CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022523Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	22-523
Type of submission:	Original Submission
Brand Name:	Pancreaze
Generic Name:	Pancrelipase
Sponsor:	Johnson & Johnson
Submission date:	06/23/09
PDUFA Goal date:	04/23/10
Priority:	Standard (10 months)
Clinical Division:	Division of Gastroenterology Products
OCP Division:	DCP III
Primary Reviewer:	Lanyan Fang, Ph.D.
Secondary Reviewer:	Jang-Ik Lee, Pharm.D, Ph.D.
Dosage form and Strength:	Delayed release capsules, 4,200, 10,500, 16,800 and 21,000 Units
Route of administration:	Oral
Indication:	Treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions

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1. Executive Summary

Pancreaze (pancrelipase) capsule and several other pancreatic enzyme products are currently on the market without FDA approval. On April 28, 2004 (69 FR 23410), the Food and Drug Administration (FDA) announced that all orally administered pancreatic enzyme products (PEPs) are new drugs that will be approved for prescription use only, and explained the conditions for continued marketing of these drug products. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) submitted this original New Drug Application (NDA) for Pancreaze (pancrelipase) Capsules on 23 June 2009.

Pancreaze delayed-release capsules contain enteric-coated microtablets of porcine pancreatic enzyme concentrate, predominantly lipase, amylase, and protease. Pancreaze is indicated for use in diseases and procedures that result in significant reduction of exocrine pancreatic enzyme secretions, such as cystic fibrosis (CF), and chronic pancreatitis. Pancreaze capsules are manufactured in 4 strengths: 4,200, 10,500, 16,800 and 21,000 USP units of lipase.

An optional intra-division level Clinical Pharmacology briefing was held on March 11, 2010.

1.1 Recommendations

From a Clinical Pharmacology standpoint, the application is acceptable provided a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Studies Conducted and Reviewed

Three clinical studies were conducted to support the approval of this NDA: two clinical studies to evaluate the safety and efficacy and one clinical pharmacology study to evaluate intraduodenal enzyme delivery of Pancreaze in subjects with severe exocrine pancreatic insufficiency. In addition, three *in vitro* clinical pharmacology or biopharmaceutics studies were submitted including two studies assessing the stability of enteric-coated microtablets in infant formula and baby foods and one *in vitro* dissolution study across four strengths of Pancreaze.

Overview of Clinical Pharmacology and Biopharmaceutics:

In vitro Compatibility Study with baby foods

The objective of this study is to determine the *in vitro* compatibility of enteric minitablets after exposure to baby foods, of pH range from approximately 4 to 7. The results of *in vitro* stability of Pancreaze content (minitablets) gently mixed with baby foods (applesauce, sweet potato, vanilla and chocollate pudding) showed that, after 15 minutes of contact with baby foods tested and 60-min dissolution testing in simulated gastric fluid (SGF) at 37 ºC, the mean lipase activity ranged from 97 to 107% relative to that of control. The coefficient of variation (CV%) of remaining lipase activity across three microtablet replicates from all four Pancreaze capsule strengths against all six baby food matrices (Apple sauce from Gerber and Beechnut, Sweet potato from Gerber and Beechnut, Vanilla Pudding and Chocolate Pudding) ranged from 0 to 4%. Thus, the pre-specified acceptance criteria (CV% ≤10% and mean remaining lipase activity of 90-110%) were met for compatibility.

In vitro Compatibility Study in infant formula

The results indicated that physical appearance of enteric-coated microtablets remained unchanged for up to 45 minutes in incubation with baby formula (Nutrilon 2, Solagen and Fantomalt provided by Nutricia, the Netherlands). The remaining lipase activity for up to 45 minutes after dissolution testing began ranged from 96.7% to 103.2%. Disintegration of coating was observed starting at the 60-minute time point. Physical appearance of infant formula showed no difference for up to 150 minutes of dissolution time in the presence of microtablets at 37 °C. The pH of the formula remained at approximately 6.7 in the presence of microtablets throughout the first 45 minutes of dissolution, after which time the pH started to decrease and reached a value of approximately 6.2 after a total dissolution time of 150 minutes.

Overall, the results of the in vitro compatibility studies with baby foods and infant formula demonstrate that: 1) under test condition, the enteric-coated microtablets contained in the Pancreaze capsule formulation are stable in acidic baby foods (pH ≤ 5.5) for up to 15 minutes at room temperature; 2) enteric-coated microtablets maintain integrity and compatibility in infant formula for up to 45 minutes at 37°C under the test condition (high viscosity of formula and weak agitation).

2. Question Based Review

2.1 General Attributes

Q: What is the drug substance?

Pancreaze contains pancrelipase, a purified extract of porcine exocrine pancreatic enzymes. The major enzymes of pancrelipase are pancreatic lipase, free proteases, and α-amylase.

Q: What are the formulations?

Pancreaze contains enteric-coated pancrelipase minitablets or granules within the capsules for oral administration. The enteric coating protects pancreatic enzymes against gastric acid and is designed to dissolve at pH ≥ 5.5 which allows delivery of the enzymes to duodenum, the main site of action for food digestion. Pancreatic enzymes are not materially absorbed by the gastrointestinal tract. The Pancreaze capsules are available in four strengths 4.2, 10.5, 16.8 and 21, corresponding respectively to 4200, 10500, 16800, and 21000 USP units of lipase.

Q: What is the mechanism of action?

Chronic pancreatitis (CP) is an ongoing inflammatory disorder associated with the loss of the exocrine and endocrine parenchyma and its replacement by fibrotic tissue, resulting in maldigestion subsequent to exocrine pancreatic insufficiency (EPI) and diabetes mellitus. Exocrine pancreatic insufficiency (EPI) is often associated with conditions such as Cystic Fibrosis (CF), CP, postpancreatectomy, post-GI bypass surgery and ductal obstruction of the pancreas or common bile duct. In CP subjects, fat digestion is impaired as well as carbohydrate and protein digestion; steatorrhea is one of the main symptoms observed. Pancrelipase is an extract of porcine pancreatic glands. Pancreatic enzyme supplements improve digestion by catalyzing the hydrolysis of fats to glycerol and fatty acids, protein to proteoses and derived substances, and starch into dextrins and short chain sugars.

Q: What is the proposed indication?

Pancreaze (Pancrelipase Capsules) is a pancreatic enzyme replacement therapy indicated for the treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions.

Q: What is the proposed dosing regimen?

Patients with pancreatic insufficiency should consume a high-calorie diet with unrestricted fat appropriate for age and clinical status. A nutritional assessment should be performed regularly as a component of routine care and, additionally, when dosing of pancreatic enzyme replacement is altered.

Dosage should be individualized and determined by the degree of steatorrhea and the fat content of the diet. Therapy should be initiated at the lowest possible dose and gradually increased until the desired control of symptoms is obtained.

The labeling recommends the dosing regimen shown below for different age groups:

Infants (up to 12 months)
Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Do not mix Pancreaze capsule contents directly into formula or breast milk prior to administration.

Children Older than 12 Months and Younger than 4 Years
Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Adults
Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

The sponsor proposed that Pancreaze capsules should be taken orally with meal or snack. Where swallowing of capsules is difficult, the capsules may be opened, and the minitablets sprinkled on a small quantity of a soft food (e.g., applesauce, gelatin, etc.) and swallowed immediately. To protect enteric coating, minitablets must not be crushed or chewed.

2.2 General Clinical Pharmacology

Q: Is the *in vivo* intubation study reliable clinical pharmacology study to assess bioavailability (BA) or bioequivalence (BE) of pancreatic enzyme products?

No. Based on the experiences gathered so far on the intubation study, it is concluded that many challenges in the study design, study conduct, and assay methodology remain to be overcome before the study can be used reliably to assess BA or BE of pancreatic enzyme products. Additionally, when demonstration of BA or BE is necessary, the sponsor will be encouraged to conduct clinical studies for that purpose rather than utilizing the intubation studies.

In vivo intubation study (PNCRLP-CYS-1001)
It was a single-dose, open-label, randomized, 2x2 crossover study to evaluate the intra-duodenal delivery of enzyme (lipase, amylase, and protease) of enteric-coated capsule formulations of 3 Pancreaze capsules (Eudragit L30D-55 coating). A total of 13 subjects who had severe exocrine pancreatic insufficiency (EPI) were enrolled. Twelve subjects completed the study and were evaluable for both Treatments A (High-fat liquid meal) and B (3 PANCREASE MT 21 capsules administered simultaneously with a high-fat liquid meal). Mean duodenal pH during the entire perfusion ranged from 4.9 to 6.3 for Treatment A (CV less than 33%) within each collection interval. Duodenal pH during

perfusion for Treatment B was comparable, with mean values ranging from 5.2 to 6.3 (CV less than 32%).

Variability seemed to be relatively high during the washout, baseline periods and the second hour of post-treatment perfusion. The within-treatment, baseline-corrected enzyme activities between two crossover treatments were not clearly differentiable. The conversion factor between different analytical methods for lipase activity was determined to be 2.03. Mean relative local bioavailability of lipase in PANCREASE MT was 19% with a CV of 156% after taking into consideration the conversion factor and utilizing the double correction method (Table 1). Due to the lack of a conversion factor for the other 2 enzyme (amylase and protease) assays, relative bioavailability could not be calculated. Residual gastric enzyme activities were negligible after either treatment. Median withintreatment baseline-adjusted duodenal enzyme activities were slightly higher for Treatment B. However the total drug-related duodenal enzyme activities were relatively low when compared to the administered dose.

Table 1. Summary of Total Drug-Related Enzyme Activity and Relative Bioavailability of Lipase

	Total Drug-Related Enzyme Activity in Duodenum*, U			Lipase Relative Bioavailability**, %
Subject	ACTadj, lip	ACTadj, amy	ACTadj, pro	Frel, lip
100102	0*	1869	768	0**
100103	5246	3445	969	16.9
100104	0*	3161	0*	0**
100105	113368	3870	11619	100**
100107	15455	13856	7872	49.8
100108	8941	898	0*	28.8
100109	4596	228	0	14.8
100110	1069	2845	0	3.4
100111	0*	1282	0	0**
100112	0*	0*	0*	0**
100114	4700	7124	0	15.1
100115	0*	0*	0	0**
N	12	12	12	12
Mean	12781.3	3215.0	1769.0	19.1
SD	32026.5	3927.1	3825.1	29.7
Min	0.0	0.0	0.0	0.0
Median	2832.8	2357.1	0.0	9.1
Max	113368.1	13856.0	11618.9	100.0
CV%	250.6	122.2	216.2	155.6

* Adjusted value is reported as zero if < 0.

** Relative bioavailability is reported as zero if < 0% and reported as 100% if >100%.

Reviewer's comment:

Because of the assay limitation and large inter-subject variability, data from the *in vivo* intubation study could not be used for the purpose of establishing bioavailability of Pancreaze. As such, these results can not be used for the labeling purpose.

Q: Dose the in vitro compatibility study (No. 12010169VB01) with Pancreaze on baby foods support the proposed statement in the labeling:

Yes. The results of *in vitro* stability showed that after 15 minutes of contact with baby foods tested and 60-min dissolution testing in simulated gastric fluid (SGF) at 37 °C, the mean lipase activity ranged from 97 to 107% relative to that of control. The CV% of remaining lipase activity across three microtablet replicates from all four Pancreaze capsule strengths against all six baby food matrices (Table 2) ranged from 0 to 4%. Thus, the pre-specified acceptance criteria (CV% ≤10% and mean remaining lipase activity of 90-110%) were met for satisfactory stability.

Thus, the above *in vitro* study supports the proposed labeling claim to sprinkle the content (minitablets) of Pancreaze capsules on an acidic food when intact capsules could not be swallowed. The results of *in vivo* compatibility study are shown in Table 2 below:

Table 2. Mean Functionality of Pancreaze When Mixed With Foods at Room Temperature

Food types	pH-Value	15-min Contact Time with food (Remaining activity; mean % with CV%)
Applesauce, Gerber	pH 3.7	97-100% with CV 0-3.0%
Applesauce, Beechnut	pH 3.8	98-101% with CV 1-3.0%
Sweet Potato, Beechnut	pH 5.1	97-103% with CV 1-4.0%
Sweet potato, Gerber	pH 5.2	97-102% with CV 0-2.0%
Pudding, Hunt's (vanilla)	pH 6.8	99-107% with CV 0.0-3%
Pudding, Jell-O (chocolate)	pH 6.8	97-103% with CV 1-3.0%

Capsules were opened (batch No. 20643 of 4.2 and batch No. V01/08 of 10.5, 16.8 and 21) and an amount of minitablets equivalent to 6000 USP units was carefully weighted, gently mixed into approximately 15 mL (1 tablespoon) of baby foods tested and incubated at room temperature for 15 minutes. The pH of the food matrix was measured prior to addition of the microtablets. At the end of incubation period, the food matrix was rinsed off the microtablets using simulated gastric fluid over a strainer with 0.08″ holes. The clean microtablets were transferred into a rotating basket and the dissolution in simulated gastric fluid is performed for 60 minutes. After 60 minutes, the solids remaining in the dissolution basket were isolated and analyzed for lipase activity. Any changes in the visual appearance of the microtablets will be noted after the simulated gastric fluid wash step and again after the 60 min dissolution stage.

It was noted that some microtablets mixed with almost neutral pH-value (pH 6.8) of pudding showed superficial surface damage after dissolution stage in simulated gastric fluid. They had brown discolorations and/or a bit swollen. However, based on the submitted results, this surface change did not have effect on lipase activity within the period of 15 minutes. Therefore, it was recommended not to exceed this time limit (15

minutes) to avoid a possible loss of enzyme activity. Microtablets mixed into applesauce or sweet potato mash had no change in appearance.

Reviewer's comments: Pancreaze capsule is a dosage form with a pH-dependent delayed release. The release mechanism of enteric-coated microtablet preparation is based on the pH-dependent solubility of the film-forming polymer Eudragit L30D-55, a propriety brand of methacrylic acid – ethyl acrylate copolymer. The film coating of the microtablets dissolves with increasing pH at approximately the nominal limit of pH=5.5. Based on the observation that some microtablets mixed with almost neutral pH-value (pH 6.8) of pudding showed superficial surface damage after dissolution stage in simulated gastric fluid, it should limit baby foods to acidic baby foods (pH≤5.5) in the label to avoid possible loss of enzyme activity.

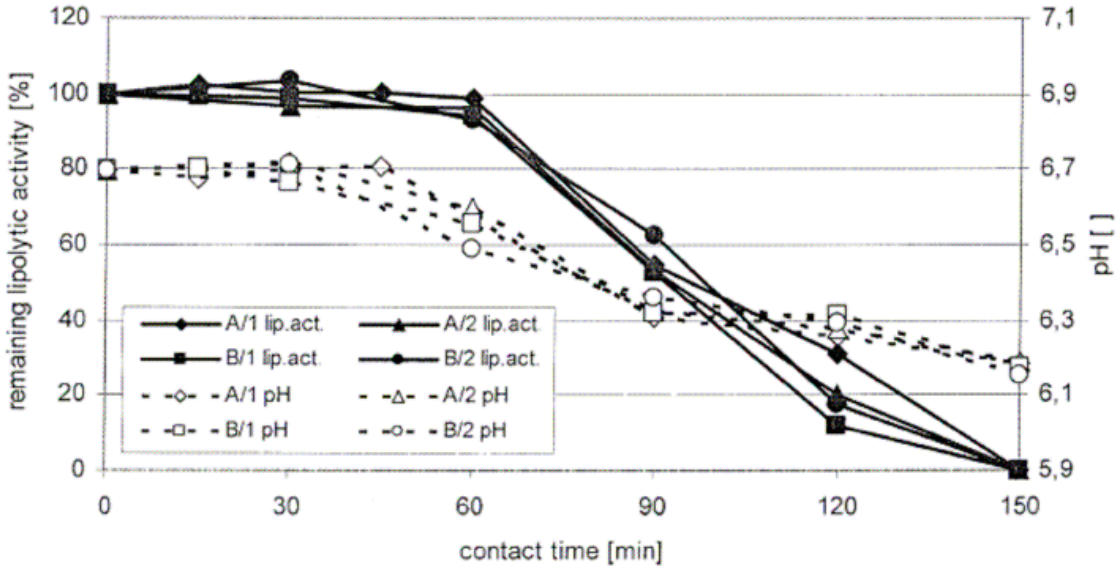
Q: Dose the in vitro compatibility study in infant formula support the proposed statement in the labeling:

(b) (4)

No. It should be noted that the study was conducted with baby formula of Nutricia from Netherlands not a popular product in USA, such as Enfamil and Similac. However, it was found that the results with Nutricia can be applied to the commercially available products in USA. Please refer to the reviewer's comment in this section for more details. The results indicated that : 1) physical appearance of enteric-coated microtablets remained unchanged for up to 45 minutes after dissolution testing began; 2) the remaining lipase activity for up to 45 minutes after dissolution testing began ranged from 96.7% to 103.2% (Figure 1). However, the test condition in this *in vitro* study (high viscosity of formula and weak agitation) may not reflect the real situation, the below language is instead recommended in the labeling for baby formula or breast milk:

Contents of the capsule should not be mixed directly into formula or breast milk.

Figure 1. Remaining Lipase Activity After Various Incubation Times in Infant Formula at 37°C



A and B refers to batch numbers of enteric-coated microtablets.
1 and 2 refers to run numbers for each batch of microtablets.

A two-part in vitro study was conducted to 1) determine the compatibility of enteric-coated microtablets when dispersed in infant formula; and 2) assess the effect of bile acid concentration on the dissolution characteristics of enteric-coated microtablets.

In Part 1, 50 enteric-coated microtablets were subject to a modified version of USP dissolution method using 500 mL of infant formula as the dissolution medium. Infant formula was prepared and maintained at 37°C throughout the dissolution test period. At pre-specified time points (from 15 to 150 minutes), the microtablets were removed from the dissolution testing apparatus (basket apparatus), rinsed, and assessed for physical appearance. The microtablets were then analyzed for lipase activity using the Pharm. Eur. method. After removal of the microtablets, the formula was incubated at 37°C for additional times to make a total test time of 150 minutes. The appearance and pH value of formula were assessed at the end of this incubation time. Two batches of enteric-coated microtablets (A and B) were tested. For each batch, two runs were performed (N=2).

Disintegration of coating was observed starting at the 60-minute time point. Physical appearance of infant formula showed no difference for up to 150 minutes of dissolution time in the presence of microtablets at 37°C. The pH of the formula remained at approximately 6.7 in the presence of microtablets throughout the first 45 minutes of dissolution, after which time the pH started to decrease and reached a value of approximately 6.2 after a total dissolution time of 150 minutes (Figure 1).

The dissolution study in Part II was reviewed by ONDQA and please see the review in DARRTS by Dr. Tien-Mien Chen.

Review's comment

Since the baby formula used in this study was Nutricia from Netherlands not a popular product in USA, such as Enfamil and Similac, the below Information Requests (IR) was sent to the sponsor on December 10, 2009.

1. Please compare the baby formula used in your in vitro food compatibility study (i.e., Nutricia from Netherland) with each of the baby formulas commercially available in the United States (e.g., Enfamil and SimiIac) in terms of the following:
   - Composition;
   - pH;
   - Ingredients, if any, that may affect the physical, chemical, or clinical performance of your product.

The sponsor's response quoted below is deemed to be acceptable.

"…All infant formulas in the US conform to the US FDA nutrient requirements for specific macronutrients, micronutrients, and trace elements. Nutrilon 2, a European infant formula, also conforms to these nutrient requirements. The differences seen in infant formulas relate to minor amounts of additional constituents or differences in the composition of trace elements or minimal percentages of the major macronutrients.

Given the similarity of the composition of the infant formulas, and the compliance of all products with the nutrient requirements of the US FDA, we conclude that the administration of TRADENAME® (pancrelipase) microtablets in infant formulas commonly used in the U.S. (eg, Enfamil, Similac) should not impact the product's chemical or clinical performance…"

Table 2: Chemical Composition (per 100 kcal) of Milk-based Infant Formulas

Product	Protein (g)	CHO (g)	Fat (g)	pH	Osmolality
Similac	2.3	10.7	5.3	7	300
Human Milk	1.9	10.4	5.9	7	280
Nutrilon 2	2.2	10.7	5.4	7	260
Enfamil	2.2	11	5.3	7	300

2. Please provide us with the results of your analysis and the rationale, including supporting data, for your conclusion that comparable food compatibility results will be seen regardless of the particular baby formula used.

The sponsor's response quoted below is deemed to be acceptable.

"…Minimal differences exist among infant formulas with respect to macronutrients, micronutrients, trace elements, pH, and osmolality. These minimal differences in composition among the infant formulas are not expected to result in differences in dissolution of the enteric coating. J&JPRD did not test stability in nonsupplemented

infant formula, as infants with cystic fibrosis routinely have their formula supplemented; the supplements and their percentages added to the formula were chosen to replicate as closely as possible formulas supplemented with exogenous macronutrients used in infants with cystic fibrosis…"

2.3 Intrinsic Factors

Not applicable since the drug product is not systemically observable

2.4 Extrinsic Factors

Not applicable since the drug product is not systemically observable

2.5 General Biopharmaceutics

Not applicable

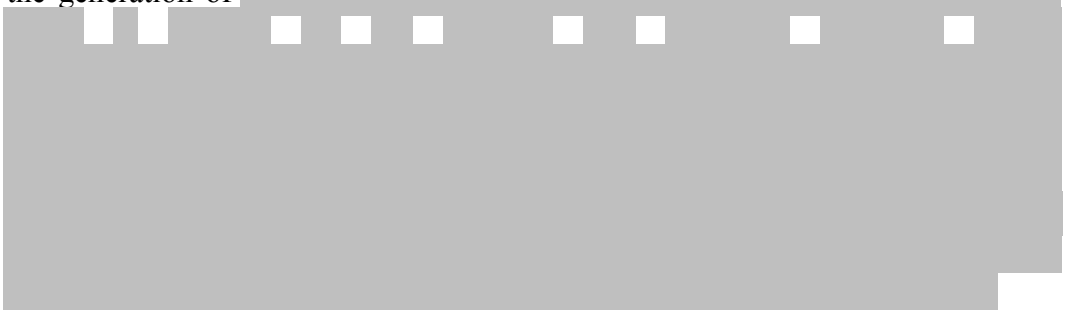
2.6 Analytical Section

Q. Is the assay methods adequately validated?

Yes. The assay method is acceptable. Intra-assay accuracy ranged from 100.00% to 106.67%, with a maximum precision (%CV) of 7.71%. Inter-assay accuracy ranged from 99.44 to 109.41% with a maximum precision of 9.40%. The lower limit of quantitation was 5 U/mL. Recovery of spiked samples ranged from 90.0% to 100.0%. Stability of samples at 4°C for 5 hours was maintained within 3.91% of the original values; for 24 hours, within 5.46% of the original values. The calibration curve was linear over working concentration range of 5-40 U/mL, with the correlation coefficient of the calibration curve of r^2=0.999.

USP Method:
A method was used to measure lipase content in the capsule *in vitro* based on that described in the USP monograph using olive oil as a substrate. Results are reported as USP units/capsule, where one USP unit of lipase activity is defined as the amount of pancreatin that liberates 1.0 microequivalent of fatty acid per minute at a pH of 9.0 and a temperature of 37°C.

Potentiometric Method for Pancreatic Lipase:
The assay used for assay of pancreatic lipase is a potentiometric method based on the generation of (b) (4)



Lipase activity is expressed in International Units (IU), where 1 IU is defined as the amount of lipase that catalyzes 1 μmol of substrate hydrolysis per min per L at 37°C, pH 8.4. By comparing the results using the potentiometric assay with the USP method, the conversion factor for lipase was determined to be (b) (4) meaning that the compendial method reported (b) (4) times more enzyme activity from a standard pancrelipase preparation than the clinical method on identical samples prepared in relevant biological fluids.

3. Detailed Labeling Recommendations

Agency proposed labeling revisions related to clinical pharmacology are shown below:

2.2 Administration

(b) (4)

(b) (4)

Agency's recommended language in this section:

Pancreaze should always be taken as prescribed by a healthcare professional.

Infants (up to 12 months)

Pancreaze should be administered to infants immediately prior to each feeding, using a dosage of 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Contents of the capsule may be sprinkled on small amounts of soft acidic food with a pH of 5.5 or less (e.g., applesause or sweet potato) and give it to the infant within 15 minutes. Contents of the capsule may also be administered directly to the mouth. Administration should be followed by breast milk or formula. Contents of the capsule **should not** be mixed directly into formula or breast milk. Care should be taken to ensure that Pancreaze is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

Children and Adults

Pancreaze should be taken during meals or snacks, with sufficient fluid. **Pancreaze capsules and capsule contents should not be crushed or chewed.** Capsules should be swallowed whole.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on small amounts of acidic soft food with a pH of 5.5 or less (e.g., apple sauce or sweet potato). The Pancreaze-soft food mixture should be swallowed immediately (e.g., within 15 minutes) without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

11 DESCRIPTION

(b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

Agency's recommended language in this section:

12.1 Mechanism of Action

The pancreatic enzymes in Pancreaze catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

(b) (4)

Reviewer's comment:

In the ^{13}C breath test study, the mean percent difference in cumulative $\%^{13}C$ from randomization to the end of study was -1.77%, -1.60%, 15.35%. and 125.32% in the 500 units lipase/kg/meal, 1000 units lipase/kg/meal, 1500 units lipase/kg/meal, and 2000 units lipase/kg/meal groups, respectively. However, several deficiencies exist which preclude definitive conclusions including high variability, lack of assay validation, and small sample size (n=3 for each dose level). Thus the results were deleted for the labeling purpose.

4. Appendices

4.1 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-523**	**Brand Name**	**Pancreaze**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**pancrelipase**
Medical Division	**DGIP**	**Drug Class**	**Pancreatic Enzyme Extracts**
OCP Reviewer	**Lanyan Fang, Ph.D.**	**Indication(s)**	**Exocrine pancreatic insufficiency due to cystic fibrosis or other conditions**
OCP Secondary Reviewer	**Jang-Ik Lee, PharmD, Ph.D.**	**Dosage Form**	**Capsules**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Infants and children (0 to < 5 years)** The recommended starting dose is 375 U lipase/kg/meal or feeding with infant formula or breast milk. The dosage can be increased in increments of 500 U lipase/kg/meal up to a maximum of 10,000 U lipase/kg/day. **Adult and pediatric (≥5 years)** The recommended starting dose of Pancreaze is 375-1,000 U lipase/kg/meal. The maximum recommended dosage is 10,000 U lipase/kg/day.
Date of Submission	**June 23, 2009**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review	**Feb 23, 2010**	**Sponsor**	**Johnson and Johnson**
Medical Division Due Date	**March 23, 2010**	**Priority Classification**	**S**
PDUFA Due Date	**April 23, 2010**	**Dosing Strength**	**4200 USP units of lipase; 10500 USP units of lipase; 16800 USP units of lipase; 21000 USP units of lipase**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				

single dose:	**X**	**1**		**In vivo intubation study to establish the delivery of pancrelipase**
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**Two food stability studies: baby food and baby formula**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**7**		

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/

LANYAN FANG
03/12/2010

JANG IK LEE
03/15/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-523 (N-000)
Submission Date:	06/23/09
Brand Name:	Pancrease MT (microtablets)
Generic Name:	Pancrelipase
Formulation:	Delayed release (DR) oral capsule
Strength:	MT 4.2, MT 10.5, MT 16.8, and MT 21 (4,200, 10,500, 16,800, and 21,000 USP units of lipase, respectively)
Sponsor:	Johnson and Johnson
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

EXECUTIVE SUMMARY

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic and proteolytic activity. The active ingredient, pancrelipase, is monographed in the USP and is obtained by extraction from hog pancreata. Pancrelipase is an enzyme therapy for the treatment of steatorrhea secondary to pancreatic insufficiency in disorders such as cystic fibrosis or chronic pancreatitis.

On 06/23/09, Johnson and Johnson submitted NDA 22-523 (Pancrease MT capsule) for review. It is an oral DR formulation which consists of pancrelipase in microtablets filled in a hard gelatin capsule. The sponsor proposed four strengths, each containing a specific lipase unit activity, MT21 (21,000 USP units of lipase), MT16.8 (16,800 USP units of lipase) MT10.5 (10,500 USP units of lipase), and MT4.2 (4,200 USP units of lipase). The sponsor developed two types of microtablets: low potency (LP) used to fill MT4.2, 10.5 and 16.8 capsules; and high potency (HP) used to fill MT21 capsules. The compositions of the LP and HP microtablets are identical from a quantitative perspective; however, they differ in the enzyme activity.

The highest strength, MT21, was used in an *in-vivo* intubation, bioactivity study. Two strengths, MT21, and MT10.5, were used in the pivotal clinical efficacy study. The sponsor also submitted the comparative dissolution testing/data on the proposed four strengths using the USP dissolution methodology as shown below.

USP Dissolution Methodology for Delayed Release Pancrelipase Capsules

	Part 1: Test for resistance to gastric fluid, after the acid stage, pH 1	**Part 2: Dissolution testing, phosphate buffer, pH 6**
Apparatus:	Apparatus with rotating basket (USP apparatus 1)	Apparatus with paddle stirrer (USP apparatus 2)
Test medium:	simulated gastric fluid (without pepsin), USP; 800 ml	Phosphate puffer pH 6.0, USP; 800 ml
Test temperature:	37°C	37°C
Rotation speed:	100 min^{-1}	100 min^{-1}

The proposed dissolution methodology and specifications using the USP method with the proposed Q=(b)(4)% in 30 min for Pancrease MT capsules are found acceptable. The similarity factors calculated are all >50 indicating that the two lower strengths (MT 16.8 and MT 4.2) which were not tested clinically are similar to the highest strength (MT 21). Therefore, the biowaiver for the two lower strengths, MT16.8 and 4.2 capsules, is granted.

RECOMMENDATION

From the Biopharmaceutics perspective, the proposed dissolution methodology and specifications are acceptable and the biowaiver for the two lower strengths, Pancrease MT16.8 and 4.2 capsules is granted. No further comments are to be sent to the sponsor.

BACKGROUND

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic and proteolytic activity. Pancrelipase is a form of enzyme therapy for the treatment of steatorrhea secondary to pancreatic insufficiency in disorders such as cystic fibrosis or chronic pancreatitis. Pancrease MT (microtablets) capsule is an oral DR formulation which consists of pancrelipase MT filled in a hard gelatin capsule. The active ingredient, pancrelipase, is monographed in the USP and is obtained by extraction from hog pancreata.

These enzymes, especially lipase, are acid-sensitive in that they are increasingly and irreversibly inactivated with further decreasing pH-values below pH 4. Therefore, the enteric-coating protects the acid-sensitive enzymes in the MT from the gastric fluid while in the stomach. The USP lipase assay is used to determine the appropriate capsule fill to ensure that the labeled enzyme activity is met. The lactose-free formulation of the dosage form allows pancrelipase treatment to be tolerated by lactose-intolerant patients.

CURRENT SUBMISSION

On 06/23/09, Johnson and Johnson submitted NDA 22-523 (Pancrease MT) to the Agency for review. The sponsor proposed four strengths, each containing a specific lipase unit activity, MT21 (21,000 USP units of lipase), MT16.8 (16,800 USP units of lipase) MT10.5 (10,500 USP units of lipase), and MT4.2 (4,200 USP units of lipase). The highest strength, MT21, was used in an *in-vivo* intubation, bioactivity study (No. PNCRLPCYS-1001). Two strengths, MT21, and MT10.5, were used in the pivotal clinical efficacy study No. PNCRLPCYS-3001. The sponsor also submitted dissolution testing/data using the USP dissolution methodology on the proposed four strengths for review. A biowaiver for the two lower strengths, M16.8 and 4.2, however, was not submitted.

FORMULATION COMPARISONS

Due to the natural origin of pancrelipase, both the specific enzymatic activities and their pattern (i.e., the ratio of these enzyme fractions) are subject to batch-to-batch quantitative variation. Therefore, the active substance is standardized based on the labeled enzymatic activities to guarantee exact enzyme dosing of the finished drug product as shown below.

Table 1: Enzyme Activity for To-be-Marketed PANCREASE MT Capsules

Capsule	Lipase USP Units	Amylase USP Units	Protease USP Units
PANCREASE MT 4.2	4,200	17,500	10,000
PANCREASE MT 10.5	10,500	43,750	25,000
PANCREASE MT 16.8	16,800	70,000	40,000
PANCREASE MT 21	21,000	61,000	37,000

KEY: USP=United States Pharmacopeia

The sponsor developed two types of microtablets: low potency (LP) used to fill MT4.2, 10.5 and 16.8 capsules; and high potency (HP) used to fill MT21 capsules. The LP microtablets have a specification of (b) (4) USP units/microtablet lipase activity and the HP microtablets have a specification of (b) (4) USP units/microtablet lipase

activity. The compositions of the LP and HP microtablets are identical from a quantitative perspective; however, they differ in the enzyme activity. Pancreas MT capsules are filled with the appropriate amount of microtablets based on the labeled lipase activity specified for each strength as shown below.

Table 2: Quantitative Ingredient Statement for Pancrease® MT Capsules

Components	Composition per Pancrease® MT Capsule			
	MT 4.2	MT 10.5	MT 16.8	MT 21
Film-Coated Microtablets[a]	LP	LP	LP	HP
mg	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Gelatin Capsule	Size 4	Size 1	Size 0	Size 0

[a] Capsule fill depends on lipase activity assay of microtablets.
LP: Low potency microtablets; HP: High potency microtablets

The compositions of Pancrease MT capsules are provided below.

Table 3. Composition and Formulation of Pancrease MT Capsules

Component	Quality Reference	Function	Quantity (mg/unit)
(b) (4)			
Pancrelipase	Manufacturer[a]	API	(b) (4)
Microcrystalline Cellulose	NF/Ph. Eur.	(b) (4)	
Crospovidone	NF/Ph. Eur.		
Colloidal Anhydrous Silica	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)			
(b) (4)			
(b) (4)[c]	NF/Ph. Eur.	(b) (4)	(b) (4)
Triethyl Citrate	NF/Ph. Eur.		
Talc	Ph. Eur.		
Simethicone Emulsion (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.

DISSOLUTION COMPARISONS

The comparative dissolution study was conducted on the four strengths of Pancrease MT capsules to estimate the *in vitro* release according to the USP monograph for pancrelipase delayed-release capsules. The dissolution performance of pancrelipase is characterized by the representative dissolution profile of lipase. The sponsor reported that the Pancrease MT capsules comply with the USP monograph for pancrelipase delayed-release capsules test for *in vitro* dissolution. The dissolution methodology used is shown as follows:

Medium I: Acid stage
Simulated gastric fluid (SGF); pH 1.2; V = 800 mL; T = 37 °C
Apparatus I: Basket with a rotation speed = 100 rpm/min
Time: 60 min

Medium II: Buffer Stage
Phosphate buffer pH 6.0; V = 800 mL; T = 37 °C
Apparatus II: Paddle with a rotation speed = 100 rpm/min
Times: t = 13, 15, 17 and 25 min
Assay for Lipolytic activity: According to USP monograph for pancrelipase DR capsules
Proposed Q= (b) (4) % at 30 min

The mean dissolution data (n=12/batch) of the four strengths and the f2 calculation for the three lower strengths compared with the highest strength are shown in the tables below.

Table 4. Mean Dissolution Data of the Four Strengths of Pancrease MT Capsules

Time (minutes)	13			15			17			25		
Strength	Mean	SD	CV(%)	Mean	SD	CV(%)	Mean	SD	CV(%)	Mean	SD	CV(%)
MT21	11.5	3.4	29.8	36.0	4.7	13.1	60.0	5.1	8.5	85.1	2.2	2.5
MT4.2	13.7	3.0	22.2	38.4	3.7	9.5	62.8	2.6	4.2	87.5	2.4	2.8
MT10.5	10.4	2.6	25.5	34.6	3.9	11.3	58.9	3.5	6.0	84.9	2.6	3.1
MT16.8	8.5	2.3	27.3	31.4	3.5	11.1	57.3	3.6	6.3	85.3	2.9	3.4

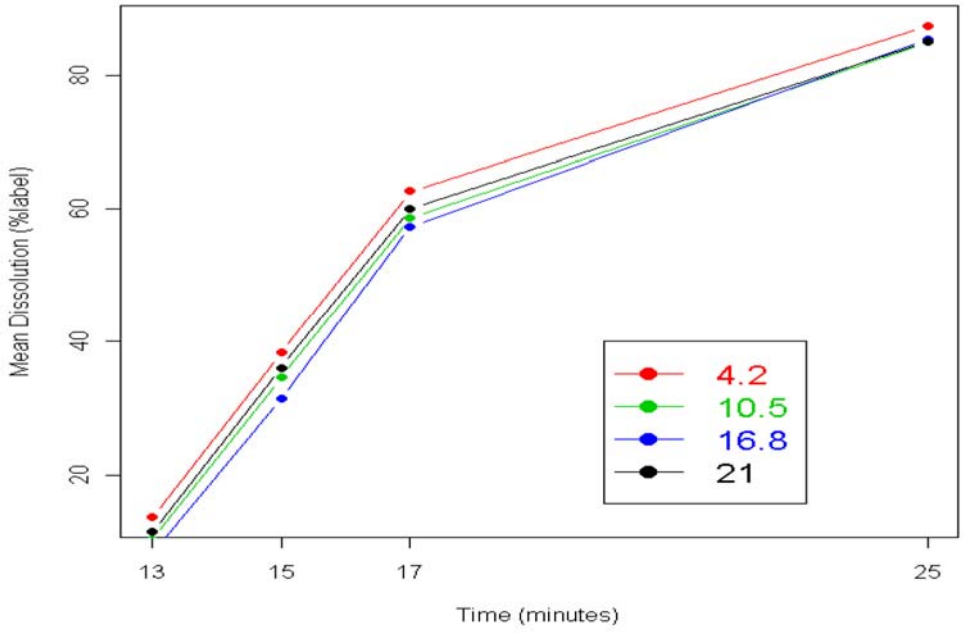
All statistics were based on 12 replicates.

Table 5. Results of f2 Calculations:

MT 21-vs-MT 4.2	MT 21-vs-MT 10.5	MT 21-vs-MT 16.8
79.0	91.9	74.6

The Pancrease MT capsules of different strengths showed by graphical comparison similar dissolution release up to a dissolved activity of approximately 90% label claim as shown below.

Figure 1. Mean Dissolution Profiles of Four Strengths for Pancrease MT Capsules



The sponsor reported that all three f2 statistics (MT21 vs. MT4.2, MT21 vs. MT10.5, and MT21 vs. MT16.8 respectively) were > 50, thus indicating statistically similar *in vitro* dissolution profiles between the three lower capsule strengths and the highest, Pancrease MT21.

An exploratory, four-parameter (amplitude, shift, scale, shape) Weibull model was also used to compare the dissolution profiles across the 4 strengths in order to assess interchangeability of the 4 strengths (Study No. JNJ-4671901 PNCRLPCYS).

In the Weibull model, the 95% level confidence interval estimates of the differences of each of the four parameters between MT21 and each of the lower three strengths included zero, suggesting strong similarity. The sponsor further concluded that the model-based comparisons, in addition to f2 statistics, further support the similarity of the dissolution characteristics across 4 capsule strengths (Tables 6 and 7).

Table 6. Parameter Estimates and Standard Errors of the Weibull Model by Strength

Parameter	Amplitude		Shift		Scale		Shape	
Strength	Est	SE	Est	SE	Est	SE	Est	SE
MT21	85.2	0.98	10.8	0.73	4.7	0.77	2.0	0.40
MT4.2	87.5	0.96	10.3	0.93	5.1	0.97	2.2	0.47
MT10.5	85.0	0.98	11.0	0.69	4.6	0.72	2.0	0.38
MT16.8	85.4	0.95	10.8	0.78	5.0	0.81	2.3	0.45

Table 7. 95% Confidence Limits of the Differences of Weibull Model Parameters

Differences bet	Amplitude	Shift	Scale	Shape
MT21-vs-MT4.2	-5.0 - 0.4	-1.8 - 2.8	-2.8 - 2.0	-1.4 - 1.1
MT21-vs-MT10.5	-2.5 - 3.0	-2.1 - 1.8	-2.0 - 2.1	-1.1 - 1.1
MT21-vs-MT16.8	-2.8 - 2.5	-2.1 - 2.1	-2.6 - 1.9	-1.4 - 0.9

Reviewer's Comments: (Need NOT be sent to the sponsor)

1. The USP method suggests emptying the contents of the capsules for dissolution testing. The sponsor, however, used the whole capsules instead and reported that the capsule shell dissolved during the acid stage. Therefore, the sponsor's proposed dissolution methodology which is slightly modified from the USP methodology is considered acceptable.

2. The similarity factors calculated are all >50 indicating that the two lower strengths (MT 16.8 and MT 4.2) which were not tested clinically are similar to the highest strength (MT 21). The above results support the biowaiver for these two lower strengths.

_____ 03/05/10

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 03/05/10

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

NDA 22-523 for Pancrease MT Capsules, MT 21, MT 16.8, MT 10.5, and MT4.2

Appendix 1

Dissolution of Pancrease MT Capsules in Three Media and Batch Analysis

The dissolution profiles for Pancrease MT capsules in three media are shown in Figure 1

Figure 1: Impact of the pH of Dissolution Medium on Dissolution of PANCREASE MT Capsules

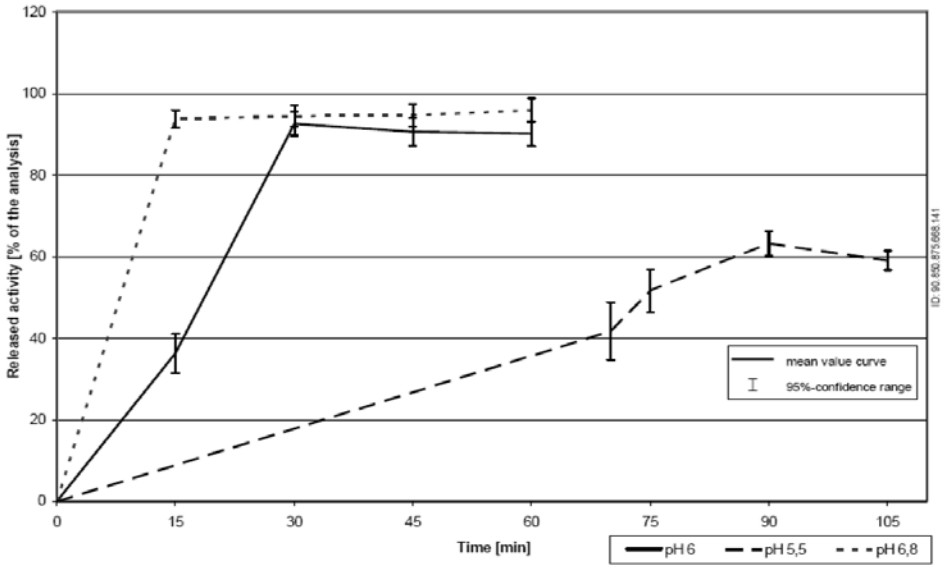


Table 1. Batch Analysis

Batch Number	Version	Strength	Batch Purpose	Date of Manufacture
26130005	Translated English Original German	Low potency microtablets	Clinical Trial Material	(b) (4)
VS-8308-00-A-E	Translated English Original German	MT 10.5 Capsules	Clinical Trial Material/Stability	
21290005	Translated English Original German	High potency microtablets	Clinical Trial Material	
VS-8310-00-A-E	Translated English Original German	MT 21 Capsules	Clinical Trial Material	
V01/07	Translated English Original German	MT 10.5 Capsules	Primary Stability	
V01/07	Translated English Original German	MT 21 Capsules	Primary Stability	

Table 2. Formulations/Strengths Used

Batch Number	Strength	Date of Manufacture[a]	Batch Purpose	Table Number
V01/07P2[d]	MT 4.2	(b) (4)	Stability	Table 2
V02/07P2[d]	MT 4.2		Stability	Table 2
V03/07P2[d]	MT 4.2		Stability	Table 2
V01/07P	MT 10.5		Stability	Table 3
V02/07P	MT 10.5		Stability	Table 3
V03/07P	MT 10.5		Stability	Table 3
VS-8308-00-A-E	MT 10.5		Clinical Material[c]/Stability	Table 3
V01/07P1	MT 16.8		Stability	Table 4
V02/07P1	MT 16.8		Stability	Table 4
V03/07P1	MT 16.8		Stability	Table 4
V01/07P1	MT 21		Stability	Table 5
V02/07P1	MT 21		Stability	Table 5
V03/07P1	MT 21		Stability	Table 5
VS-8310-00-A-E	MT 21		Clinical Material[b,c]/Stability	Table 5

[a] Manufacturing date: (b) (4)
[b] Used in Phase I Clinical Study PNCRLPCXS1001
[c] Used in Phase III Clinical Study PNCRLPCXS3001
[d] Pancrease® MT 4.2 Capsules were encapsulated at Janssen Ortho LLC, Gurabo, Puerto Rico; future commercial batches will be encapsulated at Nordmark.

NDA 22-523 for Pancrease MT Capsules, MT 21, MT 16.8, MT 10.5, and MT4.2

Appendix 2

Individual Dissolution Data of Pancrease MT Capsules

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/

TIEN MIEN CHEN
03/10/2010

PATRICK J MARROUM
03/10/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-523**	**Brand Name**	**Pancrease MT**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**pancrelipase**
Medical Division	**DGIP**	**Drug Class**	**Pancreatic Enzyme Extracts**
OCP Reviewer	**Lanyan Fang, Ph.D.**	**Indication(s)**	**Exocrine pancreatic insufficiency due to cystic fibrosis or other conditions**
OCP Secondary Reviewer	**Jang-Ik Lee, PharmD, Ph.D.**	**Dosage Form**	**Capsules**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Infants and children (0 to < 5 years)** The recommended starting dose is 375 U lipase/kg/meal or feeding with infant formula or breast milk. The dosage can be increased in increments of 500 U lipase/kg/meal up to a maximum of 10,000 U lipase/kg/day. **Adult and pediatric (≥5 years)** The recommended starting dose of PANCREASE® MT is 375-1,000 U lipase/kg/meal. The maximum recommended dosage is 10,000 U lipase/kg/day.
Date of Submission	**June 23, 2009**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review	**Feb 23, 2010**	**Sponsor**	**Johnson and Johnson**
Medical Division Due Date	**March 23, 2010**	**Priority Classification**	**S**
PDUFA Due Date	**April 23, 2010**	**Dosing Strength**	**4200 USP units of lipase; 10500 USP units of lipase; 16800 USP units of lipase; 21000 USP units of lipase**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:	**X**	**1**		**In vivo intubation study to establish the delivery of pancrelipase**
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**Two food stability studies: baby food and baby formula**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**7**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?		X		Dose selection is based on similar approved products
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X		Partial waiver is requested
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		Partial waiver is requested
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Lanyan Fang, Ph.D.

Clinical Pharmacology Reviewer Date

Jang-Ik Lee, PharmD, Ph.D.

Secondary Reviewer Date

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

/s/

LANYAN FANG
08/04/2009

JANG IK LEE
08/04/2009