

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022523Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FROM: David B. Joseph, Acting Pharmacology Team Leader

DATE: April 8, 2010

SUBJECT: NDA 22,523 (Submission dated June 23, 2009)

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

Drug Product: Pancreaze® MT (pancrelipase) delayed release capsules

Comments:

1. The submitted safety information on the excipients in Pancreaze® MT is sufficient to provide a reasonable assurance of safety at the maximum recommended dose (6000 lipase units/kg/meal, for patients in whom symptoms and signs of steatorrhea persist after escalation to 2500 lipase units/kg/meal).
2. I concur with Dr. Ke Zhang's recommendation for approval, and the recommendations for changes in the Sponsor's proposed labeling (Pharmacology/Toxicology review dated April 2, 2010).

Recommendations:

1. From a nonclinical viewpoint, Pancreaze® MT should be approved.
2. The Sponsor's proposed labeling should be changed as recommended in Dr. Zhang's Pharmacology/Toxicology review.

David B. Joseph, Ph.D.
Acting Pharmacology Team Leader
Division of Gastroenterology Products

Date

cc:

NDA 22,523

DGP

DGP/CSO

DGP/Dr. Joseph

DGP/Dr. Zhang

OND IO/Dr. Jacobs

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

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/s/

DAVID B JOSEPH
04/08/2010

Comments on IND 22523 PANCREAZE™ (pancrelipase), a combination of porcine-derived lipases, proteases, and amylases

From: Abigail Jacobs

Date: April 9, 2010

There are no pharm tox issues with this NDA.

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

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/s/

ABIGAIL ABBY C C JACOBS
04/08/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22,523

SERIAL NUMBER: 0000, 0001, 0008, 0018, and 0024

DATE RECEIVED BY CENTER:

0000: April 27, 2009
0001: June 2, 2009
0008: September 14, 2009
0018: December 23, 2009
0024: February 4, 2010

DRUG NAME: Pancreaze[®] MT (pancrelipase) delayed release capsules

INTENDED CLINICAL POPULATION: Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

SPONSOR: Johnson and Johnson Pharmaceuticals Research and Development, L.L.C., Raritan, NJ

DOCUMENTS REVIEWED: EDR - Module 4

REVIEW DIVISION: Division of Gastroenterology Products
(DGP/HFD-180)

PHARM/TOX REVIEWER: Ke Zhang, Ph.D.

PHARM/TOX SUPERVISOR: David Joseph, Ph.D.

DIVISION DIRECTOR: Donna Griebel, M.D.

PROJECT MANAGER: Stacy Barley, R.N., M.S.N., M.H.A.

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Executive Summary**1. Recommendations****1.1 Recommendation on approvability**

From a preclinical standpoint, approval of Pancreaze is recommended for treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendation for labeling: The labeling should be revised as follows:

Sponsor's Proposed Version:

Pregnancy



Evaluation: The sponsor's reference to embryo-fetal developmental studies in rats and rabbits is not appropriate, since it cannot be determined as to whether the drug substance used in these studies is comparable to the drug substance in Pancreaze® MT. The recommended version below is consistent with the "Pregnancy" subsection of the Zenpep (pancrelipase) label.

Recommended Version:

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C: Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PANCREAZE should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

Sponsor's Proposed Version:

8.3 Nursing Mothers

Evaluation: The minipig data is not appropriate for this section. The recommended version below is consistent with the "Nursing Mothers" subsection of the Zenpep (pancrelipase) label.

Recommended Version:

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PANCREAZE is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.

Sponsor's Proposed Version:

Evaluation: The proposed subsection 13.2 (Animal Toxicology and/or Pharmacology) should be deleted. The inclusion of the cited toxicology studies in the label is not appropriate, since it cannot be determined as to whether the drug substance used in these studies is comparable to the drug substance in Pancreaze® MT.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase.

2. Summary of nonclinical findings:

The sponsor provided information to assure the safety of the excipients, as recommended in the FDA Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs (2006). The recommendations for toxicology studies in this guidance are limited to studies that would address any safety questions related to excipients. The estimated maximum daily intake of the excipients from Pancreaze MT administration is not considered to be a safety concern.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,523

Review number: 01

Sequence number/date/type of submission:

0000: April 27, 2009

0001: June 2, 2009

0008: September 14, 2009

0018: December 23, 2009

0024: February 4, 2010

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Johnson and Johnson Pharmaceuticals
Research and Development, L.L.C., Raritan, NJ

Reviewer name: Ke Zhang

Division name: Division of Gastroenterology Products (DGP)

HFD #: 180

Review completion date: April 2, 2010

Drug: Pancreaze[®] MT (pancrelipase) delayed release capsules

Molecular Weight/Formula: Not applicable

Relevant INDs/NDAs/DMFs: IND 74,893

Drug class: Pancreatic enzyme preparation

Indication: Pancreaze[®] MT is indicated for treatment exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. The recommended starting dose of Pancreaze[®] MT is 375-1,000 units lipase/kg/meal. The maximum recommended dosage is 10,000 units lipase/kg/day.

Clinical formulation: Film-coated pancrelipase microtablets, encapsulated in a hard gelatin capsule. The capsules are manufactured in four strengths: MT 4.2 (4,200 USP units of lipase), MT 10.5 (10,500 USP units of lipase), MT 16.8 (16,800 USP units of lipase) and MT 21 (21,000 USP units of lipase).

The ingredients in the microtablets are presented in the sponsor's Table 1.

Table 1: Quantitative Ingredient Statement for Pancrelipase Microtablets

Component	Quality Reference	Function	Quantity (mg/unit)
(b) (4)			
Pancrelipase Microcrystalline	Manufacturer ^a	API	(b) (4)
Cellulose	NF/Ph. Eur.	(b) (4)	(b) (4)
Crospovidone	NF/Ph. Eur.		
Colloidal Anhydrous Silica	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)			
(b) (4)			
(b) (4)			
Triethyl Citrate	NF/Ph. Eur.	(b) (4)	(b) (4)
Talc	NF/Ph. Eur.		
Simethicone Emulsion	Ph. Eur.		
(b) (4) dry mass (b) (4)	USP		
Montan Glycol Wax	Non-compendial ^b		
Total Film-Coated Microtablet			7.6923

^a Meets manufacturer's specification (Nordmark DMF No. 7090), which complies with USP/Ph. Eur. requirements

^b Meets manufacturer's specification

^c (b) (4) is the proprietary name for methylacrylic acid ethyl acrylate copolymer (b) (4) dispersion (b) (4) supplied by (b) (4). A letter of authorization is included in [Module 1.4.1](#).

The ingredients in the capsules are presented in the sponsor's Table 3.

Table 3: Capsule Ingredient Summary for Pancrease[®] MT Capsules

Components	Function	MT 4.2	MT 10.5	MT 16.8	MT 21
Gelatin Capsule					
Gelatin	(b) (4)	X	X	X	X
Titanium Dioxide (b) (4)		X	X	X	X
Sodium Lauryl Sulfate		X	X	X	X
Sorbitan Monolaurate					
		X	X	X	X
(b) (4) Iron Oxide		X	---	X	X
(b) (4)					
(b) (4) Iron Oxide (b) (4)		---	X	---	---
(b) (4) Iron Oxide (b) (4)		---	---	---	---
Gelatin Capsule Imprint Ink					
(b) (4)	Imprint	X	X	X	---
	Imprint	X	X	X	---
	Imprint	---	---	---	X

Based on the proposed labeling, the maximum daily dose is 10,000 units lipase/kg/day or 500,000 units/day if a 50 kg body weight is assumed. Using the capsules containing 21,000 units lipase (MT 21), one would consume up to 24 capsules/day to reach the maximum daily dose of 10,000 units/kg/day or 500,000 units/day.

Route of administration: Oral capsule.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

1. A 6-month oral toxicity study with (b) (4) in rats
2. A 1-year oral toxicity study with (b) (4) in dogs

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Not applicable.

2.6.6 TOXICOLOGY

The FDA Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs (2006) indicates that no pharmacology or toxicology studies of pancrelipase are needed. Therefore, the nonclinical review is focused on the inactive ingredients in the drug product. The results of the following toxicity studies should not be included in the labeling, since it cannot be determined as to whether the drug substance used in these studies is comparable to the drug substance in Pancreaze® MT: (1) acute single dose toxicity study in dogs, (2) 4-week oral toxicity study in rats, and (3) 6-month oral toxicity study in dogs.

The following tables, provided by the Sponsor, summarize the inactive ingredients in Pancreaze® MT. The tables provide an estimate of the maximum daily intake of each excipient based on daily ingestion of 25 capsules (MT21, containing 21,000 lipase units/capsule) in a patient weighing 50 kg. However, the maximum daily intake in mg/kg of two excipients, methacrylic acid-ethyl acrylate co-polymer and talc, was calculated based on ingestion of 50 capsules/day. The reason for the discrepancy in calculation methods is unknown, but was likely due to a clerical error.

Excipient (Function) CAS No.	Composition mg / MT Maximum MT/ capsule	Maximum mg/ capsule (mg /50 kg)	Maximum mg/ dose Based on 25 capsules per dose (mg /50 kg)	Regulatory References	Summary of Toxicology Information	Summary of Safety Evaluation
Microcrystalline cellulose (b) (4) 9004-34-6	(b) (4) mg x (b)	(b) (4) mg (b) mg/kg	(b) (4) mg (b) mg/kg	<u>FDA Inactive Ingredient Database</u> 261.19 mg max potency for oral tablet <u>World Health Organization (WHO)</u> concluded that tox data from humans and animals provided no evidence that the ingestion of this excipient can cause toxic effects in humans.	<u>Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS</u> LD50 rat, oral >5 g/kg TDLo rat, oral = 120 g/kg TDLo rat, oral = 420 g/kg/4 weeks TDLo rat, oral = 159 g/kg/90 days <u>World Health Organization</u> Rat NOEL = 3.8 to 4.4 g/kg/day <u>HAZARTEXT Database</u> Humans may tolerate up to 30 g/day (ACGIH, 1991) <u>Handbook of Pharmaceutical Excipients</u> Not orally systemically absorbed Relatively nontoxic Nonirritant	Toxicological safety margins greatly exceed proposed maximum clinical dose on a mg/kg basis.
Crospovidone (b) (4) 9003-39-8	(b) (4) mg x (b)	(b) (4) mg (b) mg/kg	(b) (4) mg (b) mg/kg	<u>FDA Inactive Ingredient Database</u> 75 mg max potency for oral capsule <u>21 CFR 173.55</u> not to exceed a limit of 60 ppm (60 mg/kg)	<u>Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS</u> LD50 rat, oral = 100 g/kg LD50 mouse, oral >40 g/kg LD50 rabbit, oral = 1040 mg/kg LD50 guinea pig, oral = 100 g/kg TDLo rat, i.v. = 35 g/kg/4 weeks	Regulatory referenced allowances exceed proposed maximum clinical dose on a mg/kg basis AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.

Excipient (Function) CAS No.	Composition mg / MT Maximum MT/ capsule	Maximum mg/ capsule (mg /50 kg)	Maximum mg/ dose Based on 25 capsules per dose (mg /50 kg)	Regulatory References	Summary of Toxicology Information	Summary of Safety Evaluation
Colloidal anhydrous silica (b) (4) 7631-86-9	(b) (4) mg x (b) (4)	(b) (4) mg (b) (4) mg/kg	(b) (4) mg (b) (4) mg/kg	FDA Inactive Ingredient Database 7.2 mg max potency for oral tablet 21 CFR 172.480 not to be used in an amount to exceed 2% by weight of the food (2% of 25 capsule dose w/w = 215 mg) EU Food Additives (1333/2008/EC) 2 g/kg for dry cereals	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS LD50 rat, oral >3.16 g/kg LDLo rat, oral = 5 g/kg TDLo dog, oral = 224 mg/kg/4 weeks	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.
Magnesium stearate (b) (4) 557-04-0	(b) (4) mg x (b) (4)	(b) (4) mg (b) (4) mg/kg	(b) (4) mg (b) (4) mg/kg	FDA Inactive Ingredient Database 100 mg max potency for oral capsule 21 CFR 184.1440 The ingredient is used in food with no limitation other than current GMP practice.	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS TDLo rat, oral = 1092 g/kg/13 weeks Handbook of Pharmaceutical Excipients LD50 rat, oral >10 g/kg Nontoxic when administered orally.	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.
Methacrylic acid-ethyl acrylate co-polymer (b) (4) (b) (4) 25212-88-8	(b) (4) mg x (b) (4)	(b) (4) mg (b) (4) mg/kg	(b) (4) mg (b) (4) mg/kg	FDA Inactive Ingredient Database 140.0 mg max potency for oral capsule	(b) (4) Proprietary Toxicity Data Provided to FDA Acute oral toxicity > 2 g/kg NOAEL rat, oral = 1 g/kg/4 weeks NOEL rat, oral = 200 mg/kg/6 month NOAEL dog, oral = 80 mg/kg/1 year	Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.

Excipient (Function) CAS No.	Composition mg / MT Maximum MT/ capsule	Maximum mg/ capsule (mg /50 kg)	Maximum mg/ dose Based on 25 capsules per dose (mg /50 kg)	Regulatory References	Summary of Toxicology Information	Summary of Safety Evaluation
Triethyl citrate (b) (4) 77-93-0	(b) (4) mg x (b) (4)	(b) (4) mg (b) (4) mg/kg	(b) (4) mg (b) (4) mg/kg	FDA Inactive Ingredient Database 20.17 mg max potency for oral tablet 21 CFR 184.1911 The ingredient is used in food with no limitation other than current GMP practice.	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS LD50 rat, oral = 5.9 g/kg LD50 guinea pig, oral >25 mL/kg LD50 cat, oral = 3.5 g/kg TDLo cat, oral = 15.9 g/kg/8 weeks	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.
Talc (basic magnesium silicate) (b) (4) 14807-96-6	(b) (4) mg x (b) (4)	(b) (4) mg (b) (4) mg/kg	(b) (4) mg (b) (4) mg/kg	FDA Inactive Ingredient Database 220.4 mg max potency for oral capsule FDA Database of Select Committee on GRAS Substances (SCOGS) Reviews Silicon compounds ... as direct food ingredient ... are insoluble or very slightly soluble in water and appear to be biologically inert. Maximum per capita intake of talc ... appears to be 0.5 g/day. There is no evidence in the available information on talc that demonstrates or suggests reasonable grounds to suspect a hazard to the public when talc is used at levels that are now current or that might reasonably be expected in the future.	Hazardous Substance Data Base, National Library of Medicine, US Dept of HHS and WHO /IARC Monographs Rat oral/diet 50 mg/kg/lifetime = no carcinogenicity Rat oral/diet 100 mg/day/5 months = no carcinogenicity Rat/mouse oral 1600 mg/kg/days 6-15 of gestation = no teratology Hamster oral 1200 mg/kg/days 6-10 of gestation = no teratology Rabbit oral 900 mg/kg/days 6-18 of gestation = no teratology No genotoxicity Handbook of Pharmaceutical Excipients Not orally systemically absorbed Relatively nontoxic	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.

Excipient (Function) CAS No.	Composition mg / MT Maximum MT/ capsule	Maximum mg/ capsule (mg /50 kg)	Maximum mg/ dose Based on 25 capsules per dose (mg /50 kg)	Regulatory References	Summary of Toxicology Information	Summary of Safety Evaluation
Simethicone emulsion (b) (4) 8050-81-5	(b) (4)mg x (b)	(b)mg (b) (4)mg/kg	(b)mg (b)mg/kg	FDA Inactive Ingredient Database 15.63 mg max potency for oral capsule	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS LD50 dog, i.v. = 900 mg/kg	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.
Montan glycol wax (b) (4) 73138-45-1	(b) (4)mg x (b)	(b)mg (b)mg/kg	(b)mg (b)mg/kg	IUCLID Dataset European Commission, European Chemicals Bureau LD50 rat oral > 2 g/kg LD50 mouse > 20 g/kg LD50 rabbit >12 g/kg	Lori References LD50 rat oral > 2 g/kg	Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.

Excipient (Function) CAS No.	Composition mg / MT Maximum MT/ capsule	Maximum mg/ capsule (mg /50 kg)	Maximum mg/ dose Based on 25 capsules per dose (mg /50 kg)	Regulatory References	Summary of Toxicology Information	Summary of Safety Evaluation
Gelatin 9000-70-8 (b) (4)	Not Applicable	(b) (4)mg (b)mg/kg	(b) (4)mg (b) (4)mg/kg	FDA Inactive Ingredient Database 756 mg max potency for oral capsule FDA Database of Select Committee on GRAS Substances (SCOGS) Reviews There is no evidence in the available information on gelatin that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS TDLO mouse, i.p. = 700 mg/kg Handbook of Pharmaceutical Excipients LD50 rat, oral. = 5000 mg/kg	Regulatory referenced allowances exceed proposed maximum clinical dose per capsule AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis.
Sodium Lauryl Sulphate (b) (4) 151-21-3	Not Applicable	(b) (4)mg (b) (4)mg/kg	(b) (4)mg (b) (4)mg/kg	FDA Inactive Ingredient Database 51.69 mg max potency for oral tablet 21 CFR 172.822 The ingredient is used in food (egg white solids) with a limitation of 1000 ppm (1000 mg/kg)	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS LD50 rat, oral. = 1288 mg/kg LD50 mouse, i.v. = 188 mg/kg LD50 cat, oral = 3.5 g/kg	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis

Excipient (Function) CAS No.	Composition mg / MT Maximum MT/ capsule	Maximum mg/ capsule (mg /50 kg)	Maximum mg/ dose Based on 25 capsules per dose (mg /50 kg)	Regulatory References	Summary of Toxicology Information	Summary of Safety Evaluation
Sorbitan Mono Laurate (b) (4) 9005-64-5	Not Applicable	(b) (4) mg (b) (4) mg/kg	(b) (4) mg (b) (4) mg/kg	FDA Inactive Ingredient Database 56.25 mg max potency for oral capsule	Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety, US Dept of HHS LD50 mouse, oral = 33.6 g/kg LD50 rat, oral = 36.7 mL/kg TDLo rat, oral = 832 g/kg/59 days TDLo rat, oral = 931 g/kg/70 days TDLo rat, oral = 2756 g/kg/21 weeks TDLo mouse, oral = 33250 g/kg/95 weeks TDLo hamster, oral = 3276 g/kg/39 weeks	Regulatory referenced allowances exceed proposed maximum clinical dose AND Toxicological safety margins exceed proposed maximum clinical dose on a mg/kg basis

The following excipient levels from the FDA Inactive Ingredient Database differ from the values stated in the above tables under "Regulatory References". The values below are the maximum levels in oral dosage forms.

Microcrystalline cellulose: 1385.3 mg
 Crospovidone: 792 mg
 Magnesium stearate: 1200 mg
 Montan glycol wax is not listed
 Montan wax: 0.06 mg

All of the inactive ingredients in Pancreaze® MT are listed in the FDA Inactive Ingredient Database. It appears that the amounts of these inactive ingredients per capsule (except montan wax) are within the maximum acceptable level per capsule in the FDA Inactive Ingredient Database. However, based on the proposed labeling, the maximum recommended daily dose is 10,000 units lipase/kg/day or 500,000 units/day if a 50 kg body weight is assumed. Using the capsules containing 21,000 units lipase, one would consume up to 24 capsules/day to reach the maximum daily dose of 10,000 units/kg/day or 500,000 units/day. Therefore, the total amounts of the following inactive ingredients in 24 capsules would exceed the maximum acceptable level (per dosage form) in the FDA Inactive Ingredient Database [this database does not provide the number of dosage forms (e.g. capsules or tablets) ingested to achieve the maximum recommended dose]: methacrylic acid-ethyl acrylate co-polymer ((b) (4)), triethyl citrate, gelatin, colloidal anhydrous silica, talc, and montan glycol wax.

Methacrylic acid-ethyl acrylate co-polymer ((b) (4)):

In a 6-month oral toxicity study in rats, (b) (4) was given to rats (30/sex/group) by stomach tube at 0, 200, 600, and 1500 mg/kg/day for 6 months. The following parameters were examined: clinical signs of toxicity, mortality, body weight, food consumption, ophthalmology, clinical chemistry, hematology,

urinalysis, organ weights, gross pathology, and histopathology. The test article reduced body weight gain in the high-dose group (17-19%) and induced inflammation in the intestine in the intermediate- and high-dose groups (1/60 and 2/60 rats, respectively). The tolerated dose was 600 mg/kg/day.

In a 1-year oral toxicity study in dogs, (b) (4) was given to dogs by oral capsules at 0, 20, 40, and 80 mg/kg/day for 52 weeks. There were no clear treatment-related changes in any treatment group as compared to the control. The high dose of 80 mg/kg/day is considered as the no effect dose or tolerated dose.

The maximum daily intake of (b) (4) in 24 Pancreaze® MT capsules is (b) (4) mg/kg. The tolerated doses in the above toxicity studies provide a reasonable assurance of safety for the maximum daily intake of (b) (4).

Triethyl citrate

Triethyl citrate (CAS Reg. No. 77-93-0) is considered as GRAS under 21 CFR part 184.1911 at levels not exceeding current good manufacturing practice when used as a flavoring agent, a solvent or vehicle, or a surface-active agent. An acceptable daily intake (ADI) of up to 10 mg/kg was established for triethyl citrate by the Joint FAO/WHO Expert Committee on Food Additives. The estimated maximum daily intake of triethyl citrate from Pancreaze® MT is (b) (4) mg/kg/day.

Gelatin:

Gelatin, a hydrolysis product of naturally occurring collagen, has been widely used in the pharmaceutical and food industries. It is listed as a food category in 21 CFR 170.3. The FDA Select Committee on GRAS Substances (SCOGS) reviewed the available information on gelatin and concluded that there is no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public when gelatin is used at the currently accepted levels, or at levels that might reasonably be expected in the future.

Colloidal silica:

Silicon dioxide (colloidal anhydrous silica) is a food additive (anti-caking agent). In accordance with 21 CFR 172.480, silicon dioxide may be safely used in food if it is used in an amount not to exceed 2% by weight of the food.

Talc:

Talc has been widely used as a food additive or as an anti-caking agent, coating agent, or texturing agent in pharmaceutical products. It is GRAS for use as a direct food ingredient. Talc is also classified as a color additive for drugs (21 CFR 73.1550). The FDA Select Committee on GRAS Substances (SCOGS) reviewed available information on talc and concluded that there is no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public when talc is used at the currently accepted levels, or at levels that might reasonably be expected in the future.

Montan glycol wax

Montan wax is listed in the FDA Inactive Ingredient Database at a maximum potency of 0.06 mg per oral tablet. Montan wax and montan glycol wax (a glycerol ester of montan wax) are listed in 21 CFR parts 175.105, 177.2600, or 178.3770 as indirect food additives.

The following non-GLP toxicity studies with montan glycerol ester from the IUCLID Dataset were provided by the sponsor. The dataset was created by the EUROPEAN COMMISSION-European Chemicals Bureau.

In a 32-day oral toxicity study in rats, the dose of 1000 mg/kg/day did not induce any toxicity. In a 6.5-month oral (dietary) toxicity study in rats, doses up to 5% in feed did not induce any toxicity (behavior, body weight, blood, urine, and histopathology were evaluated). In a 140-day oral toxicity study in dogs, doses up to 50,000 ppm did not induce any toxicity (body weight, blood count, urine, and histopathology were evaluated).

The estimated maximum daily intake of montan glycol wax from Pancrease[®] MT is (b) (4) mg/kg/day. The tolerated doses in

the above toxicity studies provide a reasonable assurance of safety for the maximum daily intake of montan glycol wax.

2.6.6.4 Genetic toxicology

Not applicable.

2.6.6.5 Carcinogenicity

Not applicable.

2.6.6.6 Reproductive and developmental toxicology

The sponsor submitted Segment II studies of pancrelipase in rats and rabbits in this NDA. However, it cannot be determined as to whether the drug substance used in these studies is comparable to the drug substance in Pancreaze® MT. Therefore, the relevance of the study results to the potential developmental effects of the drug substance (pancrelipase) in Pancreaze® MT is unknown. In addition, these studies should not be described or cited in the labeling.

2.6.6.7 Local tolerance

Not applicable.

2.6.6.8 Special toxicology studies

Not applicable.

Overall Conclusions and Recommendations:

Pancreatic enzyme preparations (PEPs) have been available in the U.S. for the treatment of exocrine pancreatic insufficiency (EPI) prior to the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. On April 28, 2004 (69 FR 23410), the FDA announced that all orally administered PEPs are new drugs that will require approval, and will be available through prescription only. In the present application, the sponsor is seeking approval to market Pancreaze® MT for treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

In support of this NDA, the sponsor did not conduct any nonclinical studies with Pancreaze[®] MT, but provided published information on the excipients in the clinical formulation of Pancreaze[®] MT. The sponsor also provided toxicity studies and embryo-fetal developmental studies of pancrelipase, although it is uncertain whether the drug substance used in these studies is comparable to the drug substance in Pancreaze[®] MT. The sponsor submitted a letter of authorization from (b) (4) to allow FDA access to Drug Master File (DMF) (b) (4), which contains toxicity studies of the excipient (b) (4). The submitted information is compliant with the pharmacology and toxicology requirements in the FDA guidance: Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs (2006). This guidance indicates that no new pharmacology studies for such products are necessary and no toxicology studies are needed if excipients are classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable.

All of the inactive ingredients in Pancreaze[®] MT are listed in the FDA Inactive Ingredient Database. It appears that the amounts of these inactive ingredients per capsule (except montan glycol wax) are within the listed maximum amount per capsule in the FDA Inactive Ingredient Database. However, based on the proposed labeling, the maximum recommended daily dose is 10,000 units lipase/kg/day or 500,000 units/day if a 50-kg body weight is assumed. Using the capsules containing 21,000 units lipase (MT 21), a 50-kg patient would consume up to 24 capsules/day to reach the maximum daily dose of 10,000 units/kg/day or 500,000 units/day. Therefore, the total amounts of the following inactive ingredients in 24 capsules would exceed the listed maximum level per oral tablet or capsule in the FDA Inactive Ingredient Database (the FDA Inactive Ingredient Database does not provide the number of tablets or capsules ingested daily at the approved dose): methacrylic acid-ethyl acrylate co-polymer ((b) (4)), triethyl citrate, gelatin, colloidal anhydrous silica, talc, and montan glycol wax.

The maximum daily intake of (b) (4) in 24 Pancreaze[®] MT capsules is (b) (4) mg/kg. The tolerated doses in the 6-month oral toxicity study in rats (600 mg/kg/day) and 1-year oral toxicity study in dogs (80 mg/kg/day) exceed the maximum dose from Pancreaze[®] MT by approximately 35-fold and 5-fold, respectively. Therefore, these studies provide a reasonable assurance of safety for the maximum daily intake of (b) (4).

Triethyl citrate is considered as GRAS under 21 CFR 184.1911. An acceptable daily intake (ADI) of up to 10 mg/kg was established for triethyl citrate by the Joint FAO/WHO Expert Committee on Food Additives. The ADI exceeds the estimated maximum daily intake of triethyl citrate of (b) (4) mg/kg/day. Therefore, the estimated maximum daily dose of triethyl citrate resulting from Pancreaze® MT administration is not considered to be a safety concern.

Gelatin has been widely used in the pharmaceutical and food industries. It is listed as a food category in 21 CFR 170.3. The FDA Select Committee on GRAS Substances (SCOGS) reviewed the available information on gelatin and concluded that there is no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public when gelatin is used at the currently accepted levels, or at levels that might reasonably be expected in the future.

Silicon dioxide is a food additive (anti-caking agent). In accordance with 21 CFR 172.480, silicon dioxide may be safely used in food if it is used in an amount not to exceed 2% by weight of the food. The content of silicon dioxide in Pancreaze® MT is (b) (4). Therefore, the estimated maximum daily dose of silicon dioxide resulting from Pancreaze® MT administration is not considered to be a safety concern.

Talc is a finely powdered mineral composed of hydrated magnesium silicate $[H_2Mg_3(SiO)_4]$, and is widely used as a food additive and texturing agent in pharmaceutical products. It is classified as GRAS for use as a direct food ingredient. Talc is also classified as a color additive for drugs (21 CFR 73.1550). The FDA Select Committee on GRAS Substances (SCOGS) reviewed the available information on talc and concluded that there is no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public when talc is used at the currently accepted levels, or at levels that might reasonably be expected in the future. The Joint FAO/WHO Expert Committee on Food Additives has designated the ADI as "not specified", a term that is applied to a food substance of very low toxicity. Based on the regulatory information and the recommended ADI, the estimated maximum daily dose of talc resulting from Pancreaze® MT administration is not considered to be a safety concern.

Montan wax is listed in the FDA Inactive Ingredient Database at a maximum potency of 0.06 mg per oral tablet. Montan wax and montan glycol wax, a glycerol ester of montan wax, are listed in CFR 21 parts 175.105, 177.2600, and 178.3770

as indirect food additives. The estimated maximum daily dose of montan glycol wax from Pancreaze® MT is (b) (4) mg/kg. The submitted summary of toxicity studies on this excipient provides a reasonable assurance of safety for the estimated maximum daily dose.

The above safety evaluation of excipients was based on the maximum recommended starting dose of 10,000 lipase units/kg/day. However, the dosing recommendations allow for dose increases in order to achieve a therapeutic effect; the dose can be increased up to 6000 U/kg/meal. In this extreme situation, the maximum daily dose is estimated to be 21,000 U/kg/day (6000 U/kg/meal x 3.5 meals/day). A patient weighing 50 kg would need to take 50 Pancreaze MT21 capsules/day to achieve the dose of 21,000 U/kg/day. The resulting daily dose of excipients would be 2 times the dose levels shown in the sponsor's tables (with the exception of the mg/kg doses for methacrylic acid-ethyl acrylate co-polymer and talc, which are based on 50 capsules/day). The safety information on each excipient provides a reasonable assurance of safety for an estimated maximum dose of 21,000 lipase units/kg/day.

In conclusion, the estimated maximum daily intake of the excipients in Pancreaze MT is not considered to be a safety concern and therefore, from a nonclinical standpoint, this NDA is approvable.

Recommendations:

1. From a nonclinical standpoint, approval of Pancreaze® MT is recommended for treatment of exocrine pancreatic insufficiency.
2. The labeling should be revised as recommended.

Ke Zhang, Ph.D. Date
Pharmacologist, DGP

David Joseph, Ph.D. Date
Acting Pharmacologist Team Leader
DGP

CC:
NDA
DGP
DGP/CSO
DGP/Dr. Joseph
DGP/Dr. Zhang

R/D Init.: D. Joseph 3/24/10

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

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

/s/

KE ZHANG
04/02/2010

DAVID B JOSEPH
04/02/2010

I concur with Dr. Zhang's recommendations. Please see my Team Leader memo for additional comments.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22,523 **Applicant:** Johnson & Johnson **Stamp Date:** June 23, 2009
Drug Name: Pancrease MT **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		x	Non-GLP studies of excipients may be acceptable to assure safety.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		x	See IR letter dated July 22, 2009

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ke Zhang, Ph.D. August 11, 2009

 Reviewing Pharmacologist Date

David Joseph, Ph.D. August 11, 2009

 Team Leader/Supervisor Date

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

/s/

KE ZHANG
08/11/2009

DAVID B JOSEPH
08/11/2009