVER SURVEY

The next set of questions asks for personal information, which will help us to analyze the data. Your individual answers will be kept strictly confidential

1. **Age:** _____

2. **Sex** (please check one)

   ☐ Female ☐ Male

3. **What is the highest level of education you have completed or the highest degree you have received** (please check one)

   ☐ Less than high school

   ☐ Completed some high school

   ☐ High school graduate or equivalent (e.g., GED)

   ☐ Completed some college, but no degree

   ☐ College graduate (e.g., BA, BS)

   ☐ Completed some graduate school, but no degree

   ☐ Completed graduate school (e.g., MS, PhD, MD)

Thank you for filling out this survey. Your participation will help us to improve these education programs and better serve all* TRADENAME *users. If you still have any questions about* TRADENAME*, please talk with your physician/healthcare provider

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
Division of Gastroenterology Products

NDA:	022523
Products:	Tradename (pancrelipase) Capsules
SPONSOR:	Johnson & Johnson Pharmaceutical Research & Development, LLC
FROM:	Joyce Korvick, MD, MPH
THROUGH:	Julie Beitz, MD
DATE:	September 24, 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 Tradename (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, if treated with Tradename (pancrelipase) Capsules. 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 strictures. Doses greater than 6,000 lipase units/kg of body weight (kg)/per meal have been associated with colonic strictures, 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 doses higher 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):

Tradename (pancrelipase) Capsules is a new chemical entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Tradename (pancrelipase) Capsules. FDA has determined that porcine-derived PEPs, including Tradename (pancrelipase) Capsules, 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, including Tradename (pancrelipase). FDA has determined that porcine-derived PEPs, including Tradename (pancrelipase) Capsules, 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 including Tradename (pancrelipase) Capsules. FDA has also determined that porcine-derived PEPs including Tradename (pancrelipase) Capsules, 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, including Tradename (pancrelipase) Capsules, will be a Medication Guide and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22523	ORIG-1	JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH & DEVELOPMENT LLC	Pancrelipase Microtablets

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/s/

KRISTEN A EVERETT
09/24/2009

JOYCE A KORVICK
09/24/2009