CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-222Orig1s000

PHARMACOLOGY REVIEW(S)

REV-NONCLINICAL-05 (Review Noted (NAI))
NDA-022222
ORIG-1
Supporting Document 78
Resubmission/Class 2
Submit Date: 09/01/2011 - FDA Received Date: 09/01/2011

No additional nonclinical studies were included in this submission. All nonclinical information was reviewed in my review of NDA 22,222 dated March 4, 2008.

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/s/

DAVID B JOSEPH
02/22/2012

REV-NONCLINICAL-05 (Review Noted (NAI))
NDA-022222
ORIG-1
Supporting Document 43
RESUBMIT/CLASS 2
Submit Date: 11/05/2009 - FDA Received Date: 11/05/2009

No additional nonclinical studies were provided in this submission. All nonclinical information was reviewed in my review dated March 4, 2008.

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

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/s/

DAVID B JOSEPH
03/16/2010

Comments on N22-222 Ultrase
From A. Jacobs
Sept 7, 2009

There are no pharm/tox issues with this product. This replaces the memo of 9/5/09.

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

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/s/

ABIGAIL ABBY C C JACOBS
09/07/2009
This replaces my memo of 9/5/09

REV-NONCLINICAL-05 (Review Noted (NAI))
NDA-022222
ORIG-1
Supporting Document 28
LEGACY/AMEND MULTI
RESUBMIT/CLASS 2
Submit Date: 04/07/2009 - FDA Received Date: 04/07/2009

All pharmacology/toxicology information was reviewed in the previous review cycle (see review by David Joseph dated March 4, 2008). The present submission contains no additional preclinical information.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22222	ORIG 1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES
NDA 22222	ORIG 1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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/s/

DAVID B JOSEPH
08/21/2009

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:	**22,222**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/1/07**
PRODUCT:	**ULTRASE® MT (pancrelipase, USP) Capsules**
INTENDED CLINICAL POPULATION:	**Patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions**
SPONSOR:	**Axcan Scandipharm Inc.**
DOCUMENTS REVIEWED:	**Not applicable (electronic submission)**
REVIEW DIVISION:	**Division of Gastroenterology Products (HFD-180)**
PHARM/TOX REVIEWER:	**David B. Joseph, Ph.D.**
ACTING PHARM/TOX TEAM LEADER:	**Sushanta K. Chakder, Ph.D.**
DIVISION DIRECTOR:	**Donna Griebel, M.D.**
PROJECT MANAGER:	**Maureen Dewey, M.P.H.**

Date of review submission to Division File System (DFS): March 3, 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The application is recommended for approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

The preclinical sections/subsections of the Sponsor's proposed labeling include the "INDICATIONS AND USAGE" section of the "HIGHLIGHTS OF PRESCRIBING INFORMATION", "Pregnancy" subsection, and the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection.

Sponsor's Proposed Version:

"**HIGHLIGHTS OF PRESCRIBING INFORMATION**"

"**INDICATIONS AND USAGE**

(b) (4)

Evaluation: The term "pancreatic enzyme replacement therapy" is used as the established pharmacologic class in the proposed labeling. This term is descriptive of the pharmacodynamic activity of ULTRASE®. However, the term "pancreatic enzyme preparation digestant" is preferable for use as the established pharmacologic class. "Pancreatic enzyme preparation" is commonly used as a classification term for products that contain pancreatic enzymes of porcine or bovine origin. Given that "pancreatic enzyme preparation" is an accurate description of the chemical nature and origin of the drug, it is considered to be a scientifically valid pharmacologic class. The term "digestant" accurately describes the pharmacologic effect of pancreatic enzyme preparations such as ULTRASE®. Therefore, "digestant" is also considered to be a scientifically valid pharmacologic class. Both "pancreatic enzyme preparation" and "digestant" are terms that provide useful information about ULTRASE®, and are each considered as a clinically meaningful pharmacologic class. Therefore, it is recommended that the established pharmacologic class under the "INDICATIONS AND USAGE" section of the Highlights should be "pancreatic enzyme preparation digestant".

Recommended Version:

"**HIGHLIGHTS OF PRESCRIBING INFORMATION**"

"**INDICATIONS AND USAGE**

ULTRASE® is a pancreatic enzyme preparation digestant indicated for the treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions (1)"

Sponsor's Proposed Version:

"**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether ULTRASE® MT Capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ULTRASE® MT Capsules should be given to a pregnant woman only if clearly needed."

Evaluation: The proposed labeling is not compliant with labeling regulations (21 CFR 201.57). The subheading "Teratogenic effects" should be listed under "Pregnancy". The term "pancrelipase" should be used in place of "ULTRASE® MT Capsules", given that the statements in this subsection are applicable to all pancrelipase products.

Recommended Version:

"**8 USE IN SPECIFIC POPULATIONS**

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. Pancrelipase should be given to a pregnant woman only if clearly needed."

Sponsor's Proposed Version:

"**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Evaluation: The information in this subsection is accurate. However, changes in the language are recommended, as shown below.

Recommended Version:

"**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The submitted toxicology information was mostly related to the excipients and phthalic acid, a major impurity in Ultrase® MT Capsules. This information provides a reasonable assurance of safety for the estimated maximum daily dose of any excipient or phthalic acid that could result from Ultrase® administration.

B. Pharmacologic activity

Porcine pancreatic enzyme preparations (i.e. pancrelipase) improve digestive function under the condition of exocrine pancreatic insufficiency by delivering lipase, protease, and amylase into the small intestine, resulting in the increased digestion of fat, protein, and starch.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,222

Review number: 1

Sequence number/date/type of submission: 001/July 31, 2007/Rolling review presubmission
002/August 20, 2007/Rolling review presubmission
000/September 28, 2007/Original
000/October 26, 2007/Amendment

Information to sponsor: Yes (x) No ( )

Sponsor and/or agent: Axcan Scandipharm Inc.
Birmingham, Alabama

Manufacturer for drug substance: (b) (4)

Reviewer name: David B. Joseph, Ph.D.

Division name: Gastroenterology Products

HFD #: 180

Review completion date: March 3, 2008

Drug:

Trade name: ULTRASE® MT Capsules
Generic name: Pancrelipase
Code name: none
Chemical name: Pancrelipase
CAS registry number: 9001-62-1
Molecular formula/molecular weight: not applicable
Structure: not applicable

Relevant INDs/NDAs/DMFs: IND 41,387 (ULTRASE® MT Capsules)/NDA 20,580 (COTAZYM®)/DMF (b) (4) (Pancrelipase USP)/DMF 15,681 (Eurand Minitablets® Pancrelipase Products)

Drug class: pancreatic enzyme preparation/digestant for treatment of exocrine pancreatic insufficiency

Intended clinical population: Patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions.

Clinical formulation: Capsules containing enteric-coated minitablets. The minitablets are composed of pancrelipase and compendial excipients in a compressed form. The ingredients for each capsule strength are shown in the table below (taken from DMF 15,681 for Eurand Minitabs® Pancrelipase Products). **THIS IS PROPRIETARY INFORMATION AND SHOULD NOT BE RELEASED TO THE PUBLIC.**

Table 3.2.P.2.2 - 16 Theoretical unit composition of HP55 coated ULTRASE® without overfill

Component	Reference to Quality Standard	Function	13,800 USP units capsule (mg)	20,700 USP units capsule (mg)	23,000 USP units capsule (mg)
[redacted]					

(b) (4)

The information in the above table is presented in a simplified form in the table below, to clarify the actual contents for each capsule strength. **THIS IS PROPRIETARY INFORMATION AND SHOULD NOT BE RELEASED TO THE PUBLIC.**

	ULTRASE® MT12	ULTRASE® MT18	ULTRASE® MT20
Active Ingredients	**mg/capsule**	**mg/capsule**	**mg/capsule**
Pancrelipase	(b) (4)		
	Enzyme Activity/Capsule		
	USP Units/capsule	**USP Units/capsule**	**USP Units/capsule**
Lipase	13,800	20,700	23,000
Amylase	27,600	41,400	46,000
Protease	27,600	41,400	46,000
Excipients	**mg/capsule**	**mg/capsule**	**mg/capsule**
Croscarmellose sodium	(b) (4)		
Hydrogenated castor oil			
Colloidal silicon dioxide			
Microcrystalline cellulose			
Magnesium stearate			
Hydroxypropyl methylcellulose phthalate (HP 55)			
Triethyl citrate			
Talc			
Gelatin			
Titanium dioxide			
Black iron oxide			
Yellow iron oxide			

Two types of ink are used in ULTRASE®. The ingredients of both inks meet the requirements of the Code of Federal Regulations, Title 21, Parts 73 and 184, or are classified as GRAS, and are accepted for use in printing on ingested pharmaceutical dosage forms.

Route of administration: oral

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

Studies reviewed within this submission:

Preclinical Study	Testing Laboratory	Study #	Lot #	Page
PHARMACOLOGY	Not applicable	Not applicable	Not applicable	10
PHARMACOKINETICS/ TOXICOKINETICS				
Study of Amylase Absorption in Dogs	Not applicable	Not applicable	Not applicable	11
TOXICOLOGY SUMMARIES FOR EXCIPIENTS AND IMPURITIES				
Croscarmellose Sodium	Not applicable	Not applicable	Not applicable	15
Hydroxypropyl Methylcellulose Phthalate (HP 55)	Not applicable	Not applicable	Not applicable	15
Triethyl Citrate	Not applicable	Not applicable	Not applicable	17
Talc	Not applicable	Not applicable	Not applicable	17
Iron Oxide (Black/Yellow)	Not applicable	Not applicable	Not applicable	18
Gelatin	Not applicable	Not applicable	Not applicable	18
Phthalic Acid	Not applicable	Not applicable	Not applicable	18
SPECIAL TOXICOLOGY STUDIES				
Pancreatic Enzyme-Induced Intestinal Injury in Rats Under Conditions of Normal and Increased Intestinal Permeability	Not applicable	Not applicable	Not applicable	23

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Pancreatic enzyme preparations act by delivering functional digestive enzymes into the small intestine. Under the condition of exocrine pancreatic insufficiency, pancreatic enzymes produce increased digestion of fat, protein, and starch.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Porcine pancreatic enzyme preparations improve digestive function under the condition of exocrine pancreatic insufficiency by delivering lipase, protease, and amylase into the small intestine. Pancreatic enzymes produce increased digestion of fat, protein, and starch.

Drug activity related to proposed indication: Porcine pancreatic enzyme preparations improve digestion under the condition of exocrine pancreatic insufficiency.

2.6.2.3 Secondary pharmacodynamics

No studies were submitted.

2.6.2.4 Safety pharmacology

No studies were submitted.

2.6.2.5 Pharmacodynamic drug interactions

No studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

A study of amylase absorption in dogs indicates that absorption is either negligible or completely absent.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

Study of Amylase Absorption in Dogs

(Levitt et al, Am J Physiol, 241, pg. G54-G58, 1981)

Methods: Mongrel dogs were used in this study. Laparotomy and endoscopic procedures were performed to allow for the experimental procedures. Amylase was purified from dog pancreas using a glycogen precipitation technique. The purity of the amylase preparation was confirmed through gel filtration and isoelectric focusing, which demonstrated that all detectable protein was associated with amylase activity. For some experiments, purified amylase was labeled with ^{125}I. [^{125}I]Amylase was demonstrated to have the same enzymatic activity as that of unlabeled amylase. The absorption of unlabeled purified pancreatic amylase from the intestine was evaluated by infusing approximately 8000 IU into 10-cm segments of jejunum (two experiments) or ileum (two experiments) isolated between ligatures. During the next 2 hr, blood samples were collected simultaneously from the femoral artery and the draining vein from the isolated intestinal segment. Amylase activity was measured in these blood samples. The absorption of [^{125}I]amylase from the entire intestinal tract was evaluated by infusing approximately 50 μCi into

the duodenum via an endoscope. The dogs were allowed to recover from the light pentobarbital anesthesia and eat normally over the next 24 hr. Blood samples were collected during this period, and serum protein-bound ^{125}I was measured. For the purpose of comparison, the pharmacokinetics of serum protein-bound ^{125}I was evaluated using intravenous administration of 25 µCi [^{125}I]amylase. Amylase activity associated with serum protein-bound ^{125}I was measured following intraduodenal and intravenous administration of [^{125}I]amylase.

Results: Following infusion of purified amylase into ligated intestinal segments, no significant increases in the venous drainage of amylase (i.e. venous amylase activity/arterial amylase activity) was detectable, indicating the absence of absorption. The results are shown in the figure below (taken from the study report).

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FIG. 2. Venous-arterial amylase concentration ratio across small bowel loops containing 8,000 IU of luminal amylase.

The authors claim that the maximum increase in the venous/arterial ratio for amylase activity at any time-point was 3%, and that such an increase would require amylase absorption of less than 0.2%/hr for the administered dose of amylase.

Following intraduodenal infusion of [^{125}I]amylase, extremely low levels of protein-bound ^{125}I was detected in serum. A comparison of the AUCs for serum protein-bound ^{125}I resulting from intraduodenal and intravenous administration (normalized for dose based on dpm/kg) indicates that less than 0.3% of protein-bound ^{125}I was present in the systemic circulation after intraduodenal administration. Furthermore, the low level of serum protein-bound ^{125}I following intraduodenal infusion was not associated with amylase activity, whereas a strong association between radioactivity and amylase activity in serum was observed in animals treated intravenously with [^{125}I]amylase. These results are shown in the figures below (taken from the study report).

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FIG. 4. Isoelectric focusing pattern of serum obtained 6 h after instillation of ^{125}I-amylase into duodenum. No significant radioactivity was observed in fractions containing amylase activity.

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FIG. 5. Isoelectric focusing pattern of serum obtained 6 h after intravenous infusion of ^{125}I-amylase. Bulk of radioactivity is in fractions containing amylase activity.

Conclusions: The results indicate that the intestinal absorption of amylase is either negligible or completely absent. The authors excluded the possibility that absorption of amylase occurs via lymphatics, based on previous studies in dogs and humans which demonstrated that amylase concentration in the thoracic duct lymph is nearly identical to that of serum.

2.6.4.4 Distribution

No studies were submitted.

2.6.4.5 Metabolism

No studies were submitted.

2.6.4.6 Excretion

No studies were submitted.

2.6.4.7 Pharmacokinetic drug interactions

No studies were submitted.

2.6.4.8 Other Pharmacokinetic Studies

No studies were submitted.

2.6.4.9 Discussion and Conclusions

A study in dogs was performed to evaluate the absorption of amylase, one of the major enzyme components in pancreatic enzyme products. Certain experiments were performed with [^{125}I]amylase, to allow for increased sensitivity in the detection of intestinal absorption. The results indicate that the absorption of amylase is either negligible or completely absent.

2.6.4.10 Tables and Figures

Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

One published toxicology study on a porcine pancreatic enzyme preparation was submitted. This study was directed at the evaluation of intestinal injury in rats following administration of high dose levels of pancreatic enzymes, and the potential relevance of the intestinal lesions to fibrosing colonopathy, a severe condition that has been associated with high-dose pancreatic enzyme therapy in cystic fibrosis patients. The rest of the toxicology information included brief safety reviews of several excipients in Ultrase®, and a comprehensive safety review of o-phthalic acid, which has been identified as a product impurity. The presence of o-phthalic acid, also known as phthalic acid, is due to degradation of the excipient, hydroxypropyl methylcellulose phthalate. For ease of comprehension, the complete information for the individual excipients and o-phthalic acid is presented in this subsection, rather than dividing this information among the other toxicology subsections (e.g., single-dose, repeat-dose, genetic toxicology, etc.).

Toxicology information on croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP 55), triethyl citrate, talc, and iron oxide was submitted in the present application and in IND 41,387. The submitted information on these excipients was in the form of a summary report, along with reprints of the cited references. The information was reviewed in the Pharmacologist's review of IND 41,387 dated March 9, 2007. The reviews for each of these excipients are shown below. Certain reviews are followed by an addendum that summarizes relevant safety information not reviewed in the IND.

Croscarmellose Sodium

A 90-day oral (dietary) toxicity study in rats was performed using dose levels of 0, 10,000, and 50,000 ppm croscarmellose sodium. No treatment-related deaths or clinical signs occurred. The following parameters were unaffected: bodyweight, food consumption, ophthalmology, hematology, clinical chemistry, gross pathology, and histopathology. The NOAEL (no observed adverse effect level) was 50,000 ppm, equivalent to 3922 mg/kg/day in males and 4712 mg/kg/day in females (Freeman et al, Int J Toxicol, 22(3), pg. 149-157, 2003). In a teratogenicity study in rats, dietary administration of up to 50,000 ppm croscarmellose sodium (approximately 4554 mg/kg/day) during days 6-15 of gestation produced no maternal toxicity, embryo-fetotoxicity, or teratogenic effects (Freeman et al, Int J Toxicol, 22(3), pg. 149-157, 2003).

Hydroxypropyl Methylcellulose Phthalate (HP 55)

A 30-day oral toxicity study in rats was performed using dose levels of 0, 1.3, 2, 3, 4.5, and 10 g/kg/day HP 55 (hydroxypropyl methylcellulose phthalate). The test and control articles were administered by gavage. A different dose volume was used for each dose level of HP 55. Therefore, a separate control group was utilized for each dose level. The control groups were treated with vehicle (1.5% sodium bicarbonate solution) using the dose volume of the corresponding treatment group. The dose volumes were 16.3, 24.5, 36.8, 55.2, and 125 ml/kg in groups treated with 1.3, 2, 3, 4.5, and 10 g/kg/day, respectively. Each animal in the 10 g/kg/day group and the corresponding control group died on days 10-16 of treatment. These animals exhibited severe diarrhea and ataxia within one hour post-dose. Emaciation and shock were also observed prior to death. Thus, the severe toxicity that occurred in the 10 g/kg/day group appeared to be related to the vehicle, rather than HP 55. The following parameters were unaffected at 4.5 g/kg/day or lower: mortality, clinical signs, and histopathology (Kitagawa et al, Pharmacometrics, 4(6), pg. 1017-1025, 1970).

A 6-month oral toxicity study in rats was performed using dose levels of 0, 1.5, 3, and 6 g/kg/day HP 55. The test and control articles were administered by gavage. A different dose volume was used for each dose level of HP 55. Therefore, a separate control group was utilized for each dose level. The control groups were treated with vehicle using the dose volume of the corresponding treatment group. HP 55 had no effect on behavior, bodyweight, hematology, urinalysis, organ weights, or histopathology. Therefore, HP 55 was well tolerated at doses of up to 6 g/kg/day (Kitagawa et al, Pharmacometrics, 7(5), pg. 689-701, 1973).

A 27-week oral (dietary) toxicity study in Beagle dogs was performed using dose levels of 0, 0.75, 1.5, and 3 g/kg/day HP 55. No deaths occurred. Soft stools and occasional diarrhea were observed in the 1.5 and 3 g/kg/day groups during the first six weeks of treatment. HP 55 had no effects on bodyweight, heart rate, blood pressure, ECG, respiration rate, body temperature, ophthalmology, hematology, clinical chemistry, or urinalysis. Since the study report did not include results from histopathologic evaluation, this study is of limited value for assessing the safety of HP 55. However, most of the reported toxicity parameters were unaffected at dose levels of up to 3 g/kg/day. Overt signs of toxicity were limited to soft stools and occasional diarrhea during the first six weeks of treatment (Woodward Research Corporation, unpublished report, 1973).

In a teratogenicity study in rats, oral administration of up to 2400 mg/kg/day HP 55 during pregnancy produced no maternal toxicity, embryo-fetotoxicity, or teratogenic effects. Fetuses in the high-dose group (2400 mg/kg/day) exhibited a tendency towards delayed ossification, although the effect was not significant. Similarly, no adverse fetal effects occurred in mice following oral administration of up to 4000 mg/kg/day on days 7-12 of pregnancy (Ito and Toida, J Med Soc, 19(5), pg. 453-461, 1972).

Addendum: Kitagawa et al (Pharmacometrics, 5(1), pg. 1-4, 1971) studied the absorption, distribution, and excretion of HP 55 (referred to as HPMCP) in rats by administering oral doses of 1.3 and 3.0 g/kg [^{14}C]HPMCP (labeled at the methyl group). Approximately 92-96% of the radioactivity was excreted in feces within 48 hr after dosing. Less than 1% of radioactivity was excreted in urine within 96 hours. However, radioactivity was detected in whole blood within 12 hr post-dose. The level reached a maximum at 24 hr and thereafter declined slowly up to 96 hr post-dose. Radioactivity was distributed in the liver and kidney. The peak levels of radioactivity were noted in liver at 24 hr and in kidney at 12 hr. The radioactivity in both liver and kidney was almost negligible at 96 hr after administration. The authors concluded that HPMCP is excreted rapidly in feces, with only a small amount absorbed by the gastrointestinal tract.

In a follow-up study, Kitagawa et al (Pharmacometrics, 8(8), pg. 1123-1132, 1974) orally administered [^{14}C]HPMCP (labeled at the carboxybenzoyl group) to rats at a dose of 1.3 g/kg. The concentration of radioactivity in blood reached the maximum value at 6 hr post-dose in males and 2 hr post-dose in females, followed by a rapid decline thereafter. Distribution of radioactivity occurred in several organs, with liver and kidney showing the highest levels. Only 0.03% of the administered radioactivity was contained in liver. The distribution of radioactivity in the gastrointestinal tract decreased sharply during the first 24 hr and was negligible after 72 hr. Excretion in bile was extremely low (0.01%) at 24 hr. Excretion in urine was only 0.7% in males and 1.2% in females at 72 hr post-dose. Excretion in feces accounted for 95% and 91% of total radioactivity in males and females, respectively, through 72 hr. Most of the radioactivity in urine was associated with the metabolite, phthalic acid, whereas most of the radioactivity in feces was the unchanged compound.

Triethyl Citrate

In a 2-year oral (dietary) toxicity study, rats were treated with approximately 0, 150, 1000, or 1500 mg/kg/day triethyl citrate. A dose-dependent decrease in weight gain and food intake was observed. No test article-related effects on mortality, hematology, urinalysis, gross pathology, or histopathology were observed (LaWall and Harrison, unpublished report, 1954).

A 6-month oral toxicity study in Beagle dogs was performed using dose levels of 0, 60, and 280 mg/kg/day. Triethyl citrate had no effects on bodyweight, organ weights, hematology, urinalysis, or histopathology. In a separate study, oral administration of 2800 or 4000 mg/kg/day in dogs for 7-12 weeks produced liver pathology (Hodge, unpublished report, 1954).

Addendum: Triethyl citrate tested negative in the Ames reverse mutation assay with *Salmonella typhimurium* strains TA1535, TA1537, and TA1538. A negative result also occurred in a mutation assay in *Saccharomyces cerevesiae* D4 yeast. This test was performed in the absence and presence of a metabolic activating system (Litton Bionetics, Inc., "Mutagenic Evaluation of Compound. FDA 75-10. 000077-93-0, Triethyl Citrate, FCC" National Technical Information Service, U.S. Department of Commerce, PB257866, 1976).

Talc

No oral toxicology studies are available. However, results from animal studies suggest that the absorption of talc is limited. An excretion study in rats, mice, and guinea pigs showed that 94-100% of [^{3}H]talc was excreted in feces following oral administration, with 0.2-1.7% excreted in urine. No [^{3}H]talc was detected in mouse carcasses (Phillips et al, Food Cosmet Toxicol, 16, pg. 161-163, 1978). Similar results were obtained from an excretion study in hamsters (Wehner et al, Food Cosmet Toxicol, 15, pg. 453-455, 1977). One study was performed in rats using dietary administration of talc for the assessment of carcinogenic potential. From a regulatory perspective, this study is not considered to be a valid carcinogenicity study, based on the study design. Rats were of age 21-26 weeks at study initiation. The treatment duration was 101 days, after which the rats were allowed to live through their normal lifespan. The only dose tested was 100 mg/day talc (200 mg/kg/day in a 500-g animal). Survival duration was unaffected. The results suggested that talc was not tumorigenic under the study conditions (Wagner et al, In: Inhaled Particles IV, Proceedings of an International Symposium, Part 2, Pergamon Press, pg. 647-654, 1977). Teratology studies were performed in rats and mice using oral administration of 1600 mg/kg/day, and in hamsters using oral administration of 1200 mg/kg/day. Talc was administered on days 6-15 of pregnancy in rats and mice, and on days 6-10 in hamsters. Embryo-fetal development was unaffected (Lord, Food Cosmet Toxicol, 16, pg. 51-57, 1978).

Addendum: The genotoxicity of talc was evaluated using the Ames test, a mutation assay in *Saccharomyces cerevisiae*, an *in vivo* chromosomal aberration assay in rats, an *in vitro* chromosomal aberration assay in cultured human cells, and a dominant lethal assay in rats. For each of the *in vivo* assays, doses of 30, 300, and 3000 mg/kg were used, while doses of 2, 20, and 200 mg/ml were used in the *in vitro* assays. No significant increases in gene mutations were observed in *Salmonella typhimurium* or *Saccharomyces cerevisiae*. No detectable chromosomal

aberrations occurred in rat bone marrow, and aberrant anaphase chromosomes in cultured human cells were not observed. Talc was considered to be non-clastogenic in the dominant lethal assay in rats (Lord, Food Cosmet Toxicol, 16, pg. 51-57, 1978).

Iron Oxide (Black/Yellow)

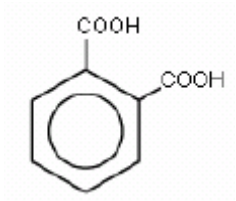
The oral LD_{50} for iron oxide in both rats and mice was reported to be > 15 g/kg (WHO Food Additives Series 6, 1975). No other toxicity information is available. Regulatory information about iron oxide and daily iron intake is described in the "SUMMARY AND EVALUATION" section of this review.

Gelatin

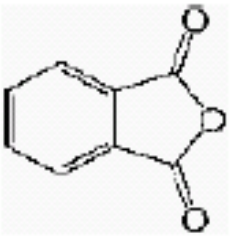
Regulatory information about gelatin was submitted in the present application and in IND 41,387. No toxicity information is available. The regulatory information is described in the "SUMMARY AND EVALUATION" section of this review.

Phthalic Acid

Introduction: The Sponsor submitted a summary report of the available preclinical information about o-phthalic acid, commonly referred to a phthalic acid. This compound is a major impurity in Ultrase®. The report was prepared by (b) (4) a toxicology consultant. The Sponsor did not submit the references that were cited by the author. The report includes toxicology information from studies with o-phthalic acid, and pharmacokinetic and toxicology information about phthalic anhydride. The structures of these compounds are shown below.



o-phthalic acid



phthalic anhydride

Phthalic anhydride rapidly converts to o-phthalic acid in water and biological fluids. Based on an analysis of the kinetics for hydrolysis of phthalic anhydride to o-phthalic acid, the predicted half-life of phthalic anhydride would be less than 10 seconds at physiological pH values (Andres et al, J Org Chem, 66, pg. 7653-7657, 2001). Therefore, information from studies of phthalic anhydride is considered to be relevant to the safety evaluation of o-phthalic acid. The U.S. Environmental Protection Agency has reviewed the available toxicity data for phthalic anhydride and concluded that the results from oral toxicity studies were likely indicative of the systemic toxicity of o-phthalic acid, based on the rapid hydrolysis of phthalic anhydride (U.S.

Environmental Protection Agency, TSCA Section 4 Findings for 21 Hazardous Air Pollutants, pg. 56, June 25, 1996).

Pharmacokinetics:

No animal studies with either o-phthalic acid or phthalic anhydride were cited. Early studies on the metabolism of phthalic anhydride indicated that this compound was hydrolyzed to o-phthalic acid and excreted in urine without further metabolism (Williams, Detoxication mechanisms, 2nd Ed., Chapman and Hall, London, pg. 373, 1959). The exposure of workers to phthalic anhydride vapors during the manufacture of unsaturated polyester resins was associated with excretion of o-phthalic acid in urine. Urine concentrations of o-phthalic acid were well correlated with airborne concentrations of phthalic anhydride, and no metabolites of o-phthalic acid were detected (Pfaffli, Int Arch Occup Env Health, 58, pg. 209-216, 1986).

Acute Toxicity:

The author stated that no oral LD_{50} values have been reported for o-phthalic acid. However, an oral LD_{50} value of 7900 mg/kg was reported for sodium and potassium salts of o-phthalic acid in rats (BIBRA Toxicity Profile: ortho-Phthalic acid and its sodium and potassium salts, 1989). The intraperitoneal LD_{50} for o-phthalic acid in mice was reported to be 400 mg/kg (Jha et al, Mutation Res, 422, pg. 207-212, 1998). The oral LD_{50} of phthalic anhydride in rats was reported to be 800-1600 mg/kg (Fasset, Industrial Hygiene and Toxicology, Vol. 2, Interscience Publishers, New York, pg. 1824-1825, 1963).

Subacute/Subchronic Toxicity:

A 34-day oral toxicity study in rats was performed using dietary administration of 2500 mg/kg/day o-phthalic acid. Histopathologic examination was limited to kidney, liver, spleen, and testes. No effects were observed in these organs. The results also showed no effects on liver diagnostic enzymes (Murakami et al, Jap J Hyg, 41(4), pg. 775-781, 1986). Mice treated for four days with dietary administration of 714 mg/kg/day o-phthalic acid showed no overt signs of toxicity, no evidence of peroxisome proliferation, and no microscopic changes in liver (the only tissue examined) (Lundgren et al, Eur J Biochem, 163(2), pg. 423-431, 1987).

7-Week oral toxicity studies of phthalic anhydride in F344 rats and B6C3F1 mice were performed as dose range-finding studies for a NTP carcinogenicity bioassay. Groups of five male and five female animals were given diets containing 0, 6200, 12,500, 25,000, or 50,000 ppm phthalic anhydride. The estimated dose levels were 0, 310, 625, 1250, and 2500 mg/kg/day for rats and 0, 750, 1500, 3000, and 6000 mg/kg/day for mice. Bodyweight was recorded and tissues were examined microscopically. The only treatment-related effect was a reduction in bodyweight gain of rats in the 1250 and 2500 mg/kg/day groups (10% and 25% reduction, respectively). Microscopic examination did not reveal treatment-related lesions. However, the authors did not indicate whether a complete set of tissues were examined (NTP Study Report, “Bioassay of phthalic anhydride for possible carcinogenicity”, Technical report No. 159, 1979).

Genetic Toxicology:

The mutagenicity of phthalic acid was evaluated in the Ames test. *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538, and TA 2637 were used in this test. Concentrations of up to 2000 μg/plate were used in the absence and presence of S9 liver fraction. Phthalic acid was negative in this assay (Agarwal et al, J Toxicol Environ Health, 16, pg. 61-69, 1985). A negative result for phthalic acid in the Ames test was also reported by Sayato et al (Mutat Res, 189, pg. 217-222, 1987). Phthalic acid was not damaging to the DNA of *B. subtilis* when tested in the Rec +/- assay at amounts up to 500 μg per disk (Tomita et al, Environ Health Perspectives, 45, pg. 119-125, 1982). Phthalic acid was evaluated for induction of chromosomal aberrations, sister chromatid exchanges, and mutation in CHO (Chinese hamster ovary) cells. Mutation at the HPRT locus was determined in hypoxanthine-free growth medium. Phthalic acid was negative for induction of chromosomal aberrations, sister chromatid exchanges, and mutation at the HPRT locus (Phillips et al, Mutat Res, 102, pg. 292-304, 1982). Each of these assays omitted the use of metabolic enzymes. However, this is not considered to be a major deficiency given that phthalic acid does not appear to undergo any significant biotransformation.

Phthalic acid was also evaluated *in vivo* for the induction of dominant lethal mutations (40 or 80 mg/kg ip for five days) and sperm head abnormalities (50, 100, 150, 200, or 300 mg/kg ip as a single treatment) in male Swiss albino mice. Dose selection was based on results of a preliminary toxicity study in mice, in which intraperitoneal doses of 400 mg/kg and higher were lethal. Following the end of treatment in the dominant lethal assay, the males were mated with untreated females during a 4-week period. Pregnant females were sacrificed on gestation day 14-16, and the uterine contents were examined for live and dead implants. The results of the dominant lethal assay showed a statistically significant increase in dominant lethal mutations at both dose levels of phthalic acid. The strongest effects were observed on days 15-21 and 22-28 days post-treatment. A reduction in the proportion of pregnant females occurred when males were mated on days 15-21 post-treatment, an effect that was indicative of impaired reproductive performance. There was also a reduction in the total number of implants per female and an increase in the number of dead implants per female. In the sperm head morphology assay, the mice were sacrificed at 1, 3, and 5 weeks after a single administration of phthalic acid, and smears of spermatozoa were prepared. Treatment with phthalic acid resulted in a statistically significant and dose-related increase in sperm head abnormalities at dose levels of 100 mg/kg and higher. This effect was observed at 1 and 3 weeks after treatment. No effects were observed at 50 mg/kg (Jha et al, Mutat Res, 422, pg. 207-212, 1998).

The mutagenicity of phthalic anhydride was evaluated using the Ames test, in which *Salmonella typhimurium* strains TA 98, TA 100, TA 1537, and TA 1538 were used. This study utilized the pre-incubation method, whereby the cultures were incubated with the test article for 20 min prior to plating in agar and incubation for 48 hr. Phthalic anhydride was not mutagenic in this assay (Zeiger et al, Environ Health Perspectives, 45, pg. 99-101, 1982).

Phthalic anhydride was tested in the SHE (Syrian hamster embryo) cell transformation assay. The tested concentrations of phthalic anhydride were as high as 400 mg/ml in the 24-hr exposure assay, and 200 mg/ml in the 7-day exposure assay. Phthalic anhydride failed to produce a

statistically significant increase in morphologically transformed colonies, and was therefore considered to be negative in this study (LeBoeuf et al, Mutat Res, 356, pg. 85-127, 1996).

Phthalic anhydride has also been tested for its ability to damage DNA in the rat hepatocyte alkaline elution assay, which detects DNA fragments resulting from double stranded breaks. Cultured rat hepatocytes were incubated with up to 10 mM phthalic anhydride for 3 hr. Weak signs of cytotoxicity were observed. However, no consistent or concentration-related increases in DNA fragments were detected (Storer et al, Mutat Res, 368, pg. 59-101, 1996).

Carcinogenicity:

A 105-week carcinogenicity study of phthalic anhydride in F344 rats was performed using dietary administration of 0, 7500, or 15,000 ppm (approximately 375 and 750 mg/kg/day phthalic anhydride). Survival of rats was not affected by the test article. Weight gain was reduced in the high-dose males. No treatment-related neoplastic or non-neoplastic lesions were observed (NTP Study Report, "Bioassay of phthalic anhydride for possible carcinogenicity", Technical report No. 159, 1979).

A 104-week carcinogenicity study of phthalic anhydride in B6C3F1 mice was performed using dietary administration. The dose levels during the first 32 weeks of treatment were 0, 25,000, and 50,000 ppm (approximately 3000 and 6000 mg/kg/day phthalic anhydride). Because of excessive growth depression, dose levels were reduced to 12,500 and 25,000 ppm for males (equivalent to 1500 and 3000 mg/kg/day) and 6250 and 12,500 ppm for females (equivalent to 750 and 1500 mg/kg/day). These dose levels were administered for the remaining 72 weeks of the study. Survival of mice was unaffected by treatment. The results demonstrated lower mean body weight gain in the low- and high-dose mice compared to the control group. Depression of body weight gain was dose-related throughout the study. The authors of the original study report concluded that no treatment-related neoplastic or non-neoplastic effects were observed. However, the Sponsor's summary report of phthalic acid/phthalic anhydride toxicity indicates that an increased incidence of non-neoplastic lesions was observed, based on examination of the histopathology data. Specifically, an increased incidence of lymphocytosis in lungs occurred in the low- and high-dose males (19/50 and 30/49 males, respectively, as compared to 6/20 males in the control group). The same was observed in the low- and high-dose females (32/48 and 34/48 females, respectively, as compared to 2/20 females in the control group). Lymphocytosis in kidneys occurred in the treatment groups, with no incidence in the control groups (15/50 and 37/49 males in the low- and high-dose groups, respectively; 22/48 and 26/48 females in the low- and high-dose groups, respectively). The incidence of bile duct inflammation in the control, low-dose, and high-dose groups was 1/20, 7/50, and 17/49 males, respectively, and 10/20, 30/48, and 36/48 females, respectively (NTP Study Report, "Bioassay of phthalic anhydride for possible carcinogenicity", Technical report No. 159, 1979).

Reproductive and Developmental Toxicology:

An embryo-fetal developmental study (Segment II study) of phthalic acid in rats was performed using dietary administration of 0%, 1.25%, 2.5%, or 5% phthalic acid on days 7-16 of pregnancy. The average daily dose levels were determined to be 1021, 1763, and 2981 mg/kg/day. The dams were sacrificed on day 20 of gestation and C-sections were performed. Live fetuses were examined for external, visceral, and skeletal malformations. Maternal toxicity (i.e. reduced weight gain and food consumption) was observed in the 1763 and 2981 mg/kg/day groups. The weight of male fetuses in the 2981 mg/kg/day group was significantly reduced, but female fetuses were not affected. No other changes in fetal parameters were observed. Since the reduction in weight of male fetuses occurred at a dose which produced maternal toxicity, the results indicate that phthalic acid did not produce embryo-fetotoxicity. No treatment-related external, visceral, or skeletal malformations were noted. The extent of caudal vertebrae ossification was significantly reduced in fetuses of the 2981 mg/kg/day group. This effect may also be secondary to maternal toxicity (Ema et al, Toxicol Lett, 93(2-3), pg. 109-115, 1997).

Special Toxicology Studies:

A study was performed in mice to determine if o-phthalic acid exerts adjuvant effects on the antibody response to ovalbumin. Female BALB/cJ mice, age 6-7 weeks, were sensitized to ovalbumin using subcutaneous administration in the neck region. All groups were given a standard low-dose regimen of ovalbumin to produce sensitization. The ovalbumin dose regimen was the following: 1 mg in vehicle (negative control) or adjuvant on day 1, 0.1 mg in saline on day 11, and 0.1 mg in saline on day 16. The test group was treated with 50 µl of a phthalic acid solution (1064 mg/ml), co-administered with the 1 mg ovalbumin dose on day 1. The vehicle used for ovalbumin and phthalic acid on day 1 was PEG 400/ethanol/saline, 494:5:1. Mice in the positive control group were injected with ovalbumin in aluminum hydroxide adjuvant solution on day 1. A separate group was treated with the adjuvant dimethyldioctadecyl ammonium bromide DDA. Serum from these animals was used as the IgG_{2a} control serum in the assay for IgG_{2a}. Blood was collected on days 15 and 20. The serum levels of ovalbumin-reactive IgE, IgG_1, and IgG_{2a} antibodies were measured using an ELISA method. Phthalic acid had no effect on the levels of ovalbumin-reactive antibodies, relative to the negative (vehicle) control group. In contrast, the aluminum hydroxide adjuvant produced elevated levels of IgE, IgG_1, and IgG_{2a} antibodies. Under the study conditions, phthalic acid did not exhibit adjuvant activity. In addition, no suppression of the antigenic response to ovalbumin was observed with phthalic acid administration (Larsen et al, Food Chem Toxicol, 41(3), pg. 439-446, 2003).

2.6.6.2 Single-dose toxicity

No studies on the drug substance or drug product were submitted. For information about excipients and impurities in Ultrase®, see “Overall toxicology summary” (section 2.6.6.1).

2.6.6.3 Repeat-dose toxicity

No studies on the drug substance or drug product were submitted. For information about excipients and impurities in Ultrase®, see "Overall toxicology summary" (section 2.6.6.1).

2.6.6.4 Genetic toxicology

No studies on the drug substance or drug product were submitted. For information about excipients and impurities in Ultrase®, see "Overall toxicology summary" (section 2.6.6.1).

2.6.6.5 Carcinogenicity

No studies on the drug substance or drug product were submitted. For information about excipients and impurities in Ultrase®, see "Overall toxicology summary" (section 2.6.6.1).

2.6.6.6 Reproductive and developmental toxicology

No studies on the drug substance or drug product were submitted. For information about excipients and impurities in Ultrase®, see "Overall toxicology summary" (section 2.6.6.1).

2.6.6.7 Local tolerance

No studies on the drug substance or drug product were submitted.

2.6.6.8 Special toxicology studies

Pancreatic Enzyme-Induced Intestinal Injury in Rats Under Conditions of Normal and Increased Intestinal Permeability

(Lloyd-Still et al, J Pediatr Gastroenterol Nutr, 26(5), pg. 489-495, 1998)

Methods: The objective of this study was to investigate the underlying mechanism of fibrosing colonopathy, a condition observed in cystic fibrosis patients (age 2-7 years) after treatment with high dose levels of pancreatic enzymes. Sprague Dawley rats weighing 300-350 g were surgically implanted with a duodenal catheter. Ultrase® was used as the pancreatic enzyme preparation. This product was pulverized and suspended in 0.9% saline before administration through the duodenal catheter. Analysis of enzyme activity before and after pulverization showed no loss of lipase, protease, or amylase activity. The study group treatments were as follows: 60,000 lipase U/kg tid Ultrase® for 5-56 days (7 rats); 3 ml of 32 mM oleic acid in 10 mM taurocholic acid bid for 7-10 days (7 rats); 60,000 lipase U/kg tid Ultrase® + 3 ml of 32 mM oleic acid in 10 mM taurocholic acid bid for 7-10 days (9 rats); 20,000 lipase U/kg tid Ultrase® + 1 mg/kg/day ip reserpine (2 rats were treated for 7 days and 5 rats were treated for 12-14 days prior to death); 20,000 lipase U/kg tid Ultrase® + 1 mg/kg/day ip reserpine + 3 ml of 32 mM oleic acid in 10 mM taurocholic acid bid for 2-7 days (7 rats). All test articles, except for reserpine, were administered through the duodenal catheter. Reserpine treatment was used because it is known to produce a condition similar to cystic fibrosis in rats (i.e. pancreatic

insufficiency). Oleic acid is known to increase intestinal permeability and produce mucosal injury in the developing piglet. Since intestinal permeability has been reported to be increased in cystic fibrosis patients, oleic acid was used in the present study for induction of increased intestinal permeability. Thus, reserpine and oleic acid were used to allow for the evaluation of intestinal injury induced by a commercial pancreatic enzyme preparation under pathological conditions similar to those in cystic fibrosis patients. Histopathologic examination of jejunum, ileum, cecum, and colon was performed.

Results: Lesions that are characteristic of fibrosing colonopathy in cystic fibrosis patients (i.e. submucosal fibrosis and strictures) were not observed in any intestinal segment. However, lesions in the small intestine were present in most groups. The microscopic observations of intestine and bodyweight data are summarized in the table below (taken from the publication).

TABLE 1. *Experimental groups, duration of treatment, and effects on intestinal permeability and weight*[a]

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Administration of Ultrase® (pancreatic enzymes) alone was associated with only minor changes in jejunum and ileum. Increased eosinophilic infiltration was observed after 40 days of treatment with Ultrase® alone. Since no vehicle control group was included in the study, the significance of these observations is uncertain. The most severe effects occurred in the group treated with Ultrase®, reserpine, and oleic acid (group 5). All rats in this group exhibited necrosis of muscle layers in jejunum and ileum, with loss of nuclei and thinning of the intestine. The severe intestinal lesions developed after only 2-7 days of treatment, and weight loss was observed during this period. No signs of inflammation or increased fibrosis were observed in the area of necrosis. Similar effects were observed when Ultrase® and reserpine were co-administered for 12-14 days. Treatment with Ultrase® + oleic acid or oleic acid alone (7-10 days) also produced intestinal lesions, but with less frequency.

Conclusions: The results suggest that high dose levels of pancreatic enzymes can produce injury in the small intestine. Under the study conditions, this effect was dependent on simultaneous treatment with oleic acid and/or reserpine. The strongest effect was observed with the combination of these compounds. Given the ability of oleic acid to produce increased intestinal permeability, a condition that is characteristic of cystic fibrosis, the results suggest that the experimental model in this study may be relevant to the mechanism of fibrosing colonopathy development. Fibrosing colonopathy has occurred in cystic fibrosis patients treated with high doses of pancreatic enzymes over a long period. The authors claim that the pancreatic enzyme dose level in the present study (60,000 lipase U/kg tid) was equivalent to the highest doses

associated with fibrosing colonopathy in humans. It should be emphasized that the intestinal lesions in the present study differ from those of fibrosing colonopathy, which is characterized by submucosal fibrosis of the colon and rectum, and colonic strictures. The lesions in rats were limited to the ileum and jejunum (e.g., muscle necrosis). The authors suggest that necrosis of muscle in small intestine could be relevant to the development of fibrosing colonopathy, based on the stimulation of TGF-β (transforming growth factor-β) production and subsequent onset of submucosal fibrosis. In the intestine, muscle cells rather than fibroblasts produce high levels of TGF-β. It is noteworthy that the pancreatic enzyme preparation used in this study contained Eudragit L30 D55, an enteric coating material which has been proposed as a mediator of fibrosing colonopathy (Prescott and Bakowski, Pharmacoepidemiology Drug Safety, 8, pg. 377-384, 1999).

2.6.6.9 Discussion and Conclusions

The Sponsor provided toxicity and regulatory information about the following excipients: croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP 55), triethyl citrate, talc, iron oxide, and gelatin. This information is limited to those excipients for which the daily intake could exceed the maximum daily oral dose among all approved drug products, as determined from the maximum daily dose of Ultrase® and information from the FDA Inactive Ingredients Database. The NOAEL (no observed adverse effect level) for croscarmellose sodium in a 90-day oral (dietary) toxicity study in rats was 50,000 ppm, equivalent to 3922 mg/kg/day in males and 4712 mg/kg/day in females. No adverse effects were observed in this study. In a teratogenicity study in rats, dietary administration of up to 50,000 ppm croscarmellose sodium (approximately 4554 mg/kg/day) did not affect embryo-fetal development. HP 55 produced no adverse effects at doses of up to 6 g/kg/day in a 6-month oral toxicity study in rats. A 27-week oral (dietary) toxicity study in Beagle dogs was performed using dose levels of 0, 0.75, 1.5, and 3 g/kg/day HP 55. Soft stools and occasional diarrhea were observed in the 1.5 and 3 g/kg/day groups during the first six weeks of treatment. Histopathology evaluation was not reported in this study. However, HP 55 had no effects on most of the standard toxicology study parameters. HP 55 also had no effects on embryo-fetal development in rats, other than a tendency towards delayed ossification at the highest dose tested (2400 mg/kg/day). No embryo-fetal effects occurred in mice following oral administration of up to 4 g/kg/day on days 7-12 of pregnancy. Triethyl citrate produced a dose-dependent decrease in weight gain and food intake at dose levels of 150, 1000, and 1500 mg/kg/day in a 2-year oral (dietary) toxicity study in rats. No other adverse effects were observed. The NOAEL in a 6-month oral toxicity study of triethyl citrate in dogs was 280 mg/kg/day, the highest dose tested. However, liver injury occurred in dogs at oral doses of 2800 and 4000 mg/kg/day, given for 7-12 weeks. No oral toxicology studies of talc are available. However, results from animal studies suggest that the absorption of talc is limited. Oral administration of talc in pregnant rats, mice, and hamsters had no effects on embryo-fetal development.

The Sponsor also submitted a summary report of toxicology information on o-phthalic acid (commonly referred to as phthalic acid), a major impurity in Ultrase®. Toxicology and pharmacokinetic information about phthalic anhydride was also presented in this report. Information from studies of phthalic anhydride was considered to be relevant to the safety

evaluation of o-phthalic acid, given that phthalic anhydride rapidly converts to o-phthalic acid in water and biological fluids. Phthalic anhydride was tolerated in rats at oral doses of up to 1250 mg/kg/day given for seven weeks, whereas treatment with 2500 mg/kg/day produced a 25% decrease in weight gain. O-Phthalic acid tested negative in the Ames test, Rec +/- assay for DNA damage, chromosomal aberration assay, sister chromatid exchange assay, and HPRT mutation test. However, positive results were observed in *in vivo* assays in mice for the induction of dominant lethal mutations and sperm head abnormalities by o-phthalic acid. Phthalic anhydride was negative in the Ames test, SHE cell transformation assay, and the rat hepatocyte alkaline elution assay for DNA damage. In a 105-week carcinogenicity study in rats, phthalic anhydride produced no neoplastic or non-neoplastic lesions at oral doses up to approximately 750 mg/kg/day. A 104-week carcinogenicity study of phthalic anhydride was conducted in mice using oral dose levels of approximately 3000/1500 and 6000/3000 mg/kg/day in males and 3000/750 and 6000/1500 mg/kg/day in females. The dose levels were reduced during the study due to excessive growth depression. Tumorigenic effects were not observed. However, an increased incidence of lymphocytosis in lungs and kidneys was observed in males and females at both dose levels. The incidence of bile duct inflammation was also increased in the treatment groups. Oral administration of up to 2981 mg/kg/day phthalic acid in pregnant rats did not produce embryo-fetotoxicity or teratogenic effects. However, maternal toxicity (i.e. reduced weight gain and food consumption) was observed in the 1763 and 2981 mg/kg/day groups. Phthalic acid failed to produce adjuvant effects in the production of ovalbumin-reactive antibodies in mice following sensitization. No suppression of the antigenic response to ovalbumin was observed with phthalic acid administration.

A special toxicology study of a porcine pancreatic enzyme preparation was submitted. The objective of this study was to investigate the underlying mechanism of fibrosing colonopathy, a condition which has occurred in children with cystic fibrosis after treatment with high dose levels of pancreatic enzymes. The results showed that high dose levels of pancreatic enzymes produced injury in the small intestine under conditions of increased intestinal permeability, induced by treatment with oleic acid and/or reserpine. Cystic fibrosis patients are known to have high intestinal permeability. The intestinal lesions in this study differ from those of fibrosing colonopathy, which is characterized by submucosal fibrosis of the colon and rectum, and colonic strictures.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

LABELING:

The preclinical sections/subsections of the Sponsor's proposed labeling include the "INDICATIONS AND USAGE" section of the "HIGHLIGHTS OF PRESCRIBING INFORMATION", "Pregnancy" subsection, and the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection.

Sponsor's Proposed Version:

"**HIGHLIGHTS OF PRESCRIBING INFORMATION**"

"**INDICATIONS AND USAGE**

(b)(4)

Evaluation: The term "pancreatic enzyme replacement therapy" is used as the established pharmacologic class in the proposed labeling. This term is descriptive of the pharmacodynamic activity of ULTRASE®. However, the term "pancreatic enzyme preparation digestant" is preferable for use as the established pharmacologic class. "Pancreatic enzyme preparation" is commonly used as a classification term for products that contain pancreatic enzymes of porcine or bovine origin. Given that "pancreatic enzyme preparation" is an accurate description of the chemical nature and origin of the drug, it is considered to be a scientifically valid pharmacologic class. The term "digestant" accurately describes the pharmacologic effect of pancreatic enzyme preparations such as ULTRASE®. Therefore, "digestant" is also considered to be a scientifically valid pharmacologic class. Both "pancreatic enzyme preparation" and "digestant" are terms that provide useful information about ULTRASE®, and are each considered as a clinically meaningful pharmacologic class. Therefore, it is recommended that the established pharmacologic class under the "INDICATIONS AND USAGE" section of the Highlights should be "pancreatic enzyme preparation digestant".

Recommended Version:

"**HIGHLIGHTS OF PRESCRIBING INFORMATION**"

"**INDICATIONS AND USAGE**

ULTRASE® is a pancreatic enzyme preparation digestant indicated for the treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions (1)"

Sponsor's Proposed Version:

"**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether ULTRASE® MT Capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ULTRASE® MT Capsules should be given to a pregnant woman only if clearly needed."

Evaluation: The proposed labeling is not compliant with labeling regulations (21 CFR 201.57). The subheading "Teratogenic effects" should be listed under "Pregnancy". The term "pancrelipase" should be used in place of "ULTRASE® MT Capsules", given that the statements in this subsection are applicable to all pancrelipase products.

Recommended Version:

"**8 USE IN SPECIFIC POPULATIONS**

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. Pancrelipase should be given to a pregnant woman only if clearly needed."

Sponsor's Proposed Version:

"**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
(b) (4)

Evaluation: The information in this subsection is accurate. However, changes in the language are recommended, as shown below.

Recommended Version:

"**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase."

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

EPI (exocrine pancreatic insufficiency) is associated with cystic fibrosis, chronic pancreatitis, post-pancreatectomy, and alcoholism. Inadequate secretion of pancreatic enzymes in patients with EPI causes maldigestion, leading to inadequate absorption of fats, proteins, and carbohydrates, as well as fat-soluble vitamins and vitamin B_{12}. The malabsorption of fats is the most clinically significant aspect of EPI, since this leads to steatorrhea and eventually to wasting in adults and failure to thrive in infants and children.

Ultrase® MT Capsules are a delayed-release capsule formulation of pancrelipase, a digestive enzyme product derived from porcine pancreas. The major classes of pancreatic enzymes in pancrelipase include lipase, protease, and amylase. These enzymes provide a therapeutic benefit to EPI patients by improving the digestion of fats, proteins, and starch. Ultrase® contains minitablets, which are enteric-coated and contain a core consisting of pancrelipase and several excipients. Thus, the formulation is designed to resist inactivation of the enzyme preparation, as would ordinarily occur in the acidic environment of the stomach prior to delivery into the duodenum. Once in the duodenum, the enteric coating dissolves in response to the increased pH, and the enzymes are released to aid in digestion. The protection of pancreatic enzymes from destruction in the gastric medium is especially important for lipase, which is the most sensitive to low pH among the pancreatic enzymes. The lipase activity is needed to resolve the steatorrhea associated with EPI. Ultrase® is indicated for the treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions.

To support the approval of NDAs for pancrelipase products, toxicology information about excipients may be needed, depending on the levels contained in the product and the previous human experience with the excipients (CDER guidance, "Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs", April 2006). The need for excipient toxicity information is based on the expected daily ingestion of a potentially large number capsules, in order to achieve therapeutic dose levels for pancrelipase products. Toxicity studies of pancrelipase are not needed, given the long history of its use in patients with exocrine pancreatic insufficiency. The Sponsor submitted the following preclinical information: study of amylase absorption in dogs; toxicology summaries of individual excipients; toxicology summary of phthalic acid (major impurity); special toxicology study of pancrelipase (intestinal effects in rats with normal and increased intestinal permeability).

A detailed study was performed in dogs to determine if amylase, a major enzyme component in pancrelipase, can be absorbed intact. Purified amylase was infused into ligated segments of the jejunum and ileum, and blood samples were collected from the draining vein of the isolated intestinal segment during the next 2 hr. No significant increases in amylase in blood from the draining vein (i.e. venous/arterial ratio of amylase activity) was detectable, indicating that amylase absorption was either negligible or completely absent. The absorption of [^{125}I]amylase from the entire intestinal tract was also evaluated. Blood was collected during a 24-hr period after intraduodenal infusion of [^{125}I]amylase. Serum protein-bound ^{125}I and the associated amylase activity were measured. Less than 0.3% of protein-bound ^{125}I was present in the

systemic circulation after intraduodenal administration. Furthermore, the low level of serum protein-bound ^{125}I following intraduodenal infusion was not associated with amylase activity. The results of this experiment also indicate that the absorption of amylase is either negligible or completely absent.

A study was performed to investigate the underlying mechanism of fibrosing colonopathy, a condition which has occurred in cystic fibrosis patients (age 2-7 years) after treatment with high dose levels of pancreatic enzymes. Rats were treated with oleic acid and/or reserpine to produce a pathological condition that is characteristic of cystic fibrosis (i.e. exocrine pancreatic insufficiency and increased intestinal permeability). Ultrase® was administered as a suspension via a duodenal catheter using dose levels of 20,000-60,000 lipase U/kg tid, either alone or in combination with oleic acid and/or reserpine. The study results suggest that high dose levels of pancreatic enzymes can produce injury in the small intestine under conditions of increased intestinal permeability. It should be emphasized that the intestinal lesions in this study differ from those of fibrosing colonopathy, which is characterized by submucosal fibrosis of the colon and rectum, and colonic strictures. The lesions in rats were limited to the ileum and jejunum (e.g., muscle necrosis).

The Sponsor's proposed labeling states the following recommendations for dosing: (b) (4) [redacted]. The proposed labeling does not definitively indicate a maximum recommended dose. For the purpose of estimating the maximum daily dose of excipients, it is assumed that the maximum recommended dose is 6000 USP lipase U/kg/meal. The Sponsor provided estimates of the maximum daily dose levels of each excipient for all three capsule strengths, based on administration of 6000 lipase U/kg/meal, the consumption of 3.5 meals per day (i.e. 21,000 lipase U/kg/day, equivalent to 257 mg/kg/day pancrelipase), and information about the excipient content for each capsule strength. The accuracy of the Sponsor's estimates was previously confirmed (Pharmacologist's review of IND 41,387 dated March 9, 2007). Dosing of Ultrase® is based on bodyweight. Therefore, for any given dose of active ingredient, the excipient dose levels relative to bodyweight (mg/kg) will be similar in all patients regardless of bodyweight. For most of the excipients (i.e. those present in the minitablets), the daily dose levels among the three capsule strengths are very similar, based on a constant dose of active ingredient.

Safety assessment of the individual excipients is based on the excipient levels reported in the DMF for Eurand Minitabs® Pancrelipase Products, to which the Sponsor refers in the present application. The maximum daily dose level for each excipient was estimated using the excipient levels from the DMF, an assumed maximum daily dose of 21,000 lipase U/kg/day, and a bodyweight of 60 kg. The Sponsor identified several excipients (i.e. hydrogenated castor oil, colloidal silicon dioxide, microcrystalline cellulose, magnesium stearate, and titanium dioxide) for which the estimated maximum daily dose is less than the "maximum previously accepted level for a single dosage form". No information about these excipients was provided, given the previous human experience from their use in other pharmaceutical products. Information in the

FDA Inactive Ingredients Database confirms that hydrogenated castor oil, colloidal silicon dioxide, microcrystalline cellulose, magnesium stearate, and titanium dioxide are present in approved oral formulations at levels (e.g., mg/tablet) which exceed the estimated maximum daily dose of Ultrase® for a 60-kg patient (mg/day). Because of the extensive use of these excipients in pharmaceutical products, no safety information is needed. For all other excipients in Ultrase® (i.e. croscarmellose sodium, hydroxypropyl methylcellulose phthalate, triethyl citrate, talc, iron oxide, and gelatin), the Sponsor provided summaries of the preclinical and regulatory information. The estimated maximum daily dose levels of croscarmellose sodium, hydroxypropyl methylcellulose phthalate, triethyl citrate, and talc vary only slightly if different capsule strengths are used to achieve a given dose of lipase. For the purpose of safety assessment, the highest excipient dose among the three capsule strengths was used.

Croscarmellose sodium is a cross-linked form of sodium carboxymethylcellulose. For patients treated with Ultrase®, the maximum daily dose of croscarmellose sodium is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60-kg patient. Since Ultrase® is intended for long-term use, chronic toxicity studies are needed for safety assessment of the expected maximum daily dose. However, the only available repeat-dose toxicity study is a 90-day oral (dietary) study in rats. The NOAEL (no observed adverse effect level) in this study was 50,000 ppm (the highest dose tested), equivalent to 3922 mg/kg/day in males and 4712 mg/kg/day in females. Thus, the NOAEL in male rats exceeded the estimated maximum daily dose in humans by 456-fold. For a preclinical safety assessment of any drug or excipient in which long-term use is expected (i.e. longer than three months), toxicity studies of at least six months duration in a rodent species and 9-12 months in a non-rodent species are generally needed. Although such studies are not available for croscarmellose sodium, some assurance of safety can be derived from the 90-day oral toxicity study in rats, given that the NOAEL exceeded the estimated maximum human dose by 456-fold. Croscarmellose sodium is widely used in oral pharmaceutical formulations. An intake of 30 g/day has been recommended as the upper limit of safety for modified celluloses in general (National Research Council, 1989), whereas the estimated maximum dose for croscarmellose sodium is approximately 0.5 g/day, based on a 60-kg bodyweight. Based on the information from the 90-day oral toxicology study in rats and the previous human experience, the estimated maximum dose of croscarmellose sodium resulting from administration of Ultrase® is not considered to be a safety concern.

The maximum daily dose of HP 55 (hydroxypropyl methylcellulose phthalate) in patients treated with Ultrase® is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60-kg patient. Chronic oral toxicity studies (6 months in rats and 27 weeks in dogs) were submitted by the Sponsor. HP 55 had no effect on behavior, bodyweight, hematology, urinalysis, organ weights, or histopathology at doses of up to 6 g/kg/day in the 6-month oral toxicity study in rats. Oral administration of 1.5 and 3 g/kg/day HP 55 in dogs produced soft stools and occasional diarrhea during the first six weeks of treatment in the 27-week study. Although most of the standard toxicology parameters were unaffected, histopathology evaluation was not reported. Therefore, this study is of limited value for assessing the safety of HP 55. However, HP 55 appeared to be tolerated in dogs at dose levels of up to 3 g/kg/day. The tolerated dose level in the 6-month study in rats was 6 g/kg/day, which exceeds the estimated maximum daily dose in humans by 135-fold. No safety margin can be derived from the 27-week study in dogs, due to the complete absence of histopathology information. However, it should be noted that the dose levels used in

this study exceeded the estimated maximum daily dose in humans by 17-68-fold, and overt signs of toxicity were limited to soft stools and occasional diarrhea during the first six weeks. The safety margin derived from the 6-month toxicity study in rats provides a reasonable assurance of safety for the estimated maximum dose level of HP 55, although the addition of histopathology information from a chronic toxicity study in a non-rodent species would have provided a more complete data set for safety assessment. It is noted that HP 55 has been used in oral pharmaceutical formulations as an enteric coating material, the same purpose for which it is used in Ultrase®. Based on the chronic toxicity studies and the previous human experience, the estimated maximum dose for HP 55 resulting from Ultrase® administration is not considered to be a safety concern.

The maximum daily dose of triethyl citrate in patients treated with Ultrase® is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60-kg patient. The Sponsor submitted a 2-year oral (dietary) toxicity study in rats, in which dose levels of approximately 0, 150, 1000, and 1500 mg/kg/day triethyl citrate were used. Adverse effects were limited to a dose-dependent decrease in weight gain and food intake was observed. In a 6-month oral toxicity study in dogs, triethyl citrate had no adverse effects at doses of up to 280 mg/kg/day, the highest dose tested. However, another study demonstrated liver pathology after oral administration of 2800 or 4000 mg/kg/day for 7-12 weeks in dogs. The tolerated dose level in the 2-year study in rats was 1500 mg/kg/day, which exceeds the estimated maximum daily dose in humans by 341-fold. The NOAEL in the 6-month study in dogs was 280 mg/kg/day, which exceeds the estimated maximum daily dose in humans by 64-fold. The safety margins derived from these studies provide a reasonable assurance of safety for the estimated maximum dose level of triethyl citrate, although the addition of a 9-12 month toxicity study in a non-rodent species would have provided a more complete data set for safety assessment. Triethyl citrate has been used in oral pharmaceutical formulations and as a direct food additive. Triethyl citrate is classified as GRAS for use as a direct food substance, with no limitation on its use other than current good manufacturing practice (21 CFR 184.1911). The Joint FAO/WHO Expert Committee on Food Additives designated the ADI (acceptable daily intake) for triethyl citrate as 0-20 mg/kg bodyweight in 1984 and again in 1999. The estimated maximum daily dose ((b) (4) mg/kg/day) falls within the ADI range. Based on the chronic toxicity studies, previous human experience, regulatory information, and the recommended ADI, the estimated maximum dose of triethyl citrate resulting from Ultrase® administration is not considered to be a safety concern.

Talc is a finely powdered mineral composed of hydrated magnesium silicate with the chemical formula $H_2Mg_3(SiO)_4$. The maximum daily dose of talc in patients treated with Ultrase® is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60-kg patient. No oral toxicology studies of talc are available. However, results from pharmacokinetic studies in animals suggest that the absorption of talc is limited. One study was performed in rats using dietary administration of talc for the assessment of carcinogenic potential. From a regulatory perspective, this study is not considered to be a valid carcinogenicity study, based on the methods used. The treatment duration was 101 days, after which the rats were allowed to live through their normal lifespan. The only dose tested was 100 mg/day talc (200 mg/kg/day in a 500-g animal). Survival duration was unaffected. The results suggested that talc was not tumorigenic under the study conditions. This study is inadequate for safety assessment of the estimated maximum dose in humans, due to flaws in the methods used. The submitted

preclinical studies are not sufficient to provide a reasonable assurance of safety for the estimated maximum daily dose of talc resulting from Ultrase® administration. However, talc is often used as a food additive or as an anti-caking agent, coating agent, or texturing agent in pharmaceutical products. Talc is classified as a color additive for drugs (21 CFR 73.1550). Talc is listed in the Food Chemical Codex, Edition V, as a food additive. 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 previous human experience, regulatory information, and the recommended ADI, the estimated maximum daily dose of talc resulting from Ultrase® administration is not considered to be a safety concern.

Black iron oxide is an excipient in the MT18 and MT20 capsule strengths of Ultrase®, whereas yellow iron oxide is present in the MT12 and MT20 capsule strengths. For the purpose of safety evaluation of iron oxide intake, no distinction is made between black and yellow iron oxide, since color is determined by particle size and shape. The maximum daily dose of iron oxide in patients treated with Ultrase® is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60-kg patient. The oral LD_{50} for iron oxide in both rats and mice was reported to be > 15 g/kg. No other toxicity information is available. Therefore, the safety of the estimated maximum daily dose of iron oxide cannot be supported by the submitted preclinical information.

Under U.S. regulations, iron oxide is classified as a color additive for ingested drugs that may be safely used in an amount no greater than 5 mg/day of elemental iron (21 CFR 73.1200). Based on the estimated maximum dose of iron oxide in a 60-kg patient treated with Ultrase® (b) (4) mg/day iron oxide), the maximum intake of elemental iron would be (b) (4) mg/day, which exceeds the dose limit stated in 21 CFR 73.1200 by more than 3-fold. Therefore, the regulatory dose limit of elemental iron from iron oxide would be exceeded even at lower bodyweights when the maximum dose of Ultrase® is administered. However, to evaluate the safety of iron intake associated with Ultrase® administration, it is essential to consider the recommendations of the health authorities. For example, the Office of Dietary Supplements in the National Institutes of Health has recommended a daily allowance of 8 mg elemental iron in adult males and 18 mg elemental iron in adult females. In 2001, the Institute of Medicine established a tolerable upper limit of daily elemental iron intake for healthy people, which is 40 mg/day for age seven months to 13 years, and 45 mg/day for age 14 years and older. Furthermore, daily iron intake originating from food sources would be expected to exceed the 5 mg regulatory dose limit for iron oxide. Based on recommendations of the health authorities and the known level of daily iron consumption in the human diet, the estimated maximum daily dose of iron oxide resulting from Ultrase® administration is not considered to be a safety concern. It is noteworthy that the FDA Inactive Ingredients Database indicates that one drug product, an oral tablet formulation, contains 50 mg of ferric (iron) oxide, a level that exceeds the estimated maximum daily dose of iron oxide for Ultrase®. Another oral tablet formulation contains 13 mg of red iron oxide. Thus, there are at least two approved oral formulations for which the regulatory dose limit of elemental iron from iron oxide is exceeded.

The maximum daily dose of gelatin in patients treated with Ultrase® is estimated to be (b) (4) mg/kg/day, equivalent to (b) (4) mg/day in a 60-kg patient. No toxicology studies of gelatin are available. "Gelatin" is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type

B gelatin) of animal collagen. The molecular weight of the protein fractions ranges from 15,000 to 250,000 Da. Gelatin is listed as a food category in 21 CFR 170.3. The Joint FAO/WHO Expert Committee on Food Additives has designated the ADI for gelatin as "not specified". Gelatin is extensively used in oral pharmaceutical formulations. Given that gelatin has a long history of safe use in foods and pharmaceutical products, the estimated maximum dose resulting from Ultrase® administration is not considered to be a safety concern.

The safety of the estimated maximum daily dose levels of the individual excipients in Ultrase® MT Capsules is supported by previous human experience, preclinical toxicity studies, regulatory information, and/or information from health authorities. Therefore, there are no safety concerns about the excipient intake associated with the administration of Ultrase®.

O-Phthalic acid, commonly referred to as phthalic acid, has been identified as a major impurity in Ultrase®. The presence of o-phthalic acid is due to degradation of the excipient, hydroxypropyl methylcellulose phthalate. The Sponsor submitted a summary report of the toxicological information on o-phthalic acid and phthalic anhydride, a compound that rapidly converts to phthalic acid in water and biological fluids. Information from this report is described below.

No pharmacokinetic information from animal studies was provided in the summary report. Results from human studies showed that phthalic anhydride was excreted in urine as o-phthalic acid.

A 34-day oral toxicity study in rats was performed using dietary administration of 2500 mg/kg/day o-phthalic acid. Histopathologic examination was limited to kidney, liver, spleen, and testes. No effects were observed in these organs.

A 7-week oral (dietary) toxicity study of phthalic anhydride in rats was performed using dose levels of approximately 310, 625, 1250, and 2500 mg/kg/day. The only treatment-related effect was a reduction in bodyweight gain in the 1250 and 2500 mg/kg/day groups (10% and 25% reduction, respectively). Microscopic examination did not reveal treatment-related lesions. However, the authors did not indicate whether a complete set of tissues was examined.

A 7-week oral (dietary) toxicity study of phthalic anhydride in mice was performed using dose levels of approximately 750, 1500, 3000, and 6000 mg/kg/day. No treatment-related lesions were observed in the histopathologic evaluation. However, the authors did not indicate whether a complete set of tissues was examined.

A 105-week carcinogenicity study of phthalic anhydride in F344 rats was performed using dietary administration of 0, 7500, and 15,000 ppm (approximately 375 and 750 mg/kg/day). Survival of rats was not affected by the test article. Weight gain was reduced in the high-dose males. No treatment-related neoplastic or non-neoplastic lesions were observed.

A 104-week carcinogenicity study of phthalic anhydride in B6C3F1 mice was performed using dietary administration. The dose levels during the first 32 weeks of treatment were 0, 25,000, and 50,000 ppm (approximately 3000 and 6000 mg/kg/day). Because of excessive growth

depression, dose levels were reduced to 12,500 and 25,000 ppm for males (equivalent to 1500 and 3000 mg/kg/day) and 6250 and 12,500 ppm for females (equivalent to 750 and 1500 mg/kg/day). These dose levels were administered for the remaining 72 weeks of the study. An increased incidence of lymphocytosis in lungs and kidneys occurred in the low- and high-dose groups. No treatment-related neoplastic lesions were observed.

Safety assessment of phthalic acid intake associated with Ultrase® administration is based on an estimated maximum dose of 21,000 lipase U/kg/day (6000 lipase U/kg/meal, 3.5 meals/day). It is assumed that this extremely high dose level would be administered using Ultrase® MT20, which contains the highest pancreatic enzyme quantity (23,000 lipase U/capsule) of the three capsule strengths. Ultrase® capsules are filled with delayed-release minitablets, which contain pancrelipase, excipients, and phthalic acid. Ultrase® MT20 capsules are expected to contain approximately (b) (4) mg of pellets. The acceptance criterion for phthalic acid at release and during shelf life is not more than (b) (4)% w/w. The maximum dose of phthalic acid from Ultrase® administration is estimated to be (b) (4) mg/kg/day, based on the following assumptions: a target dose of 21,000 lipase U/kg/day, (b) (4) mg minitablets per capsule, and a phthalic acid content of (b) (4)% w/w. It is expected that Ultrase® will be used as a long-term therapy given the irreversible nature of exocrine pancreatic insufficiency, a condition that is associated with chronic pancreatitis, cystic fibrosis, and alcoholism. Therefore, chronic toxicity studies would be most relevant to the safety assessment of phthalic acid intake from Ultrase®, although it should be noted that studies of 14 to 90 days are considered as acceptable for impurity qualification studies (ICH Guidance Q3B(R), "Impurities in New Drug Products", November 2003). Among the cited toxicity studies of phthalic acid, the study of longest duration was the 34-day dietary study in rats. A NOAEL cannot be determined from this study, given that histopathologic examination was limited to kidney, liver, spleen, and testes. No adverse effects were observed in these organs at 2500 mg/kg/day, the only dose tested. Although adequate toxicity studies of phthalic acid are not available, relevant information that is useful for safety assessment is provided by the cited toxicity studies of phthalic anhydride, a compound that rapidly converts to phthalic acid in water and biological fluids. In the 105-week carcinogenicity study of phthalic anhydride in rats using dietary administration, the NOAEL was approximately 375 mg/kg/day. Assuming that the entire dose was hydrolyzed, the exposure to phthalic acid at the NOAEL was equivalent to (b) (4) mg/kg/day, which exceeds the estimated maximum daily dose by approximately 62-fold. This safety margin provides a reasonable assurance of safety for the estimated maximum daily dose of phthalic acid ((b) (4) mg/kg/day). In summary, the 105-week carcinogenicity study of phthalic anhydride in rats and other preclinical studies of phthalic acid and phthalic anhydride provide a reasonable assurance of safety for the ingestion of phthalic acid associated with Ultrase® administration.

Unresolved toxicology issues:

None.

Recommendations:

From a preclinical viewpoint, the application should be approved, with the provision that the "INDICATIONS AND USAGE" section under the "HIGHLIGHTS OF PRESCRIBING INFORMATION", "Pregnancy" subsection, and the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the proposed labeling will be changed as described in the "LABELING" section of this review.

Suggested labeling: The labeling should be changed as described in the "LABELING" section of this review.

Reviewer Signature _____
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Supervisor Signature_____Concurrence Yes ___ No ___
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cc:
Orig NDA 22,222
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HFD-180/Dr. Joseph

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APPENDIX/ATTACHMENTS

None

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

/s/

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3/3/2008 12:09:51 PM
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