CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

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

FROM: David B. Joseph, Acting Pharmacology Team Leader

DATE: June 30, 2010

SUBJECT: NDA 22,542 (Submissions dated April 27, 2009 and October 29, 2009)

Sponsor: Axcan Pharma US, Inc.

Drug Product: Viokace® (pancrelipase) Tablets

Comments:

1. The submitted safety information on the excipients in Viokace® is sufficient to provide a reasonable assurance of safety for the maximum recommended dose (b) (4)

2. Viokace® contains lactose monohydrate. Since Viokace® administration may result in a substantial intake of lactose monohydrate (up to 6 g/day in a 60-kg patient), there appears to be a potential for adverse reactions in lactose intolerant patients. This issue is discussed in Dr. Niraj Mehta's Pharmacology/Toxicology review dated June 29, 2010. The Medical Officer (Dr. Marjorie Dannis) should determine whether this issue needs to be addressed in the labeling.

3. I concur with Dr. Mehta's recommendation for approval, and the recommendations for changes in the Sponsor's proposed labeling (Pharmacology/Toxicology review dated June 29, 2010).

Recommendations:

1. From a nonclinical viewpoint, Viokace® should be approved.

2. The Sponsor's proposed labeling should be changed as recommended in Dr. Mehta's Pharmacology/Toxicology review.

_____ _____

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

cc:
NDA 22,542
DGP
DGP/CSO
DGP/Dr. Joseph
DGP/Dr. Mehta
OND IO/Dr. Jacobs

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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

/s/

DAVID B JOSEPH
06/30/2010

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22,542
Supporting document/s:	SD #2 and SD #4
Applicant's letter date:	April 27, 2009 (SD #2) and October 29, 2009 (SD #4)
CDER stamp date:	April 27, 2009 (SD #2) and October 29, 2009 (SD #4)
Product:	VIOKACE® (pancrelipase, USP) Tablets
Indication:	Exocrine pancreatic insufficiency due to chronic pancreatitis
Applicant:	Axcan Pharma US, Inc.
Review Division:	Division of Gastroenterology Products
Reviewer:	Niraj R. Mehta, Ph.D.
Supervisor/Team Leader:	David B. Joseph, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Elizabeth A.S. Ford, RN

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1 Executive Summary

1.1 Recommendations

The recommendations are presented below in sections 1.1.1, 1.1.2 and 1.1.3.

1.1.1 Approvability

The present application for VIOKACE® (pancrelipase) should be approved.

1.1.2 Additional Non Clinical Recommendations

None.

1.1.3 Labeling

Recommendations are shown below for the following subsections: "INDICATIONS AND USAGE", "Pregnancy", "Nursing Mothers", and "Carcinogenesis, Mutagenesis, Impairment of Fertility."

Sponsor's Proposed Version:

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

TRADENAME Tablets is a pancrelipase which is a mixture of porcine-derived lipases, proteases, and amylases. TRADENAME, in combination with a proton pump inhibitor, is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis (b) (4).

Evaluation: The proposed established pharmacologic class differs from that of other approved pancreatic enzyme preparations. Therefore, a minor change is needed to ensure that the language is consistent with the labeling for the approved products, Zenpep and Pancreaze (pancrelipase).

Recommended Version:

VIOKACE™ is a combination of porcine-derived lipases, proteases, and amylases. VIOKACE, in combination with a proton pump inhibitor, is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis (b) (4).

Sponsor's Proposed Version:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

(b) (4)

Evaluation: Sections 8.1 and 8.3 should be modified, such that the language is consistent with the labeling for the approved products, Zenpep and Pancreaze (pancrelipase).

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. VIOKACE should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

8.3 Nursing Mothers

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

Sponsor's Proposed Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Evaluation: The statement in this subsection is accurate. However, a minor change is recommended.

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.

1.2 Brief Discussion of Nonclinical Findings

The toxicology information submitted for VIOKACE was published literature related to the VIOKACE excipients: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, stearic acid, colloidal silicon dioxide, and talc.

The acceptable daily intake (ADI) of three of the excipients (microcrystalline cellulose, stearic acid, and talc) was designated as "not specified" through the evaluations performed by the FAO/WHO Joint Expert Committee on Food Additives (JECFA). The designation of "not specified" for ADI is used by JECFA for a food substance of very low toxicity which do not represent a hazard to health. An ADI for a food additive may be characterized as "not specified" on the basis of the available data (chemical, biochemical, toxicological and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect, and the acceptable background levels in food.

Lactose is a natural sugar found in milk that is composed of two linked monosaccharides, glucose and galactose, and is commonly found in infant foods, bakery products, confections, and pharmaceuticals as a diluent and excipient. Lactose

monohydrate meets the specifications for nutritive sweetener (21 CFR part 168.22 and the Food Chemical Codex, Edition V), and according to the Handbook of Pharmaceutical Excipients (Ed. V, 2006), the oral LD_{50} in rats for lactose is > 10 g/kg. Based on the dietary intake of lactose in humans (e.g., 33 g/day based on the USDA recommendation for dairy product consumption), the estimated maximum dose of lactose monohydrate (6.1 g/day in a 60-kg patient) resulting from VIOKACE® administration is not considered to be a safety concern for patients who tolerate lactose. However, clinical studies in lactose intolerant patients have demonstrated clinical symptoms of intolerance following administration of 3-5 g lactose (Bedine et al, Gastroenterology, 65, pg. 735-743, 1973; Gundmand-Hoyer E, Am J Dig Dis, 22(3), pg. 177-181, 1977). This finding suggests a potential for adverse reactions in lactose intolerant patients due to the daily lactose intake that will occur with VIOKACE® administration. The Medical Officer should determine whether this issue needs to be addressed in the labeling.

Both croscarmellose sodium and colloidal silicon dioxide have regulatory information and repeat-dose oral toxicity data which support the estimated maximum daily dose of these excipients from VIOKACE. For croscarmellose sodium, a 90-day oral (dietary) toxicity study in rats was performed using dose levels of 0, 10,000, and 50,000 ppm. 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 no observed adverse effect level (NOAEL) in this study was 50,000 ppm (the highest dose tested), equivalent to 3,922 mg/kg/day in males and 4,712 mg/kg/day in females. Thus, the NOAEL in male rats exceeded the estimated maximum daily dose in humans by 218-fold. To support the safety of colloidal silicon dioxide, the Sponsor cited a 6-month oral (dietary) toxicity study in rats was using fumed hydrophobic silica (FHS) at a dose level of 500 mg/kg/day. There were no treatment-related adverse clinical signs or behavioral changes. In addition, animals treated with FHS showed no significant changes in body weight gain, food consumption, gross pathology or histopathology when compared to control animals. The no observed effect level (NOEL) in this study was ≥ 500 mg/kg/day. Therefore, the results of the 6-month toxicology study using FHS showed that the NOEL in rats exceeded the estimated maximum daily dose of colloidal silicon dioxide in humans by over 27-fold.

Therefore, in addition to the previous human experience, the nonclinical information consisting of repeat-dose oral toxicology studies in rats, regulatory information, and/or the recommended ADI, provide a reasonable assurance of safety for the estimated maximum daily dose of each individual VIOKACE excipient.

2 Drug Information

2.1 Drug

VIOKACE®

2.1.1 CAS Registry Number (Optional)

53608-75-6

2.1.2 Generic Name

Pancrelipase

2.1.3 Code Name

none

2.1.4 Chemical Name

Pancrelipase

2.1.5 Molecular Formula/Molecular Weight

not applicable

2.1.6 Structure

not applicable

2.1.7 Pharmacologic class

Standardized pancreatic enzyme preparation

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 60,716, DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4)

2.3 Clinical Formulation

Immediate-release, non-enteric-coated VIOKACE® 8 Tablets (10,440 USP units lipase) and non-enteric-coated VIOKACE® 16 Tablets (20,880 USP units lipase)

2.3.1 Drug Formulation

Table 1: Composition of VIOKACE® 8 and VIOKACE® 16

Component	Function of Component	VIOKASE® 8 10,440 USP Units Lipase [1] 39,150 USP Units Amylase 39,150 USP Units Protease		VIOKASE® 16 20,880 USP Units Lipase [1] 78,300 USP Units Amylase 78,300 USP Units Protease	
		Amount per Unit	%	Amount per Unit	%
Pancreatic Enzyme Concentrate (b) (4) USP	Active Ingredient				
Microcrystalline Cellulose, NF	(b) (4)				
Croscarmellose Sodium, NF					
Lactose Monohydrate, NF					
Stearic Acid, NF					
Colloidal Silicon Dioxide, NF					
Talc, USP					
Total	-				

(b) (4)

2.3.2 Comments on Novel Excipients

not applicable

2.3.3 Comments on Impurities/Degradants of Concern

none

2.4 Proposed Clinical Population and Dosing Regimen

VIOKACE® will be used for treatment of exocrine pancreatic insufficiency due to chronic pancreatitis (b) (4) (in combination with a proton pump inhibitor). The proposed dosing regimen is as follows:

(b) (4)

(b) (4) **Adults**

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal (b) (4) 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.

(b) (4)

Usually, half of the prescribed VIOKACE® dose for an individualized full meal should be given with each snack. The total daily dosage should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

2.5 Regulatory Background

Clinical development of VIOKACE Tablets has provided safety and efficacy data from one pivotal, placebo-controlled Phase 3 study and one Phase 2b open-label study. In addition, a Phase 2b bioactivity study (Study VIO16IP07-01) has been completed.

3 Studies Submitted

3.1 Studies Reviewed

Preclinical Study	Testing Laboratory	Study #	Lot #	Page
PHARMACOLOGY	Not applicable	Not applicable	Not applicable	11
PHARMACOKINETICS/ TOXICOKINETICS	Not applicable	Not applicable	Not applicable	11
TOXICOLOGY SUMMARIES FOR EXCIPIENTS				12
Microcrystalline Cellulose	Not applicable	Not applicable	Not applicable	12
Croscarmellose Sodium	Not applicable	Not applicable	Not applicable	14
Lactose Monohydrate	Not applicable	Not applicable	Not applicable	15
Stearic Acid	Not applicable	Not applicable	Not applicable	15
Colloidal Silicon Dioxide	Not applicable	Not applicable	Not applicable	16
Talc	Not applicable	Not applicable	Not applicable	17

GENETIC TOXICOLOGY	Not applicable	Not applicable	Not applicable	18
CARCINOGENICITY	Not applicable	Not applicable	Not applicable	18
REPRODUCTIVE TOXICOLOGY	Not applicable	Not applicable	Not applicable	18
SPECIAL TOXICOLOGY STUDIES	Not applicable	Not applicable	Not applicable	19

3.2 Studies Not Reviewed

No studies were submitted.

3.3 Previous Reviews Referenced

none.

4 Pharmacology

4.1 Primary Pharmacology

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.

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

4.2 Secondary Pharmacology

No studies were submitted.

4.3 Safety Pharmacology

No studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

No studies were submitted.

5.1 PK/ADME

No studies were submitted.

5.2 Toxicokinetics

No studies were submitted.

6 General Toxicology

The Sponsor submitted toxicology information on the excipients of the drug product. The excipients in VIOKACE are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, stearic acid, colloidal silicon dioxide, and talc. The submitted information on these excipients was in the form of a summary report, along with reprints of the cited references. The information is reviewed below and listed by individual excipient.

Microcrystalline Cellulose

A 90-day oral (dietary) toxicity study in rats was performed using Avicel RCN-15 (a mixture of 85% microcrystalline cellulose with 15% guar gum) at dose levels of 0 (control), 25,000 or 50,000 mg/kg of diet. A few test animals were noted as having chromodacryorrhea/chromorhinorrhea, but this was not considered to be biologically significant. In the first few weeks the rats increased food consumption, however the body weight gain was unaffected. During the study and at necropsy, there was no evidence of treatment-related changes. Clinical chemistry, hematology and organ weights were unaffected by treatment. Histopathology of 34 organs or tissues, including the gastrointestinal tract and gut-associated lymphoid tissue of the ileum, provided no evidence of microcrystalline cellulose toxicity. The calculated daily consumption of microcrystalline cellulose was 3,769 and 4,446 mg/kg/day for males and females, respectively. The author of the study noted that the no-observed effect level (NOEL) is > 50,000 mg/kg of diet (Freeman, Unpublished Report #I91-1202 from FMC Corporation Toxicology Laboratory submitted to WHO, 1992).

A 90-day oral (dietary) toxicity study in rats was performed using Avicel CL-611 (a mixture of 85% microcrystalline cellulose with 15% sodium carboxymethyl cellulose) at dose levels of 0 (control), 25,000 or 50,000 mg/kg of diet. There were no weight gain differences in the males, however females showed a decrease in weight gain. The decrease of weight gain in females was attributed to a decreased caloric intake. No other adverse effects attributable to the treatment were observed. At necropsy, organ weights of the test groups were normal, with the exception of changes to adrenals of males receiving 50,000 mg/kg of diet and to absolute brain and kidney weights in females receiving 25,000 mg/kg of diet. Histopathology of 36 organs or tissues from the control and high-dose groups, including gastrointestinal tract and gut-associated lymphoid tissue of the ileum, provided no evidence of toxicity of microcrystalline

cellulose. The mean nominal consumptions of Avicel CL-611, averaged over weekly periods, by males and females of the high-dose group ranged from 2,768 to 5,577 and 3,673 to 6,045 mg/kg/day, respectively (Freeman, unpublished report #I92-1711 from FMC Corporation Toxicology Laboratory submitted to WHO, 1992).

In another 90-day oral toxicity study, suspensions of a special, fine particle size, microcrystalline cellulose (median particle size 6 mm) were administered at dose levels of 0 (control), 500, 2,500 or 5,000 mg/kg/day as a 25% suspension in tap water. No treatment-related deaths occurred during the study and the only treatment-related clinical sign was pale feces. There were no toxicologically significant effects in treated animals with respect to body weight, absolute and relative organ weights (5 organs weighed), food consumption, clinical chemistry, hematology, or opthalmoscopic examinations. At study termination, organs and tissues from high-dose and control animals, including multiple sections of intestine with gut-associated lymphoid tissue, were processed for light microscopy and examined under polarized light for the presence of birefringent microcrystalline cellulose particles. In animals that had received 5,000 mg/kg/day, there were no treatment-related lesions detected (36 tissues were examined, including gut-associated lymphoid tissue, liver, lung, spleen and brain), nor were there any macroscopic or microscopic findings of microemboli or granulomatous inflammatory lesions. A lack of birefringent microcrystalline cellulose particles was observed in all organs and tissues from the high-dose group (40 rats). In this study, the NOAEL (no observed adverse effect level) for microcrystalline cellulose in rats was > 5,000 mg/kg/day (Kotkoskie et al, J Anat, 95(Suppl 1), pg. 158-159, 1998).

There were no test article-related effects in embryotoxicity and teratogenicity studies conducted in rats at dietary levels up to 4.6 g/kg/day. Groups of rats were administered 0 (control), 25,000 or 50,000 mg Avicel RCN-15/kg diet (equal to 2.1 and 4.5 g/kg/day, respectively) *ad libitum* on gestation days 6 to 15. In the group receiving 50,000 mg/kg, the food consumption on days 6 to 15 was significantly higher than that of controls (possibly due to increased fiber content). On day 20 of gestation, the dams were killed and the following parameters were studied: number and distribution of implantation sites, early and late resorptions, live and dead fetuses, and corpora lutea. External, visceral and skeletal examinations of the fetuses were also performed. There was no evidence of any adverse effects of the test material on either the dams or the fetuses (Freeman, unpublished report #I91-1213 from FMC Corporation Toxicology Laboratory submitted to WHO, 1992).

In addition, presumed pregnant rats were administered 0 (control), 25,000 or 50,000 mg Avicel CL-611/kg (equal to 2.2 and 4.6 g/kg/day, respectively) diet *ad libitum* on gestation days 6 to 15. The food consumption on days 6 to 15 was significantly higher in the treatment groups compared to the control groups (possibly due to increased fiber content). The parameters studied and examinations performed were the same as in the reproduction study by Freeman (1992) (reviewed above). There was no evidence of any effects on the fetuses, and there was no evidence of a change of sex ratio in the pups or of eye defects. Under the conditions of the study, the maternal and fetal NOEL was > 50,000 mg/kg diet (equal to 4.6 g/kg/day) (Freeman, unpublished report #I92-1712 from FMC Corporation Toxicology Laboratory submitted to WHO, 1994).

Microcrystalline cellulose has been tested in numerous different mutagenicity assays. The Sponsor cited unpublished study reports claiming that microcrystalline cellulose was not genotoxic in the bacterial reverse mutation assay, however test article formulations did produce a heavy precipitate at the highest concentration, 5000 μg/plate (Batt, Unpublished Report #I91-1214 from FMC Corporation Toxicology Laboratory submitted to WHO, 1992). Solubility also affected the L5178Y/TK +/- mouse lymphoma assay, and it was not possible to include concentrations of the test material that were cytotoxic. However, the Sponsor stated that the test article (100 to 1000 μg/ml) was not mutagenic in the L5178Y/TK +/- mouse lymphoma assay (Cifone, unpublished report #I91-1230 from Hazelton Washington Inc. submitted to WHO, 1992). Due to the lack of absorption, there was little exposure of microcrystalline cellulose in the *in vivo* mammalian micronucleus assays. Avicel RCN-15 (5000 mg/kg) was mixed into the diet of male and female ICR mice. Only mice that had consumed all the diet within 10 hours were retained in the study and were sacrificed after 24, 48 or 72 hours. Because one group of control mice had 0 micronuclei per 1000 polychromatic erythrocytes, the comparison with the test group was not valid (Murli, unpublished report #I91-1228 from Hazelton Washington Inc. submitted to WHO, 1992). In addition, Cellulon™ fiber, a cellulose that most closely resembles powdered and microcrystalline cellulose, was tested for genotoxicity in four assays at a wide range of dose levels (up to 5 mg/mL), both with and without metabolic activation. Test results gave no indication that Cellulon™ fiber possessed any genotoxic potential (Schmitt et al, Food Cosmet. Toxicol, 16, pg. 161-163, 1978).

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 was 50,000 ppm, equivalent to 3,922 mg/kg/day in males and 4,712 mg/kg/day in females (Freeman et al, Int J Toxicol, 22(3), pg. 149-157, 2003).

A teratogenicity study of croscarmellose sodium showed no evidence of treatment-related maternal or developmental fetal effects in rats at dietary levels of ≤ 50,000 ppm (average dose of 4,554 mg/kg/day). In this study, groups of rats were fed diets containing 10,000 or 50,000 ppm of croscarmellose sodium on gestation days 6 to 15. Clinical signs were recorded daily, and maternal body weights and food consumption were recorded on days 0, 6, 15, and 20. At necropsy, the dams were examined for gross lesions, number and distribution of implantation sites, early and late resorptions, live and dead fetuses, and corpora lutea. Body weight, sex and external signs were recorded for all fetuses, and half were subjected to visceral examination and half to skeletal examination. No treatment-related deaths occurred during the study and no treatment-related clinical signs were noted. No significant differences in body weights, body weight gain, gravid uterine weights, adjusted weight gains or feed consumption

were noted when comparing treated dams to controls. Mean consumption of test article for dams receiving 10,000 and 50,000 ppm croscarmellose sodium in the diet was 910 and 4,554 mg/kg/day, respectively. No treatment-related differences were noted in the cesarean section parameters. All dams appeared normal at necropsy, and there was no treatment-related effect on the numbers of implants, live and dead fetuses, corpora lutea, or resorptions. No gross lesions were noted during necropsy of the dams and there were no external malformations. The incidence of visceral and skeletal malformations or variations was not affected by ingestion of croscarmellose sodium (Freeman et al, Int J Toxicol, 22(3), pg. 149-157, 2003).

Lactose Monohydrate

There were no toxicity studies submitted.

Stearic Acid

The LD_{50} in rats was reported to exceed 5 g/kg (Opdyke, Foods and Cosmetics Toxicology, 17, pg. 383-388, 1979). The Sponsor submitted chronic oral (dietary) toxicity studies from literature published in the 1950's. These studies included a dietary study, which examined the effect of different fatty acids in chick rations. Five percent stearic acid was fed to 25 chicks of both sexes in a series of experiments that were carried out for periods of 4 to 10 weeks, with the monitoring of body weight changes, feed utilization and analysis of fatty acids in the feces. No signs of toxicity were observed (Sunde, Poultry Sci., 35(2), pg. 362-368, 1956). In an 8-week subchronic feeding study, stearic acid was fed to rats at a level of 50% of their diet. Microscopic examination showed an unusual foreign-body type reaction in fat from rats fed stearic acid. The authors stated that the foreign-body type reaction was probably a response to a relative or absolute excess of saturated long chain fatty acids. Further testing was required to determine the critical ratio that produced this reaction (Herting, Proc Soc Exp Biol Med, 98(2), pg. 347-348, 1958).

In addition, a 24-week dietary study was carried out in a group of rats using a diet containing 50% stearic acid. Rats were sacrificed at 8-week intervals and examined microscopically. All of the stearic acid-fed rats (5/5) sacrificed after 24 weeks had foreign body type reactions in perigonadal fat. The diet of surviving rats at 24 weeks was switched to 20% corn oil and treatment continued for another 24 weeks, with subsequent examination of tissue from rats killed at 8-week intervals. The control group, which was fed a diet containing lard or triacetin, did not develop lipogranuloma during the entire 48-week test period. Replacement of the stearic acid diet with one containing 20% corn oil led to prompt diminution and eventual disappearance (complete after 24 weeks) of the lipogranuloma, leading investigators to conclude that the causative agent of lipogranulomas was dietary imbalance (Herting, Tocicol Appl Pharmacol, 1, pg. 505-514, 1959).

Overall, it is important to note that since the studies summarized above were published in the 1950's, the information may be of limited value for the purpose of safety assessment.

Stearic acid at concentrations of 50 μg/plate was not genotoxic in the bacterial reverse mutation assay (Okamoto, J Am Coll Toxicol, 6, pg. 321-401, 1987).

Colloidal Silicon Dioxide

A 6-month oral (dietary) toxicity study in rats was performed using fumed hydrophobic silica (FHS) at a dose level of 500 mg/kg/day. A small subset of animals was observed for an additional 3 weeks without administration of test substance in the diet (recovery period). During the treatment period of 6 months, neither clinical symptoms nor behavioral changes were seen in the treated animals. One 500 mg/kg male died, and one control male and female animal died. In the 500 mg/kg male, the cause of death was due to a lung infection. In the female control animal, enteritis followed by cachexia was noted as the cause of death. The male control animal also showed cachexia, but the cause of death could not be determined. No significant differences in food consumption or weight gain were found in the treatment and control groups. Determination of the hematological parameters during treatment and after the recovery period revealed slight, but statistically insignificant differences between the treatment and control groups. Macroscopic examination at necropsy and the comparison of organ weights revealed no abnormal or treatment-related effects. The histopathological examinations revealed an increased lipid content in the fasciculate and zone fasciculate of the adrenal glands. This effect appeared to resolve during the 3-week recovery period. This slight progressive transformation in the adrenal was reversible and attributed to chronic stress. No other differences were found between the treatment and control groups. The repeated oral administration of FHS produced no significant treatment-related effects in rats. The NOEL of the study was 500 mg/kg/day (Lewinson et al, Reg Toxicol Pharmacol, 20, pg. 37-57, 1994).

In addition, the above mentioned 6-month oral (dietary) toxicity study in rats also examined test article-related effects on developmental and reproductive toxicity. Control females and treatment group females dosed with 500 mg/kg/day FHS for 6 months and were mated with males at weeks 8 and 17 of the 6-month toxicity study (treatment was continued during the breeding experiments). There were no changes in behavior or appearance in the parental treatment and control groups. The body weight gain and food consumption were comparable in the treatment and control groups. No differences were seen in the hematological parameters or in organ weights at autopsy during pathological examination. Reproductive performance was not altered in the treated rats. The results of the pathological examination of the parents were comparable to those found in the simultaneously performed chronic 6-month study discussed above.

After the first mating procedure at week 8, 15 rats became pregnant, 6 in the control group and 9 in the treatment group. Seven dams from each group were pregnant after the second mating (post week 17). There were no treatment-related effects in the litter size or birth weights. This was true for all parameters evaluated. Physical or behavioral abnormalities were not observed, and runts did not occur in either breeding experiment.

Hematomas on the heads of three pups were seen in the litter of one control animal. The development of the progeny during lactation was without adverse effects. The weight gains of both generations were normal. After 4 weeks, the pups were examined for gross pathology and no treatment-related changes were found. Therefore, the NOEL for developmental and reproductive toxicity in this study was 500 mg/kg/day (Lewinson et al, Reg Toxicol Pharmacol, 20, pg. 37-57, 1994).

Neither silicon dioxide nor hydrophobic silicas are soluble in water, therefore a toluene extract of FHS was tested for mutagenicity. The toluene extract from FHS was not genotoxic in the bacterial reverse mutation assay when tested at doses of 5 to 1580 µg/plate (Lewinson et al, Reg Toxicol Pharmacol, 20, pg. 37-57, 1994).

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 1,600 mg/kg/day, and in hamsters using oral administration of 1,200 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).

6.1 Single-Dose Toxicity

No studies were submitted. For information about excipients in VIOKACE, see “General Toxicology” (section 6).

6.2 Repeat-Dose Toxicity

No studies were submitted. For information about excipients in VIOKACE, see “General Toxicology” (section 6).

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames Test)

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

7.4 Other Genetic Toxicity Studies

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

8 Carcinogenicity

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

9.2 Embryonic Fetal Development

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

9.3 Prenatal and Postnatal Development

No studies were submitted. For information about excipients in VIOKACE, see "General Toxicology" (section 6).

10 Special Toxicology Studies

No studies were submitted.

11 Integrated Summary and Safety Evaluation

The proposed indication for VIOKACE® (pancrelipase) Tablets, in combination with a proton pump inhibitor, is treatment of exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (b) (4). Inadequate secretion of pancreatic enzymes in patients with EPI causes maldigestion, leading to inadequate absorption of fats, proteins, vitamins, and carbohydrates. Clinical steatorrhea (increased fat excretion) is the most important digestive malfunction in pancreatic exocrine insufficiency and may be associated with severe weight loss and malabsorption of the lipid-soluble vitamins A, D, E, and K. Conversely, the resultant steatorrhea and creatorrhea (increased protein excretion) can be reversed if lipase and trypsin activities can be increased through the administration of exogenous enzymes to 10% of normal levels.

Complete correction of steatorrhea is rarely achieved. However, with appropriate treatment, it can be controlled to restore a patient's fat absorption to an acceptable level, resulting in weight gain and reduction of diarrhea. The predominant treatment for malabsorption involves the exogenous replacement of lipase through the use of pancreatic enzymes that are isolated from porcine sources. Similar to endogenous pancreatic enzymes, exogenous enzymes, delivered through the oral administration of pancreatic enzyme supplements, hydrolyze fats, proteins and carbohydrates into smaller units to facilitate absorption.

VIOKACE® Tablets are orally administered, immediate-release, non enteric-coated tablets of porcine pancreatic enzyme concentrate, consisting of pancreatic lipases, amylases and proteases as well as other pancreatic enzymes. VIOKACE® is available in two strengths, VIOKACE® 8 and VIOKACE® 16. VIOKACE is intended to provide an exogenous source of digestive enzymes for patients whose endogenous production is insufficient for normal digestion. The enzymes in VIOKACE catalyze the hydrolysis of fats into glycerol and fatty acids, starch into dextrins and sugars, and protein into peptides and amino acids.

Lipases are a group of enzymes belonging to the esterase family that can range in molecular weight from 50 kDa-3,000 kDa which catalyze the hydrolysis of fats into glycerol and free-fatty acids. Pancreatic lipase and co-lipase, together with several other lipolytic enzymes (pancreatic phospholipase A2, pancreatic cholesterolesterase,

lingual lipase, gastric lipase and human breast milk lipase), are involved in the complex process of intestinal lipid digestion (Lebenthal et al, Pancreas, 9(1), pg. 1-12).

Amylases are a group of enzymes belonging to the α–endoamylase family with a molecular weight of approximately 45 kDa which hydrolyze starch into dextrins and sugars. Amylases catalyze the hydrolysis of α-1→4 glucosidic linkages of polysaccharides such as glycogen, starch, or their degradation products.

Proteases have proteolytic activity and hydrolyze proteins into peptides and amino acids. The proteolytic enzymes trypsin, chymotrypsin, and the carboxypeptidases are the most abundant enzymes in pancreatic juice. Trypsin acts on lysyl and arginyl bonds of peptide chains and hydrolyzes esters and amides. Chymotrypsin is selective for peptide bonds with aromatic or large hydrophobic side chains on the carboxyl side of this bond. Chymotrypsin also catalyzes the hydrolysis of ester bonds. Carboxypeptidases A and B are exopeptidases which cleave the carboxy-terminal amino acid of peptides (Lebenthal et al, Pancreas, 9(1), pg. 1-12).

VIOKACE® Tablets are not enteric-coated, therefore this product releases pancreatic enzymes in the acidic environment of the stomach, exposing enzymes to conditions which may result in their inactivation (lipases are denatured at pH < 5). Acid-suppressing agents are known to increase stomach pH and reduce the inactivation of lipase in the stomach, resulting in higher delivery of lipase to the duodenum for lipid digestion and absorption. Therefore, the proposed indication for VIOKACE Tablets includes the co-administration of a proton pump inhibitor for the treatment of EPI due to chronic pancreatitis (b) (4)

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. VIOKACE is a pancreatic enzyme preparation that has been on the U.S. market as a prescription drug since 1949. Also, various pancrelipase products have been marketed since prior to modern drug law (i.e. before 1938). Therefore given the long history of pancrelipase use in patients with EPI, toxicity studies of pancrelipase are not needed to support approval. The Sponsor submitted the following nonclinical information: pharmacology, pharmacokinetic, and toxicology summaries of pancreatic enzymes, and toxicology summaries of individual excipients. In addition, the Sponsor submitted safety and efficacy data from a placebo-controlled Phase 3 study and a Phase 2b bioactivity study.

The Sponsor's proposed labeling recommends a starting dose of 500 (b) (4) lipase units/kg/meal with titration to not more than 2,500 lipase units/kg/meal (or a maximum of 10,000 lipase units/kg/meal). (b) (4)

For the purpose of estimating the maximum daily dose of excipients, it is assumed that the maximum recommended dose is (b) (4) lipase U/kg/meal and that patients would consume 3.5 meals/day (i.e. (b) (4) equivalent to (b) (4) pancrelipase). The Sponsor provided information about the excipient content for each tablet strength and estimates of the maximum daily dose levels of each excipient for both tablet strengths, based on administration of 2,500 (b) (4) lipase U/kg/meal. Dosing of VIOKACE 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.

The maximum daily dose level for each excipient was estimated using the excipient levels from VIOKACE® 8 and VIOKACE® 16, an assumed maximum daily dose of (b) (4) lipase U/kg/day, and a bodyweight of 60 kg. Based on the calculated daily exposures of excipients, the Sponsor noted that the "total daily intake of excipient for each dosage form is greater than the maximum previously accepted level for a single dosage form when administered at 2,500 (b) (4) lipase units/kg/meal." Specifically, the maximum daily dose level for each VIOKACE excipient is greater than the previously accepted maximum daily oral intake (based on information in the FDA Inactive Ingredient Database). Therefore, the Sponsor provided summaries of the nonclinical and regulatory information to assess the safety of the following excipients; microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, stearic acid, colloidal silicon dioxide, and talc.

Microcrystalline cellulose, a naturally occurring substance, is derived from a special grade of α-cellulose and is a highly crystalline particulate cellulose consisting primarily of crystallite aggregates obtained by removing amorphous regions of a purified cellulose source material by hydrolytic degradation. Microcrystalline cellulose is metabolically inert and not absorbed systemically following oral administration, however consumption of large quantities of cellulose may cause a laxative effect. As a naturally occurring substance, microcrystalline cellulose has many applications in pharmaceuticals, foods, papers and structural composites. Since VIOKACE is intended for long-term use, chronic toxicity studies are needed for safety assessment of the expected maximum daily dose. However, the only available toxicity studies are 90-day dietary or repeat-dose oral toxicity studies using microcrystalline cellulose or compounds containing specific levels of microcrystalline cellulose (i.e. Avicel RCN-15 and Avicel CL-611). In three separate 90-day toxicology studies in rats, there were no treatment-related deaths or clinical signs. In addition, animals treated with microcrystalline cellulose showed no significant changes in body weight gain, food consumption, gross pathology or histopathology when compared to control animals. The NOAEL from the studies was approximately 5,000 mg/kg/day (the highest dose tested).

For patients treated with VIOKACE, the maximum daily dose of microcrystalline cellulose is estimated to be (b) (4), equivalent to (b) (4) in a 60-kg patient. Thus, the results of the 90-day toxicology studies showed that the NOAEL in rats exceeded the estimated maximum daily dose in humans by 24-fold. For a nonclinical safety assessment of any drug or excipient in which long-term use is expected (i.e.

longer than three months), toxicity studies of 6 months duration in a rodent species and 9 months in a non-rodent species are generally needed. Although such studies are not available for microcrystalline cellulose, 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 24-fold.

Microcrystalline cellulose is an ingredient usually used as a food additive and is an unlisted generally-recognized-as-safe (GRAS) substance in the Food Additive Status List by the FDA. In a report submitted to the WHO by Cantox Inc in 1993, the mean intake of dietary microcrystalline cellulose in the U.S. was estimated to range from 2.7 g/person per day (children 2 years of age) to 5.1 g/person per day (young adult males). The FAO/WHO Joint Expert Committee on Food Additives recommended that the acceptable daily intake (ADI) of microcrystalline cellulose be listed as “not specified”, a term that is applied to a food substance of very low toxicity. Thus, the 90-day oral toxicology studies in rats, previous human experience, regulatory information, and the recommended ADI provide a reasonable assurance of safety for the estimated maximum daily dose of microcrystalline cellulose resulting from VIOKACE administration.

Croscarmellose sodium, a substance widely used in oral pharmaceutical formulations, is a cross-linked form of sodium carboxymethylcellulose or cross-linked cellulose gum. Croscarmellose sodium is manufactured by acidifying an aqueous suspension of sodium carboxymethyl cellulose (NaCMC) and heating the suspension to achieve cross-linking. For patients treated with VIOKACE, the maximum daily dose of croscarmellose sodium is estimated to be (b) (4) equivalent to (b) (4) in a 60-kg patient. Since VIOKACE 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 in this study was 50,000 ppm (the highest dose tested), equivalent to 3,922 mg/kg/day in males and 4,712 mg/kg/day in females. Thus, the NOAEL in male rats exceeded the estimated maximum daily dose in humans by 218-fold. For a nonclinical safety assessment of any drug or excipient in which long-term use is expected (i.e. longer than three months), toxicity studies of 6 months duration in a rodent species and 9 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 218-fold.

NaCMC, the precursor of croscarmellose sodium, has a long history of safe use as a pharmaceutical excipient, and is accepted by the FDA as a multipurpose GRAS food substance (21 CFR part 182.1745). NaCMC is also listed as a thickener/stabilizer (Food Chemicals Codex, Edition V). Croscarmellose sodium meets the specifications for an “additive permitted for use in food in general unless otherwise specified under GMP” as detailed in the 2005 General Standards for Food Additives of the Food and Agriculture Organization’s Codex Alimentarius. 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 1 g/day, based on a 60-kg bodyweight. Thus, the 90-day oral toxicology study in rats, regulatory information, and the previous human experience provide a reasonable assurance of safety for the estimated maximum dose of croscarmellose sodium resulting from administration of VIOKACE.

Lactose is a natural sugar ($C_{12}H_{22}O_{11}$, disaccharide) found in milk that is composed of two monosaccharides, glucose and galactose. Bovine lactose is commonly used in infant foods, bakery products, confections, and pharmaceuticals as a diluent and excipient. Little or no animal toxicity information for lactose is available. However, according to the Handbook of Pharmaceutical Excipients (Ed. V, 2006), the oral LD_{50} in rats for lactose is >10 g/kg. In addition, lactose monohydrate meets the specifications for nutritive sweetener (21 CFR part 168.22 and the Food Chemical Codex, Edition V).

The submitted nonclinical studies are not sufficient to provide a reasonable assurance of safety for the estimated maximum daily dose of lactose monohydrate resulting from VIOKACE administration. For patients treated with VIOKACE, the maximum daily dose of lactose monohydrate is estimated to be (b) (4) equivalent to (b) (4) in a 60-kg patient. The USDA (United States Department of Agriculture) Center for Nutrition Policy and Promotion recommends 3 cups of milk or equivalent dairy consumption per day for adult males and females. Based on this recommendation, the average American would consume at least 33 g of lactose per day, which is equivalent to 550 mg/kg/day for a 60-kg individual. Therefore, the USDA recommendation for dairy product consumption provides a daily lactose intake that is over 5-fold greater than the maximal daily intake of lactose monohydrate from VIOKACE®. The USDA recommendation for dairy consumption is not intended to represent a safe limit for lactose consumption. However, since lactose is a common ingredient in dairy products, the USDA recommendation does provide a context for evaluation of lactose intake from VIOKACE®. There is no data available that supports an upper limit for lactose intake, and we are not aware of any recommended limit from public health authorities. However, adverse reactions to lactose (e.g., diarrhea) are known to occur in individuals who are lactose intolerant, due to a deficiency of the intestinal enzyme lactase. Approximately 10-20% of lactose-intolerant individuals, in two studies, showed clinical symptoms of intolerance after ingestion of 3-5 g of lactose (Bedine et al, Gastroenterology, 65, pg. 735-743, 1973; Gundmand-Hoyer E, Am J Dig Dis, 22(3), pg. 177-181, 1977). Given the daily intake of lactose that occurs with the daily consumption of dairy products as recommended by the USDA, the estimated maximum dose of lactose monohydrate resulting from administration of VIOKACE® is not considered to be a safety concern for patients who tolerate lactose. However, given the amount of daily lactose intake that will occur with VIOKACE® administration, particularly at the upper end of the recommended dose range, there appears to be a potential for adverse reactions in lactose intolerant patients. We defer to the Medical Officer for determination of whether this issue needs to be addressed in the labeling.

Stearic acid, also known as octadecanoic acid, is a type of saturated fatty acid that is derived from many animal and vegetable fats and oils. Common sources of stearic acid

are hydrogenated canola, soyabean and cottonseed oil. Most of the toxicity studies on stearic acid were conducted in the 1950's, thus the toxicology information presented from those studies are of limited value for the purpose safety assessment. However, experiments in rats have shown that stearic acid is poorly absorbed. The LD_{50} in rats is reported to exceed 5 g/kg, and there were no signs of toxicity in subchronic toxicity studies in chicks (4-10 weeks of treatment) and rats (up to 30 weeks of treatment).

The submitted nonclinical studies are not sufficient to provide a reasonable assurance of safety for the estimated maximum daily dose of stearic acid resulting from VIOKACE administration. However, stearic acid meets the specifications for a GRAS substance (21 CFR part 184.1090) when used as a flavoring agent and adjuvant and at food levels not exceeding current good manufacturing practices. In addition, stearic acid is listed in the Food Chemicals Codex, Edition V as a food additive, and the FAO/WHO Joint Expert Committee on Food Additives recommended that the ADI of stearic acid be listed as "not specified", a term used to describe flavoring agents that are of no safety concern at current levels of intake. For patients treated with VIOKACE, the maximum daily dose of stearic acid is estimated to be (b) (4), equivalent to (b) (4) in a 60-kg patient. The cited regulatory information provides a reasonable assurance of safety for the estimated maximum dose of stearic acid resulting from administration of VIOKACE®.

Silicon dioxide occurs ubiquitously in the environment and has been used medicinally for years. Furthermore, silicon dioxide is manufactured in several forms including an anti-caking and thickening agent for food and drugs. There are several different classifications of silicon dioxide based on particle surface chemistry. Colloidal silica (b) (4). To assess the safety of the excipient, the Sponsor submitted a 6-month oral (dietary) toxicity study in rats using fumed hydrophobic silica (FHS) at a dose of 500 mg/kg/day. There were no treatment-related adverse clinical signs or behavioral changes. In addition, animals treated with FHS showed no significant changes in body weight gain, food consumption, gross pathology or histopathology when compared to control animals. Therefore, the NOEL in the 6-month oral (dietary) toxicity study in rats was ≥ 500 mg/kg/day. For patients treated with VIOKACE, the maximum daily dose of colloidal silicon dioxide is estimated to be (b) (4), equivalent to (b) (4) in a 60-kg patient. Thus, the results of the 6-month toxicology study showed that the NOEL in rats exceeded the estimated maximum daily dose in humans by over 27-fold. For a nonclinical safety assessment of any drug or excipient in which long-term use is expected (i.e. longer than three months), toxicity studies of 6 months duration in a rodent species and 9 months in a non-rodent species are generally needed. Although a long-term toxicity study in a non-rodent species was not available for colloidal silicon dioxide, some assurance of safety can be derived from the 6-month oral (dietary) toxicity study in rats, given that the NOEL exceeded the estimated maximum human dose by over 27-fold.

Silicon dioxide is considered a GRAS substance and is used as a food additive, which meets the specifications for an anti-caking agent in foods at a maximum level of 2% by weight (21 CFR part 172.480 and the Food Chemical Codex, Edition V). It also meets

the specifications for an “additive permitted for use in food in general unless otherwise specified under GMP” as detailed in the 2005 General Standards for Food Additives of the Food and Agriculture Organization’s Codex Alimentarius. Thus, the 6-month oral toxicology study in rats and regulatory status of this excipient provide a reasonable assurance of safety for the estimated maximum daily dose of colloidal silicon dioxide resulting from VIOKACE administration.

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 VIOKACE is estimated to be (b) (4), equivalent to (b) (4) 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 nonclinical studies are not sufficient to provide a reasonable assurance of safety for the estimated maximum daily dose of talc resulting from VIOKACE 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 FAO/WHO Joint 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. Thus, the previous human experience, regulatory information, and the recommended ADI provide a reasonable assurance of safety for the estimated maximum daily dose of talc resulting from VIOKACE administration.

12 Appendix/Attachments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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

/s/

NIRAJ R MEHTA
06/29/2010

DAVID B JOSEPH
06/29/2010
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22,542 **Applicant:** Axcan Pharma US, Inc. **Stamp Date:** 10/30/09

Drug Name: Viokase® (Pancrelipase) **NDA/BLA Type:** Original

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		This question is not applicable to this drug, which is a porcine-derived pancreatic enzyme product (PEP). For porcine-derived PEPs, the Agency requirement for nonclinical information is limited to safety information on the excipients. The needed information may not require a complete set of nonclinical studies for each excipient. The submitted information is adequate for review.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?		X	This question is not applicable. See comment for question 4.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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

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

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

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

No potential review issues have been identified at this time.

Reviewing Pharmacologist	Date
David B. Joseph	December 9, 2009
Team Leader/Supervisor	Date

Note: This application will be reassigned to a primary reviewer.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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

/s/

DAVID B JOSEPH
12/09/2009