

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

Table of Contents

1.	Executive Summary	2
	1.1 Recommendation.....	2
	1.2 Phase IV Commitments.....	2
	1.3 Summary of Clinical Pharmacology and Biopharmaceutical Findings.....	3
2.	Question Based Review	4
	2.1 General Attributes.....	4
	2.2 General Clinical Pharmacology.....	5
	2.3 Intrinsic Factors.....	11
	2.4 Extrinsic Factors.....	11
	2.5 General Biopharmaceutics.....	11
	2.6 Analytical Section.....	11
3.	Detailed Labeling Recommendations.....	12
4.	Appendices	16
	4.1 Cover Sheet and OCP Filing Review Form.....	17

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 minitables after exposure to baby foods, of pH range from approximately 4 to 7. The results of *in vitro* stability of Pancreaze content (minitables) gently mixed with baby foods (applesauce, sweet potato, vanilla and chocolate pudding) 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 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% \leq 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 \leq 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 $\text{pH} \geq 5.5$ 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 dextrans 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 PANCREAZE 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

Subject	Total Drug-Related Enzyme Activity in Duodenum*, U			Lipase Relative Bioavailability**, %
	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	3670	11619	100**
100107	15455	13856	7872	49.8
100108	8941	898	0*	28.8
100109	4596	228	0	14.8
100110	1089	2645	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	218.2	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 Pancrease. As such, these results can not be used for the labeling purpose.

Q: Dose the in vitro compatibility study (No. 12010169VB01) with Pancrease 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% \leq 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 (minitables) 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 minitables 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.

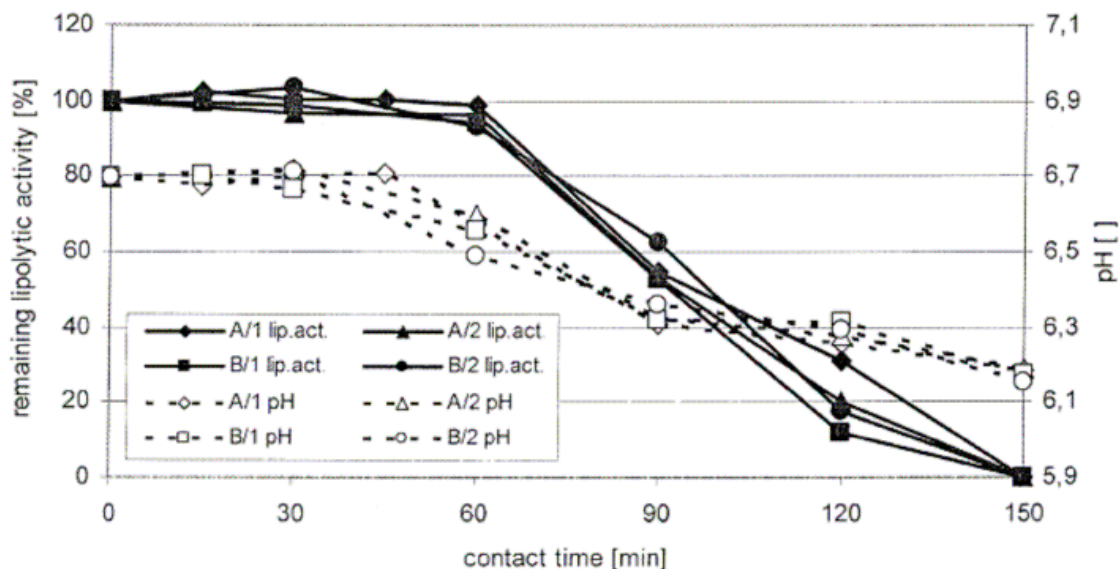
Q: Dose the in vitro compatibility study in infant formula support the proposed statement in the labeling:

(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 Similac) 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?

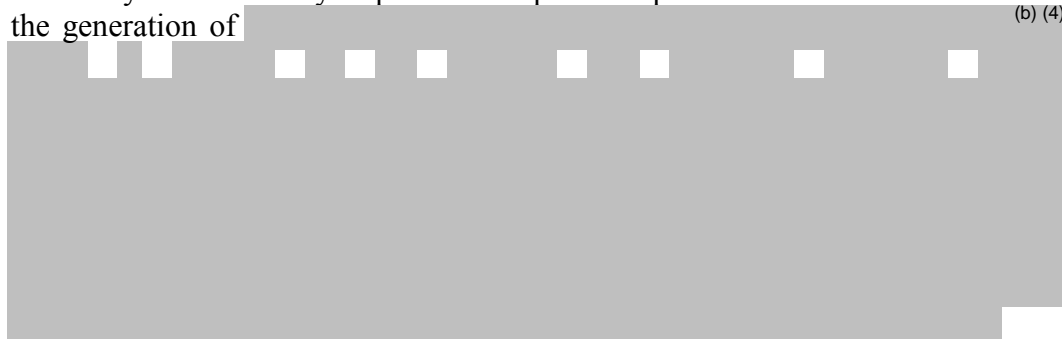
Yes. The assay method is acceptable. Intra-assay accuracy ranged from 100.00% to 106.67%, with a maximum precision (%CV) of 7.71%. Inter-assay accuracy ranged from 99.44 to 109.41% with a maximum precision of 9.40%. The lower limit of quantitation was 5 U/mL. Recovery of spiked samples ranged from 90.0% 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



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., applesauce 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



12 CLINICAL PHARMACOLOGY

(b) (4)

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 dextrans 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.

Reviewer's comment:

In the ^{13}C breath test study, the mean percent difference in cumulative $\%^{13}\text{C}$ 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	<p>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.</p> <p>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.</p>
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 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/

LANYAN FANG
03/12/2010

JANG IK LEE
03/15/2010