CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUN TO ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-542/N-000
Submission Date:	10/08/10 (Response to Agency's review comment)
Brand Name:	Viokace
Generic Name:	Pancreatic Enzyme
Formulation:	Immediate Release (IR) Oral Tablets
Strength:	8 (10,400 USP units of pancrelipase activity) and 16 (20,800 USP units of pancrelipase activity)
Sponsor:	Axcan
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

On 10/30/09, Axcan submitted for review NDA 22-542 (N-000) for Viokace 8 and 16 IR tablets which are (b) (4). The sponsor employed a new assay method, UV spectroscopy at 280 nm, to monitor the dissolution of the total protein which includes lipase, amylase, protease, and any impurities. The proposed dissolution methodology and specifications are shown below.

Apparatus:	II (Paddle) with 50 rpm
Medium:	Phosphate buffer, pH 4.5, at 37ºC
Detection:	UV at 280 nm (Lipase Assay Method No. AXC-030)
Specification:	Q= (b) (4) at (b) (4)

The higher strength was used clinically and the biowaiver request for the Viokace8 tablet was reviewed and granted on 09/28/10. The following review comment was sent to the sponsor on 10/05/10. On 10/08/10, the sponsor responded and agreed the following revisions for implementations.

Change **Specification**:	From Q= (b) (4)	at (b) (4)
	To Q= (b) (4)	at 45 min

RECOMMENDATION

From the Biopharmaceutics perspective, the 10/08/10 submission is acceptable. No further comments are to be sent to the sponsor.

10/12/10

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

Date

10/12/10

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

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

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

/s/

TIEN MIEN CHEN
10/12/2010

PATRICK J MARROUM
10/12/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-542/N-000
Submission Date:	10/30/09, 03/22/10, and 07/12/10
Brand Name:	Viokace
Generic Name:	Pancreatic Enzyme
Formulation:	Immediate Release (IR) Oral Tablets
Strength:	8 (10,400 USP units of pancrelipase activity) and 16 (20,800 USP units of pancrelipase activity)
Sponsor:	Axcan
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic, and proteolytic activities. The active ingredient, pancrelipase, is monographed in the USP and is obtained by extraction mostly from hog pancreata. PEPs (pancreatic enzyme products) were developed before the Food and Drug Administration (FDA) approval requirements for NDAs enacted in 1938. Since 2004, upon request by the Agency, NDAs for PEPs had been submitted and have been reviewed and approved.

Pancrelipase is an enzyme therapy for the treatment of steatorrhea secondary to pancreatic enzyme insufficiency (PEI), in disorders such as cystic fibrosis or chronic pancreatitis. Pancrelipase is acid labile, so most of the PEPs contain enteric-coated pancrelipase minitablets or granules within the capsules for oral administration. Pancreatic enzymes are not materially absorbed by the gastrointestinal tract.

On 10/30/09, Axcan submitted NDA 22-542 (N-000) for Viokace IR tablets for review. The sponsor developed Viokace as an IR oral tablet, therefore, it is to be given with a PPI (proton pump inhibitor). The sponsor is seeking approval for 2 tablet strengths, Viokace8 (10,400 USP units of lipase) and Viokace16 (20,800 USP units of lipase). These two tablet strengths are (b) (4).

The sponsor only tested the highest strength, Viokace16 tablet, in the clinical trials and in the bioactivity (*in vivo* intubation) study. The bioactivity study is currently under review by the Office of Clinical Pharmacology (OCP). The biowaiver request (for Viokace8 tablets), dissolution development report, comparative dissolution data, the proposed dissolution specification, and the responses (submitted on 03/22/10 and 07/12/10) to Agency's information requests are reviewed here.

The proposed dissolution methodology and specifications are shown below.

Apparatus:	II (Paddle) with 50 rpm
Medium:	Phosphate buffer, pH 4.5, at 37ºC
Detection:	UV at 280 nm (Lipase Assay Method No. AXC-030)
Specification:	Q (b) (4) at (b) (4)

The sponsor employed a new assay method, UV spectroscopy at 280 nm, to monitor the dissolution of the total protein which includes lipase, amylase, protease, and any impurities. The assay method validation report is reviewed and found acceptable, however, unlike the USP method, the above UV method is not specific per se for lipase activity.

A teleconference with the sponsor was held on 08/11/10 to discuss further the appropriateness of using the UV spectroscopic assay method at 280 nm to monitor the dissolution of total protein in the Viokace tablet at times.

In the 09/23/10 internal meeting, it was concluded that the UV spectroscopic assay method at 280 nm is considered acceptable under the assumption that since this is an IR tablet product, (b) (4)

The biowaiver request for the Viokace8 tablet is granted since 1). The two strengths are (b) (4) and 2). The mean dissolution profiles are similar with most of the f2 values being between 50 and 100. The proposed dissolution specification (Q= (b) (4) at (b) (4)), however, needs to be revised.

RECOMMENDATION
From the Biopharmaceutics perspective, the biowaiver for the lower strength (Viokace8 IR tablet) is granted. The following comment is to be sent to the sponsor.

COMMENT: (Needs to be conveyed to the sponsor)
Your proposed dissolution specification needs to be revised as shown below.

Change **Specification**: From Q (b) (4) at (b) (4)
To Q (b) (4) at 45 min

BACKGROUND

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic and proteolytic activity. The active ingredient, pancrelipase, is monographed in the USP and is obtained by extraction mostly from hog pancreata. PEPs (pancreatic enzyme products) were developed before the Food and Drug Administration (FDA) approval requirements for NDAs enacted in 1938. Before 2004, the PEPs on the US market were not reviewed and approved under NDAs by the FDA. In 2004, FDA requested manufacturers of PEPs to submit an NDA for approval of these products. Since 2004, 3 PEPs have been approved (under NDAs) for the US market.

Pancrelipase is an enzyme therapy for the treatment of steatorrhea secondary to pancreatic enzyme insufficiency, in disorders such as cystic fibrosis or chronic pancreatitis. Pancrelipase is acid labile, so most of the PEPs contain enteric-coated pancrelipase minitablets or granules within the capsules for oral administration. Pancreatic enzymes are not materially absorbed by the gastrointestinal tract.

CURRENT SUBMISSION

On 10/30/09, Axcan submitted NDA 22-542 (N-000) for Viokace IR tablets for review. The sponsor developed Viokace as an IR oral tablet, therefore, it is to be given with a PPI (proton pump inhibitor). The sponsor is seeking approval for 2 tablet strengths, Viokace8 (10,400 USP units) and Viokace16 (20,800 USP units) in terms of lipase activity.

The sponsor only tested the highest strength, Viokace16 tablets, in the clinical trials and in the bioactivity study No. VIO16IP07-01. The bioactivity study is under review by the Office of Clinical Pharmacology (OCP).

Per information request in the 74-day letter, the sponsor submitted on 03/22/10, 1). The biowaiver for Viokace8 tablets, 2). Dissolution development report (No. RE-031210-01), 3). Comparative dissolution data, and 4). Revisions to the proposed dissolution specifications. The biowaiver and the comparative dissolution data are reviewed here

FORMULATION COMPARISONS

The formulation/composition of Viokace 8 and 16 tablets are shown below.

Table 1. The Composition/Formulation of Viokace 8 and 16 Tablets

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)

(b) (4)

The above two tablet strengths are (b) (4).

DISSOLUTION METHODOLOGY AND SPECIFICATION

The sponsor proposed an assay method for pancrelipase drug product using spectroscopic UV detection method (at 280 nm) and consulted in 2006 with the Division of Therapeutic Protein (DTP)/Office Pharmaceutics Science (OPS) of FDA. The sponsor stated that the UV spectroscopy would be used to quantify total protein release. The Agency responded that 1). The proposed dissolution medium, phosphate buffer at pH 4.5, would be acceptable and 2). The proposed analytical method using a UV detection would also be acceptable assuming that the tablet's completely dissolved. If the tablet is not completely dissolved, assays to measure the activity of amylase, lipase, and protease should be used.

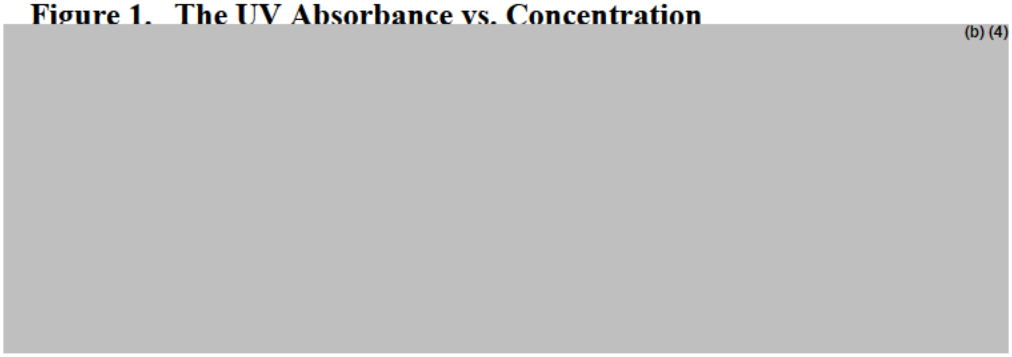
The sponsor employed the above UV spectroscopic assay method at 280 nm to monitor the dissolution of the total protein (which includes lipase, amylase, protease, and impurities). The proposed dissolution methodology and specifications for Viokace8 and Viokace16 tablets are shown below.

Apparatus: II (Paddle) with 50 rpm
Medium: Phosphate buffer, pH 4.5, at 37ºC
Detection: UV at 280 nm
Specification: Q= (b) (4) at (b) (4)

The standard curves at 20%, 40%, 60%, 80%, 100% and 120% of concentration were prepared and tested for UV absorbance. The results are shown below. Please see UV assay method validation report for details.

Figure 1. The UV Absorbance vs. Concentration

(b) (4)



A teleconference with the sponsor was held on 08/11/10 to discuss further the appropriateness of using the UV spectroscopic assay method at 280 nm to monitor the dissolution of the total protein in the Viokace tablet.

An internal meeting was held on 09/23/10 regarding the use of the UV method. It is concluded at the end of the internal meeting that the UV spectroscopic assay method at 280 nm is considered acceptable under the assumption that since this is an immediate release tablet product (b) (4)

Results of Dissolution Testing for Biowaiver:

(b) (4)

(b) (4)

The f2 values calculated are shown mostly between 50 and 100 indicating similarity between the Viokace8 and Viokace16 tablets;

- 60.0, 56.1, 67.7 for Viokace8 IR tablet (lot 116242A) vs. (Viokace16 IR tablet lots, 116659A, 117123A, and 117128A, respectively).
- 55.2, 51.4, 61.4 for Viokace8 IR tablet (lot 116235A) vs. (Viokace16 IR tablet lots, 116659A, 117123A, and 117128A, respectively).
- 51.7, 48.1, 56.5 for Viokace8 IR tablet (lot 116966A) vs. (Viokace16 IR tablet lots, 116659A, 117123A, and 117128A, respectively).

Note: Appendix 1 includes the summary of the dissolution development report for other pH, rotating speeds tested. Please see Appendix 1 for details.

Reviewer's Comments:

1. It was concluded in the 09/23/10 internal meeting that the UV spectroscopic assay method at 280 nm used for monitoring the dissolution of lipase is considered acceptable under the assumption that since this is an IR tablet product, (b) (4)

[redacted] However, unlike the USP method, the above UV method is not specific per se for lipase activity.

2. The biowaiver request for the Viokace8 tablet is granted since 1). The two strengths show [redacted] and 2). The mean dissolution profiles are similar with most of the f2 values being between 50 and 100.

3. The proposed dissolution specification needs to be revised as shown below.

   Change **Specification**: From Q [redacted] at [redacted]
   To Q [redacted] at 45 min

Tien-Mien Chen, Ph.D. 09/28/10
Reviewer Date
ONDQA Biopharmaceutics

Patrick Marroum, Ph.D. 09/28/10
ONDQA Biopharmaceutics Date

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

NDA 22-542 for Viokace (Pancrelipase Enzyme), Viokace8 and Viokace 16

Appendix 1

2 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Summary of Dissolution Development Report

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

/s/

TIEN MIEN CHEN
09/28/2010

PATRICK J MARROUM
09/28/2010

Clinical Pharmacology Review

NDA:	22-542
Type of submission:	Original Submission
Brand Name:	Viokase
Generic Name:	Pancrelipase
Sponsor:	Axcan
Submission date:	10/29/09
PDUFA Goal date:	08/30/10
Priority:	Standard (10 months)
Clinical Division:	Division of Gastroenterology Products
OCP Division:	DCP III
Primary Reviewer:	Lanyan Fang, Ph.D.
Secondary Reviewer:	Jang-Ik Lee, Pharm.D, Ph.D.
Dosage form and Strength:	Non-enteric coated tablets, Viokase 8 (10440 units of lipase) and Viokase 16 (20880 units of lipase)
Route of administration:	Oral
Indication:	Treatment of patients with exocrine pancreatic insufficiency caused by chronic pancreatitis, (b) (4)

Table of Contents

1. Executive Summary 2
- 1.1 Recommendation..... **2**
- 1.2 Phase IV Commitments..... **2**
- 1.3 Summary of Clinical Pharmacology and Biopharmaceutical Findings..... **3**

2. Question Based Review 4
- 2.1 General Attributes..... **4**
- 2.2 General Clinical Pharmacology..... **5**
- 2.3 Intrinsic Factors..... **5**
- 2.4 Extrinsic Factors..... **5**
- 2.5 General Biopharmaceutics..... **5**
- 2.6 Analytical Section..... **5**

3. Detailed Labeling Recommendations..... 7

1. Executive Summary

Viokase (pancrelipase) and several other pancreatic enzyme products are currently on the market without FDA approval. Axcan submitted this original New Drug Application (NDA) for Viokase (pancrelipase) tablets on 10/29/2009.

Viokase tablets are non-enteric coated pancreatic enzyme preparation, pancrelipase, which is a purified extract of porcine exocrine pancreatic enzymes composed of lipase, amylase and protease. The pancreatic enzymes in Viokase when administered with a proton pump inhibitor (PPI) are released in the duodenum. The released enzymes 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 as a replacement for digestive enzymes physiologically secreted by the pancreas. Viokase is indicated for exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (b) (4)

An optional intra-division level Clinical Pharmacology briefing was held on March 25, 2010.

1.1 Recommendations

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

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Studies Conducted and Reviewed

This NDA application is supported by safety and efficacy data from one pivotal, placebo controlled Phase III study and one Phase IIb open-label study. In addition, a Phase IIb bioactivity study has been completed to assess the bioavailability, which is the subject of this clinical pharmacology review.

Overview of Clinical Pharmacology and Biopharmaceutics:

An open-label two-way cross-over study (VIO16IP07-01) was conducted to evaluate the intraduodenal delivery of lipase, protease and amylase from administration of Viokase 16 in chronic pancreatitis subjects with exocrine pancreatic insufficiency (see Section 2.2).

In the per protocol (PP) population, the cumulative activity of lipase (p=0.0034), trypsin (p=0.0017), and amylase (p=0.0188) recovered during the 2-hour perfusion/aspiration

was statistically significantly greater after administration of Ensure Plus® with Viokase 16 as compared to administration of Ensure Plus® alone. A summary of the enzyme activity ratios and the percent recovery is presented below (Table 1):

Table 1. Summary of Total Enzyme Activity Ratio and Percent Recovery

Effect	Ratio (Based on Observed Values)	% Recovery
Total Lipase Activity	1.91	64.1%
Total Trypsin Activity	4.80	29.2%
Total Amylase Activity	2.91	21.3%

Ratios: Total amount accumulated over 2-hour period of *Ensure Plus®* + VIOKASE®16/*Ensure Plus®* alone
% Recovery: Percentage of enzyme recovered during 2-hour period compared to amount administered

Overall, Viokase 16 can deliver active and measurable levels of lipase, trypsin, and amylase to the site of action in CP subjects with EPI. However, based on the experiences gathered so far on the intubation study, it is concluded that many challenges in the study design, study conduct, and assay methodology render the assay incapable to assess bioavailability (BA) or bioequivalence (BE) of pancreatic enzyme products. As such, these results can not be used for the labeling purpose.

There were no food compatibility studies conducted for this NDA submission. It is considered acceptable since the recommended administration in the labeling is consistent with the conducted clinical studies, i.e., product (non-enteric coated pancreatic enzymes) were administered with meals or snacks in the clinical studies.

2. Question Based Review

2.1 General Attributes

Q: What is the drug substance?

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

Q: What is the proposed formulation?

Viokase is a non-enteric coated tablet. There are two dose strengths of Viokase tablets: Viokase 8 - 10,440 USP units of lipase; 39,150 USP units of protease; 39,150 USP units of amylase; and Viokase 16 - 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase. They are [(b) (4)] consists primarily of pancrelipase, also identified as Pancreatic Enzyme Concentrate or PEC [(b) (4)] crosscarmellose sodium [(b) (4)] lactose monohydrate [(b) (4)] microcrystalline cellulose [(b) (4)] colloidal silicon dioxide [(b) (4)], talc [(b) (4)] and stearic acid [(b) (4)].

Q: What is the mechanism of action?

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

Q: What is the proposed indication?

Viokase (Pancrelipase Tablets) is a pancreatic enzyme replacement therapy indicated for the treatment of patients with exocrine pancreatic insufficiency caused by [(b) (4)] chronic pancreatitis, [(b) (4)]

Q: What is the proposed dosing regimen?

Viokase is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of Viokase should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.

[(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.

Usually, half of the prescribed Viokase 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.

However, in order to maximize the amount of enzyme reaching the duodenum, it will be prescribed with a proton pump inhibitor (PPI) which reduces the production of acid in the stomach.

2.2 General Clinical Pharmacology

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

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

In vivo intubation study (VIO16IP07-01)

It was an open-label two-way cross-over study to evaluate the intraduodenal delivery of lipase, protease and amylase from administration of Viokase 16 in chronic pancreatitis subjects with exocrine pancreatic insufficiency. The objective of this study was to evaluate the intraduodenal lipase (primary objective), protease (secondary objective) and amylase (secondary objective) activity following administration of Viokase 16 tablets in chronic pancreatitis (CP) subjects with exocrine pancreatic insufficiency (EPI) after a liquid meal. In addition, the safety of single dose Viokase16 in CP subjects with EPI was also monitored. A total of 14 subjects who had severe EPI were randomized into two treatment arms (Ensure Plus® alone or Ensure Plus® with a dose of study drug, which constituted 3 tablets of Viokase 16). Twelve subjects were included in the per protocol (PP) population for enzyme analyses.

In the per protocol (PP) population, the cumulative activity of lipase (p=0.0034), trypsin (p=0.0017), and amylase (p=0.0188) recovered during the 2-hour perfusion/aspiration was statistically significantly greater after administration of Ensure Plus® with Viokase

16 as compared to administration of Ensure Plus® alone. A summary of the enzyme activity ratios and the percent recovery is presented below (Table 1):

Table 1. Summary of Total Enzyme Activity Ratio and Percent Recovery

Effect	Ratio (Based on Observed Values)	% Recovery
Total Lipase Activity	1.91	64.1%
Total Trypsin Activity	4.80	29.2%
Total Amylase Activity	2.91	21.3%

Ratios: Total amount accumulated over 2-hour period of *Ensure Plus®* + VIOKASE®16/*Ensure Plus®* alone
% Recovery: Percentage of enzyme recovered during 2-hour period compared to amount administered

Reviewer's comment:
Viokase 16 is a non-enteric coated enzyme preparation, and is therefore labile in acid environments. Given that lipase is inactivated within the gastrointestinal tract by acid, proton pump inhibitors are frequently utilized in clinical practice to neutralize stomach acid, thereby improving the survival of the lipolytic activity. Subjects who participated in the study received the proton pump inhibitor omeprazole (20 mg for at least 5 days prior to Day 0) to protect the enzymatic activity within Viokase16.

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

2.3 Intrinsic Factors

Not applicable since the drug product is not systemically observable

2.4 Extrinsic Factors

Not applicable since the drug product is not systemically observable

2.5 General Biopharmaceutics

Not applicable

2.6 Analytical Section

Q. Is the assay methods for lipase detection adequately validated?

Yes. The validation data demonstrates that the method is sensitive, selective, precise and accurate for the measurements of lipase activity in human intraduodenal aspirate (HIA). The lipase activity calibration curve ranged from 0.12 to 12.00 USP U/mL, with the correlation coefficient of the calibration curve of r^2>0.99.

The method lacks any matrix effect as indicated by the selectivity experiment. Lipase can be serially diluted in HIA without affecting activity measurements. Back-calculation of original lipase activity after dilution in HIA is precise and

accurate. Lipase activity in HIA is stable after two freeze thaw cycles and on ice for at least two hours. The long term stability storage at -80°C nominal of lipase stock solution and stability samples in HIA is currently ongoing.

3. Detailed Labeling Recommendations

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

12 CLINICAL PHARMACOLOGY

Sponsor proposed labeling language:

12.1 Mechanism of Action [2.2 Introduction, p. 2]

(b) (4)

Agency's recommended language in this section:

12.1 Mechanism of Action

Following administration, the released enzymes 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.

12.2 Pharmacokinetics

The pancreatic enzymes in Viokase when administered with a proton pump inhibitor are released in the duodenum. Viokase enzymes are not absorbed from the gastrointestinal tract in any appreciable amounts.

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/

LANYAN FANG
06/17/2010

JANG IK LEE
06/17/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22-542 **Applicant: Axcan** **Stamp Date: 10/29/2009**

Drug Name: TRADENAME (pancrelipase) **NDA/BLA Type : Original**

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

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A
2	Has the applicant provided metabolism and drug-drug interaction information?			N/A
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			N/A
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			N/A
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			N/A
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			N/A
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			N/A
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A
11	Is the appropriate pharmacokinetic information submitted?			N/A
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			N/A
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a	X		

	manner to allow substantive review to begin?			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

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

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

Jee Eun Lee, Ph.D.

Reviewing Pharmacologist Date

Jang-Ik Lee, Pharm.D., Ph.D.

Team Leader/Supervisor Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-542	Brand Name	TRADENAME
OCP Division	DCP3	Generic Name	pancrelipase
Medical Division	DGIP	Drug Class	Digestive enzyme
OCP Reviewer	Jee Eun Lee, Ph.D	Indication(s)	Treatment of exocrine pancreatic insufficiency due to pancreatitis (b) (4)
OCP Secondary Reviewer	Jang-Ik Lee, Pharm.D. Ph.D.	Route of Administration	Oral
Dosage Form	(1) (VIOKASE 8) 10440 USP units of lipase; 39150 units of protease; 39150 units of amylase tablet (2) (VIOKASE 16) 20880 USP units of lipase; 78300 USP units of protease; 78300 USP units of amylase tablet	Dosing Regimen	Initial dose of 500 lipase units/kg per meal Maximum dose of 2500 lipase units/kg per meal or 4000 lipase units/g fat ingested per day
Date of Submission	10/29/2009		
Estimated Due Date of OCP Review	6/15/2010	Sponsor	Axcan
PDUFA Due Date	8/30/2010	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	X	1		
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics	X	1		
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		2		

Fileability and QBR comments		
	"X" if yes	**Comments**
Application filable?	X	
Comments sent to firm?		
QBR questions (key issues to be considered)		

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

Filing Memo

Clinical Pharmacology Review

NDA:	22-542
Compound:	**pancrelipase**
Tradename	**TRADENAME (until determined)**
Sponsor:	**Axcan**
Date:	**12/09/2009**
Reviewer:	Jee Eun Lee

The sponsor initiated the original NDA for TRADENAME (VIOKASE®, pancrelipase, USP) Tablets on April 28, 2009 by submitting the first reviewable unit (Nonclinical Pharmacology and Toxicology). After submitting the second reviewable unit (Chemistry and manufacturing) on July 30, 2009, the sponsor submitted the third and final reviewable unit (Clinical Efficacy and Safety) on October 29, 2009 to finalize the NDA submission. This NDA is being submitted under Section 505(b)(2) cross-referencing the previous finding of safety and efficacy of COTAZYN (NDA 20-580).

TRADENAME tablet 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 pancreatiti[redacted] (b) (4).

TRADENAME is a non-enteric coated pancreatic enzyme preparation. In clinical use, the TRADENAME enzyme preparation is used in combination with acid suppressing agents as the absence of an enteric coating in this preparation renders it susceptible to acid degradation by the stomach. The sponsor claims that the use of acid suppressing agents enhances the capacity for TRADENAMES to improve fat absorption and decrease abdominal pain.

An enzyme preparation is believed to deliver appropriate enzyme levels to the duodenum, rather than the mid gut or distal small bowel so that the treatment effect for the patients with chronic pancreatitis suffering from exocrine pancreatic insufficiency is expected.

There is a BA study submitted where pancreatic enzyme delivery to the duodenum was measured to determine if the enzyme preparation with a liquid meal resulted in higher lipase, protease and amylase amounts than a liquid meal alone.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds that NDA 22-542 is fileable.

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/

JEE E LEE
12/18/2009

EDWARD D BASHAW
12/18/2009
I am signing this document as the acting biologics TL as the current acting TL is on leave