CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of Safety Update Report

NDA#:	22, 542 (sequence# 0029)
Sponsor:	Axcan Pharma, Inc
Product:	Viokace (pancrelipase)
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted:	September 1, 2011
PDUFA Date:	March 1, 2012
Date of Review:	December 9, 2011
Clinical Reviewer:	Marjorie F. Dannis, M.D.
Through:	Anil Rajpal, M.D.

Background

Viokace (formerly known as Viokase) is an orally administered porcine pancreatic enzyme preparation (PEP) that was previously indicated for the treatment of exocrine pancreatic insufficiency (EPI) as associated with but not limited to cystic fibrosis, chronic pancreatitis, pancreatectomy, or obstruction of the pancreas ducts. It was available in the United States as a prescription drug from 1949 until April 28, 2010, when it was removed, as all marketed PEPs were required to have an approved NDA for continued marketing. Since Viokace had never been approved under an NDA, it was no longer allowed to be marketed in the US. (Viokace was/is also available as a prescription drug on the Canadian market under the trade name Viokase.)

The initial NDA was submitted on October 30, 2009. On November 28, 2010, the Agency issued a Complete Response letter secondary to issues related to Facility Inspections and Product Quality. The complete response was submitted on September 1, 2011 and in accordance with 21 CFR 314.50(d)(5)(vi)(b), Axcan Pharma submitted a safety update with this complete response.

Safety Update

This safety update covers the period from February 1, 2010 to June 30, 2011.

Clinical Studies

There have been no clinical studies, completed or ongoing, since the original NDA submission in October 2009.

Postmarketing

This section discusses the post-marketing experience of Viokace recorded in the drug safety database maintained by Axcan Pharma Inc. and its subsidiaries. The drug safety

database includes spontaneous cases from healthcare professionals and non-healthcare professionals as well as cases from scientific literature and regulatory authorities.

Adverse Events

Between February 1, 2010 and June 30, 2011, Axcan Pharma and its subsidiaries received nine adverse event reports including a total of 29 adverse events. From these reports, eight involved Viokace and one involved an unspecified brand of pancrelipase. See Table 1 below (electronically copied from Sponsor's submission) Two of these reports were assessed as serious and are described in detail below.

1. The first serious report involved a 77 year-old patient with a history of ulcerative colitis who when treated with Viokace for pancreatitis, experienced hallucinations. According to the Sponsor, this report was not medically confirmed. Additionally, the patient had been taking unspecified concomitant medications which included an unspecified sleep medication.

(b) (6), the patient was hospitalized for pancreatitis. During this hospitalization, the patient began treatment with Viokace and developed severe hallucinations. (b) (6) The patient was placed on a low fat diet for 4 to 6 weeks and no alternative pancreatic enzymes therapy was prescribed. The hallucinations resolved.

According to the Sponsor, hallucinations are unexpected as per the approved product information. In addition, the literature contains no articles discussing pancrelipase and hallucinations, and no similar cases were retrieved in the Axcan's safety database. Thus, according to the Sponsor, "there is no reasonable possibility for a causal relationship between Viokace and hallucinations"

2. The second serious report was retrieved from the literature [Verma *et al*, 2010] and describes the occurrence of commensal bacteria induced necrotizing pancreatitis, gallstone pancreatitis, pleural effusion and elevated alanine aminotransferase/ alkaline phosphatase levels in a 68-year-old patient treated with pancrelipase (formulation not reported) for an unknown indication. The patient's medical history included hypertension, atrial fibrillation, gout, chronic kidney disease and dyslipidemia. There was no history of alcohol or tobacco use. Co-suspected medications included warfarin, amlodipine and atenolol.

On an unspecified date, the patient had an episode of gallstone pancreatitis which was complicated by pancreatic pseudocyst formation. Elective cholecystectomy was planned but not performed at that time due to the patient's unstable medical condition. Two months later, he presented to the reporter's hospital where a diagnosis of commensal bacteria induced necrotizing pancreatitis with fluid collection was made after a computerized tomogram (CT) of the abdomen/ pelvis that showed a pleural effusion, inflammation of the pancreas with prominent pseudocyst (with air-fluid levels in the tail of pancreas as well as a smaller air-filled fluid collection in the head of pancreas). CT

guided drainage of pancreatic pseudocyst was performed and drained a purulent cloudy fluid which revealed beaded gram positive rods. Patient was treated with penicillin and trimethoprim/ sulfamethoxazole for Veillonella and Bifidobacterium infection.

The patient underwent surgery after 4 weeks and had an uneventful course with serial abdominal CT scans showing resolution of peripancreatic fluid collection and inflammation. Two weeks after discharge from a rehabilitation facility, the patient had resolution of his symptoms and was back to his usual state of health.

According to the Sponsor, there is no reasonable possibility for a causal relationship between pancrelipase and any of the adverse events due to the absence of biologic plausibility and the likelihood that the patient had been prescribed pancrelipase for the gallstone pancreatitis. (The start date of pancrelipase compared to the onset date of this event could not be confirmed). Furthermore, the other adverse events were most probably secondary to known complications of gallstone pancreatitis.

Table 1. Adverse Events by System Organ Class received from 01-Feb-2010 to 30-Jun-2011

SOC / Preferred Term	VIOKASE®	Pancrelipase unspecified	Total
Eye disorders			
Eye irritation	1	0	1
Gastrointestinal disorders			
Abdominal discomfort	1	0	1
Diarrhoea	2	0	2
Lip exfoliation	1	0	1
Nausea	2	0	2
Oesophageal discomfort	1	0	1
Oral discomfort	1	0	1
Oral pain	1	0	1
Pancreatitis	0	1	1
Pancreatitis necrositing	0	1	1
Retching	1	0	1
Vomiting	2	0	2
General disorders and administration site conditions			
Asthenia	1	0	1
Concomitant disease aggravated	1	0	1
Malaise	1	0	1
Oedema peripheral	1	0	1
Therapeutic response decreased	1	0	1
Immune system disorders			
Hypersensitivity	1	0	1
Injury, poisoning and procedural complications			
Accidental exposure	1	0	1
Investigations			
Hepatic enzyme increased	0	1	1
Musculoskeletal and connective tissue disorders			
Trismus	1	0	1
Nervous system disorders			
Burning sensation	1	0	1
Psychiatric disorders			
Hallucination, visual	1	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1	0	1
Pleural effusion	0	1	1
Skin and subcutaneous tissue disorders			
Rash pruritic	1	0	1
Total	**25**	**4**	**29**

Medical Reviewer's Comment
This reviewer agrees with the Sponsor that "there is no reasonable possibility for a causal relationship" between Viokace and the serious adverse events listed above. In addition, the limited adverse event data presented above are mostly consistent with the known adverse event profile of PEPs or are single incidences of one adverse event.

Patient exposure
An estimate of the patient exposure to Viokace was calculated for the period of February 1, 2010 to June 30, 2011 from the number of product units distributed in the US. However, Viokace has not been distributed in the US since April 28, 2010. Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure was based on the following assumptions:

- The majority of patients taking Viokace are adult patients
- The average weight of males and females adults is 60 kg
- The starting dose of 500-1,000 USP lipase units/kg/meal (with titration to less than 2,500 lipase units/kg/meal) for pancreatic enzymes supplementation was recommended by the Cystic Fibrosis Foundation, therefore, an average dose of 1,500 USP lipase units/kg/meal of Viokace was assumed for calculation purposes
- Patients would be consuming a total of 4 meals/day, equivalent to three meals and two snacks

Based on these assumptions, the average dose administered was 360,000 USP lipase units/day

Sales
The patient exposure in United States was estimated to be 260,500 patient-treatment-days assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day. See Table 2 below.

Table 2: US Unit Sales of Viokace and Patient Exposure (Feb. 1, 2010 to June 30, 2011)

	VIOKASE® 8	VIOKASE® 16
Number of tablets	(b) (4)	
Number of lipase units		
Number of days of treatment	112,327	148,173
Total Number of days of treatment	260,500	

Literature

A search of medical literature for the period from February 1, 2010 to June 31, 2011 was performed and retrieved one relevant article pertaining to the safety of Viokace.

Werlin and co-authors [2010] conducted a proof of concept trial to explain the reason of failure of pancreatic enzymes treatment to completely correct malabsorption and gastrointestinal symptoms in patients with cystic fibrosis (CF). The aim of the study was to examine entire small intestine to search for evidence of inflammation by direct inspection of the mucosa of patients with CF without overt evidence of gastrointestinal disease using capsule endoscopy (CE).

The trial included 42 patients with CF ages 10 to 36 years. One patient was withdrawn from the study. Twenty-eight had pancreatic insufficiency (PI), and 13 were pancreatic sufficient (PS). All of the patients with (PI) were receiving pancreatic enzyme replacement therapy at the time of the study. The author used the fecal calprotectin test and wireless capsule enteroscopy (WCE) to quantify and localize intestinal inflammation, respectively, in patients with CF and relate these findings to clinical status. The findings on WCE showed varied pathological findings in the jejunum and ileum. Diffuse or localized small bowel lesions including villous blunting, edema, erythema, denuded mucosa, and mucosal breaks (erosions or ulcers) were observed throughout the jejunum and ileum in 26 of 41 (63%) patients. This study demonstrated a new observation, a high prevalence of small bowel injury in patients with CF, both patients with PI and those who were PS. The macroscopic appearance of the small intestine may be an integral part of the CF phenotype because it does not relate to the degree of pancreatic disease. In summary, the present proof-of-concept study suggested that there is a condition compatible with a "CF bowel" that may explain the persistence of malabsorption and gastrointestinal symptoms in patients with CF.

Summary/Conclusion

This report presented an update of the post-marketing experience and scientific literature related to Viokace. No new safety issues were identified during the covered period. The information presented in this limited safety update appears to be consistent with the known adverse event profile of PEPs.

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

/s/

MARJORIE F DANNIS
12/12/2011

ANIL K RAJPAL
12/12/2011

MEMORANDUM

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

DATE: November 24, 2010

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022542 Viokace (pancrelipase) Tablets
Axcan Pharma US, Inc.

Summary

Viokace (pancrelipase) Tablets are an exogenous source of porcine-derived pancreatic enzymes. Pancreatic enzyme products (PEPs) serve as replacement therapy for digestive enzymes physiologically secreted by the pancreas and have long been considered the main stay of therapy for exocrine pancreatic insufficiency (EPI). Several PEPs, including Viokace, have been marketed in the US for many years and have not undergone review under new drug applications (NDAs).[1] In 2004, to address concerns about variability in potency across products and within product lines, FDA published a Federal Register Notice which stated that PEPs must be marketed under approved NDAs.

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Viokace (pancrelipase) Tablets for the treatment of adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. Before this application may be approved, the following must be satisfactorily completed: 1) submission of adequate information supporting a change in the drug substance intermediate storage containers, 2) resolution of ongoing discussions involving proposed modifications to in-process microbial controls for the drug substance manufacturing process and the feasibility of *Bacillus cereus* diarrheal enterotoxin testing, 3) resolution of deficiencies identified during inspection of the drug substance manufacturing facility, and 4) resolution of discussions regarding the product label, REMS, and postmarketing study requirements and commitments.

Dosing

Viokace (pancrelipase) Tablets is an immediate release formulation that is dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Viokace should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences. Viokace is not enteric-coated and should be taken in combination with a proton pump inhibitor, so that the acid-labile enzymes contained in the formulation may be protected from the acid contents of the stomach.

Dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or $\leq$ 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. Usually, half the prescribed dose for a full meal should be given with each snack. The total daily dosage should reflect approximately three meals and 2-3 snacks per day.

Viokace (pancrelipase) Tablets are not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Viokace, is pancrelipase, which consists of the enzymes lipase, amylase and protease, as specified in the US Pharmacopeia. However, the animal source of

[1] Viokace Tablets have been marketed in the US as "Viokase", "Viokase 8", and "Viokase 16" since 1949. The to-be-marketed product and the previously marketed product have the same formulation.

pancreata and the extraction processing differ among products. Thus, if approved, the **Dosage and Administration** section of the Viokace label will state that "Viokace is not interchangeable with any other pancrelipase product."

Regulatory History

Axcan Pharma US, Inc. (formerly Axcan Scandipharm, Inc.) submitted NDA 022542 on October 29, 2009, received on October 30, 2009, and was granted a standard review. A major amendment extended the review clock to November 30, 2010. A proposed REMS was included in the original submission and amended on August 20, 2010 and September 17, 2010. Concurrent with review of this NDA, FDA reviewed submissions to DMF (b) (4) from the drug substance manufacturer, (b) (4) which support this NDA.

Inspection of (b) (4) in (b) (4) identified (b) (4) deficiencies that were described in an FDA form 483 and involved (b) (4) s.

A re-inspection of the (b) (4) facility was performed in (b) (4) deficiencies were identified on an FDA form 483. During that inspection, FDA obtained and conducted microbiological testing on samples from three drug substance lots; 4 out of 5 test samples tested positive for *E. coli*. An outside laboratory retained by (b) (4) tested the same lots using the same assay that FDA had used and all were found to be negative. In January 2010, FDA collected additional samples from seven lots; analysis showed that none of the samples tested positive for *E. coli*, but all seven contained low levels of *Bacillus cereus* and one of the seven tested positive for *B. cereus* diarrheal enterotoxin (BDE). (b) (4) retained (b) (4). to retest these lots; they found that all seven lots tested negative for BDE. According to arguments set forth by (b) (4) trace amounts of (b) (4) intrinsic to the pancreatin drug substance could interfere with the BDE assay and produce false positive results.

In a review dated April 30, 2010, the Division of Microbiology, CFSAN, did not agree that the positive assay results could represent false positive results. The review further stated that if the drug substance lots were "…made with any level of consistency and the batches are homogeneous, it seems that 7/7 samples would have tested positive…" The Office of Compliance planned to conduct another pre-approval inspection of this facility to assess the adequacy of additional, yet-to-be-implemented, microbiologic controls of the drug substance manufacturing process. In subsequent testing, CFSAN recovered enterotoxigenic *B. cereus* from 4 of these 7 lots.[2]

Inspections were conducted of (b) (4) and (b) (4) and FDA form 483s were issued to both firms. There were (b) (4) observations cited for (b) (4) (b) (4), including

There were (b) (4) observations cited for (b) (4)

, addressing

[2] See memo dated October 25, 2010, from Reginald Bennett, Jennifer Hait, and Sandra Tallent.

[3] (b) (4) was cited for not adequately investigating a complaint dated (b) (4) regarding (b) (4)

[4] (b) (4), Inc. has been used for release testing and historical testing for BDE in 726 samples since April 13, 2010.

the deficiencies listed on FDA form 483 dated [redacted], was not deemed adequate. The Office of Compliance recommends withholding NDA approval. [redacted]

A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, discussed the theoretical risk of transmission of viral disease to patients exposed to porcine-derived PEPs, including Viokace (pancrelipase) Tablets. Recommendations from this Advisory Committee included informing patients of this theoretical risk and monitoring for potential viral transmission to users of these products (see below).

Chemistry, Manufacturing and Controls (CMC) Considerations

Axcan Pharma US, Inc. intends to market two tablet strengths containing either 10,440 or 20,880 USP units of lipase. Viokace is not enteric-coated. Viokace should be swallowed whole, without crushing or chewing, and taken in combination with a proton pump inhibitor.

Drug substance [redacted] The drug substance, DS 1252, is a [redacted] DS 1206.[5] Several CMC deficiencies involving the drug substance have been identified and previously conveyed to [redacted] At this time, the Division of Therapeutic Proteins has determined that deficiencies involving the capacity of the manufacturing process to clear viruses and monitor viral load can be addressed as postmarketing commitments and do not preclude approval of the NDA. At the most recent inspection of [redacted], FDA noted the use of [redacted] blue drums for drug substance intermediate storage.[6] Given that drug substance is stored in [redacted]) in these drums for [redacted], extractable and leachable studies, evaluation of product quality, stability data, and validation studies to support re-use of the containers are needed. These information requests were conveyed to [redacted] on [redacted]. Axcan Pharma US, Inc. and [redacted] response received on November 9, 2010[7], will be reviewed in depth in the next review cycle.

Microbiology Concerns

Staff in several divisions and offices in CDER and in CFSAN's Division of Microbiology have determined that the presence of any BDE in the resulting drug product could cause gastrointestinal adverse events, including systemic illness, particularly in immunocompromised patients. [redacted] could be responsible for *B. cereus* growth and BDE production during drug substance processing. Further, relatively [redacted] employed at [redacted] (as compared to other pancreatin drug substance manufacturers) may allow the heat labile toxin to survive processing, and the drug product manufacturing process [redacted]

On May 3, 2010, [redacted] was informed that they will need to implement additional microbiologic controls of the drug substance manufacturing process, and provide 1) a justification for all in-process holding times associated with manufacture of the drug substance, 2) the maximum storage time for the [redacted] 3) information on total aerobic microbial count (TAMC) alert and action levels at particular points in the manufacturing process, 4) a commitment to test each batch of drug substance for BDE prior to release, and 5) a description of the BDE test method, the validation procedure, and a summary of the supporting validation data.

At a meeting with FDA on May 20, 2010, it was agreed that when the TAMC fell between the alert and action levels of [redacted] the materials would be tested for BDE biochemically; this agreement was reflected in an amendment to DMF [redacted] on June 6, 2010. However, since [redacted] has been unable to develop a validated assay for BDE detection, the DMF was amended on October 22, 2010 to replace the action and alert levels with a specification of no more than [redacted] at [redacted]

[5] In contrast, the drug substance DS 1286 manufactured by [redacted] for Ultresa (pancrelipase) Delayed-Release Capsules (NDA 02222) is [redacted] DS 1208. [redacted] drug substance for Pertzye (pancrelipase) Delayed-Release Capsules (NDA 022175) contains both DS 1206 and DS 1208.

[6] [redacted] did not notify the NDA applicant of this manufacturing change or submit any information to support the change for FDA review.

[7] Submitted to NDA 02222

(b) (4) and no more than (b) (4) and for the finished API; if the specification is exceeded, the batch will be rejected.

At a meeting held with FDA on November 15, 2010 (b) (4) proposed even tighter in-process microbiologic action limits. In addition to the previously specified TAMC limits, batches would be rejected if the TAMC exceeded (b) (4) argued that these in-process controls will be highly effective since detectable BDE is only produced when *B. cereus* counts exceed (b) (4) (b) (4) further stated that BDE (b) (4) cannot be recovered due to (b) (4), suggesting that the positive result from FDA testing could not have been due to the presence of BDE. (b) (4) also speculated that previously reported high in-process microbial counts were not representative of the manufacturing process, but rather the result of microbial contamination of improperly designed sampling ports. (b) (4) has relocated and replaced these ports; these changes were in place at the time of FDA's most recent facility inspection.

At the conclusion of this meeting, Axcan Pharma US, Inc. and (b) (4) agreed to submit 1) their current proposal for TAMC testing and arguments why it will prevent BDE formation during manufacturing, 2) results of all efforts to validate a BDE test method in the pancreatin matrix, 3) information that BDE is (b) (4) present in the (b) (4) 4) information regarding changes made in the ports used for sampling pancreatin during the manufacturing process, and 5) information about the pancreatin product made under the previous manufacturing process that is still on the market and what they intend to do regarding these products. Responses from Axcan Pharma US, Inc. and (b) (4) submitted on November 19 and 22, 2010, respectively, will be reviewed in depth in the next review cycle.

Clinical Pharmacology

Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount. For this reason, a thorough QT assessment for this product has not been requested.

Efficacy

As with other PEP manufacturers, Axcan Pharma US, Inc. was requested to perform at least one controlled clinical trial with Viokace to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.[8] Axcan Pharma US, Inc. conducted one double-blind, placebo-controlled trial in 50 patients, aged 24-70 years, with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. After a washout period of 6-7 days, patients were randomized to either a fixed dose of Viokace (20,888 USP units of lipase per tablet) or placebo, in combination with a proton pump inhibitor, for an additional 6-7 days. All patients received 22 tablets per day (6 tablets per meal and 2 tablets with 2 of 3 snacks) and consumed a high fat diet. Viokace treatment was associated with significantly improved fat absorption compared to placebo at the end of the double-blind period, as measured by the difference between groups in the mean coefficient of fat absorption in 72-hour stool samples ($p<0.0001$).

Safety

Delayed and immediate release formulations of porcine-derived PEPs used to treat exocrine pancreatic insufficiency have been generally well tolerated. The most common adverse events reported relate to the patients' underlying disease and are referable to the gastrointestinal tract. Pancreatic enzyme products are not absorbed from the gastrointestinal tract and are not systemically active.

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of PEPs, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. The magnitude of this risk in patients with chronic pancreatitis or pancreatectomy is unknown. Doses greater than 2,500 lipase units/kg

[8] See http://www.fda.gov/cder/guidance/6275fnl.htm

of body weight per meal (or > 10,000 lipase units/kg of body weight per day) should be used with caution. Patients receiving doses higher than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range. If approved, a Medication Guide will be required as part of a REMS for Viokace that will inform patients of this possible risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study in Viokace users to assess the incidence of and potential risk factors for developing fibrosing colonopathy.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Viokace is not retained in the mouth to avoid irritation of the oral mucosa, and/or loss of enzyme activity.

Risk of Transmission of Viral Disease to Patients. Like other porcine-derived PEPs, Viokace is derived from porcine pancreas tissue obtained as a by-product from the slaughter of pigs as a source of food. Audit procedures are in place to ensure that the pancreas raw material is derived from pigs certified as fit for human consumption and to ensure that legal requirements regarding e.g., hygienic factors, health certification of slaughtered animals, and surveillance for animal diseases are met. Two broad categories of porcine viruses, enveloped and non-enveloped viruses, may be transmissible to humans (i.e., have zoonotic potential). In addition, viruses with zoonotic potential such as HEV, the causative agent for hepatitis E, have recently emerged in pigs. Prior to approval, the required enhancements to the manufacturing process will inactivate most enveloped viruses that could be present in the drug substance but will have limited capacity to inactivate non-enveloped viruses.

Although there has been no documentation of viral transmission to humans, FDA's Anti-Viral Advisory Committee concluded that there was a theoretical risk of transmission of viral disease to patients treated with porcine-derived PEPs, including Viokace. If approved, a Medication Guide will be required as part of a REMS for Viokace that will inform patients of this theoretical risk. In addition, the applicant will be required to conduct a long-term postmarketing observational study, and be requested to conduct postmarketing commitments to ensure that the manufacturing process effectively controls viral load.

Risk of Hyperuricemia. Porcine-derived PEPs contain purines that may increase blood uric acid levels. Caution should be exercised when prescribing Viokace to patients with gout, renal impairment, or hyperuricemia.

Risk of Severe Allergic Reactions. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported in patients with a known allergy to proteins of porcine origin who are treated with PEPs.

Potential for Exacerbation of Symptoms of Lactose Intolerance. Viokace Tablets contain lactose monohydrate. Patients with lactose intolerance may not be able to tolerate Viokace.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA) has found the proposed tradename "Viokace" to be acceptable. (b) (4)

Pediatric Considerations

Pediatric Use. If approved, the **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that (b) (4)

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

At the time of approval, FDA will waive the pediatric study requirement for all pediatric age groups, since 1) Viokace, a non-enteric-coated product, does not represent a meaningful therapeutic benefit over existing enteric-coated pancreatic enzyme products that are used in pediatric patients, and 2) Viokace is not likely to be used in a substantial number of pediatric patients given the need for concurrent use of proton pump inhibitors; the safety of chronic proton pump inhibitor use in pediatric patients has not been established.

Postmarketing Requirements under 505(o)

In accordance with section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that, if this application is approved, Axcan Pharma US, Inc. will be required to conduct the following studies to assess the unexpected serious risks of fibrosing colonopathy and transmission of viral disease to patients taking Viokace (pancrelipase) Tablets:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with chronic pancreatitis or pancreatectomy treated with Viokace in the US and to assess potential risk factors for the event.

2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Viokace.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Viokace (pancrelipase) Tablets and other porcine-derived PEPs, to ensure that the benefits of the drug outweigh the possible risks of fibrosing colonopathy and transmission of viral disease to patients.

Axcan Pharma US, Inc.'s proposed REMS, submitted on October 29, 2009, and amended on August 20, 2010 and September 17, 2010, contains a Medication Guide and a timetable for submission of assessments of the REMS. Comments from the Division of Risk Management on the proposed REMS were conveyed to the applicant on August 18, 2010 and were accepted.

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

/s/

JULIE G BEITZ
11/24/2010

Cross-Discipline Team Leader Review

Date	November 24, 2010
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-542
Applicant	Axcan Pharma US, Inc.
Date of Submission	October 29, 2009; Received October 30, 2009
PDUFA Goal Date	November 30, 2010 (includes three-month extension for a major amendment)
Proprietary Name / Established (USAN) names	Viokace® pancrelipase
Dosage forms / Strength	Viokace® (pancrelipase) tablets for oral administration, in USP units ▪ Viokace 10,440 lipase/39,150 protease/39,150 amylase ▪ Viokace 20,880 lipase/78,300 protease/78,300 amylase
Proposed Indication	For the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy
Recommended Action:	Complete Response (CR) under 21 CFR 314

Table of Contents

1. Introduction

This submission, received October 30, 2009, is the initial New Drug Application (NDA) for Viokace (pancrelipase) tablets, a non-enteric coated pancreatic enzyme product (PEP). Viokace is an exogenous source of porcine-derived pancreatic enzymes intended for treatment of exocrine pancreatic insufficiency (EPI).

2. Background

2.1 Clinical Background

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due to a number of underlying diseases. The most common cause of EPI in children is Cystic Fibrosis (CF); the most common cause of EPI in adults is chronic pancreatitis (CP). There are many other causes, such as pancreatectomy.

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. The administration of pancreatic enzyme replacement therapy with exogenous sources of PEPs is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause. Dosing is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea; this is described in the Consensus guidelines established by the Cystic Fibrosis Foundation (CFF).[1,2,3]

Fibrosing colonopathy (FC) is an important safety concern regarding PEP use. Although the etiology of FC is not known with certainty, FC has been associated with high dose PEP exposure. Consensus guidelines have been established by the CFF in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.[1,2,3] (See also Section 8 and Appendix 1.)

[1] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.
[2] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[3] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

2.2 Regulatory History

2.2.1 Pancreatic Enzyme Products

Approved PEPs: Four PEPs have been approved under NDA to date:

(1) Cotazym (NDA 20-580): approved in 1996; not currently marketed
(2) Creon (NDA 20-725): approved April 30, 2009
(3) Zenpep (NDA 22-210): approved August 27, 2009
(4) Pancreaze (NDA 22-523): approved April 12, 2010

Thus, there are three approved PEPs (Creon, Zenpep, and Pancreaze) that are currently commercially available in the US; it should be noted that each of these PEPs are enteric-coated formulations.

Unapproved PEPs: Unapproved PEPs can no longer be marketed effective April 28, 2010. PEPs had been available since prior to the Federal Food, Drug, and Cosmetic Act of 1938; most PEPs had been available since before Drug Efficacy Study Implementation (DESI; pre-1962).

Federal Register Notices: Over the past many years, the FDA has published a number of notices in the Federal Register (FR) with the aim of requiring all marketed PEPs to have undergone the NDA application and review process. This is largely to address variations in formulation, dosage, and manufacturing processes, both between different PEPs and within individual PEP brands. Recent FR notices for PEPs are summarized in the table below.

Table 1. Recent Federal Register Notices for Pancreatic Enzyme Products

Year	Federal Register Notices
April 1995	Notice of Final Rule: All PEPs must obtain FDA approval under NDA in order to remain on the market.
April 2004	Notice of Requirement for NDA Approval: All PEPs must obtain NDA approval within the next four years (deadline April 28, 2008)
October 2007	Notice of Extension: FDA would use enforcement discretion for the PEPs. In order to continue marketing their products, manufacturers must have: ▪ open IND by April 28, 2008, ▪ NDA submitted by April 28, 2009, and ▪ approved NDA by April 28, 2010.

PEP Guidance: It should also be noted that the draft PEP guidance was published in 2004, and the final PEP Guidance was published in 2006 (Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs).

REMS for Creon, Zenpep, and Pancreaze: A Risk Evaluation and Mitigation System (REMS) was implemented for Creon, Zenpep, and Pancreaze for two reasons:

(1) Risk of Fibrosing Colonopathy: To address the concern that the risk of FC may be increased with high dose exposure to PEPs, a Medication Guide that informs patients of the risk of FC is part of the REMS for Creon, Zenpep, and Pancreaze. (See also Section 2.1 and Appendix 1.)
(2) Risk of Transmission of Viral Disease to Patients: There is a concern that because Creon, Zenpep, Pancreaze, and other PEPS are porcine-derived products, there may be a risk of

porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[4,5] To address the concern about the theoretical risk of viral transmission, a Medication Guide that informs patients of the theoretical risk of viral transmission is part of the REMS for Creon, Zenpep, and Pancreaze.

2.2.2 Regulatory History of Viokace

The table below summarizes the regulatory activity of Viokace for EPI.

Table 2. Pertinent Regulatory History of Viokace

Date	Event
August 2000	Original IND submission*
October 2006	End of Phase 2 Meeting
December 2006	Special Protocol Assessment for Pivotal Study (VIO16EPI07-01) submitted
February 2007	Meeting with the Sponsor to further discuss pivotal study design
May 2007	Fast Track Designation granted
July 2007	Pre-NDA Meeting
April 2009	Rolling Review granted
April 2009	Modules 1, 2, and 4 of NDA 22-542 submitted
July 2009	Module 3 of NDA 22-542 submitted#
October 2009	Module 5 of NDA 22-542 submitted†

*IND 60716
#Submission also included addition of documents to Modules 1 and 2
†Submission also included addition of documents to Modules 1, 2, and 3

It should be noted that Viokace was commercially available in the US until earlier this year (see Section 2.2.1); it was marketed under the name "Viokase." The CMP formulation that was on the market from 2003 to earlier this year and the TbMP are the same formulation.

It should also be noted that Viokace if approved would be the first approved non-enteric coated pancreatic enzyme product.

See the Clinical Review by Marjorie Dannis for details of the Viokace regulatory history.

[4] Antiviral Drugs Advisory Committee (December 2, 2008);
<http://www.fda.gov/ohrms/dockets/ac/cder08 html#AntiviralDrugs>
[5] Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

2.3 Current Submission

The NDA resubmission was received on October 30, 2009. It was classified as a ten-month resubmission with a PDUFA deadline of August 30, 2010; because of a three-month extension for a major amendment, the PDUFA deadline is November 30, 2010.

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines for this review cycle have all written review documents. The primary review documents relied upon for the current review cycle are the following:

(1) Clinical Review by Marjorie Dannis, dated November 10, 2010
(2) Statistics Review by Shahla Farr dated November 3, 2010
(3) CMC Reviews from Division of Therapeutic Proteins (DTP):
    (a) Secondary (Summary) CMC Review by Emanuela Lacana, dated November 23, 2010
    (b) Drug Product Review (filed under NDA 22-542) by Wei Guo, dated September 24, 2010
    (c) Drug Substance Review (filed under DMF (b) (4)) of Non-Viral Issues by Wei Guo, dated September 24, 2010
(4) Microbiology Reviews/Memos from New Drug Microbiology Staff (NDMS)
    (a) Reviews by Denise Miller (filed under NDA 22-542):
        - Review dated November 10, 2010
        - Review dated June 21, 2010
    (b) Review by Stephen Langille (filed under DMF (b) (4)):
        - Review dated June 9, 2010
(5) Biopharmaceutics Reviews by Albert Chen (ONDQA/Biopharmaceutics):
    - Review dated October 12, 2010
    - Review dated September 28, 2010
(6) Clinical Pharmacology Review by Lanyan Fang dated June 17, 2010
(7) Pediatric Consult Reviews by Elizabeth Durmowicz:
    - Review dated August 17, 2010
    - Review dated February 16, 2010
(8) Nonclinical (Pharmacology/Toxicology) Reviews:
    - Review by David Joseph dated June 30, 2010
    - Review by Niraj Mehta dated June 29, 2010
(9) Division of Scientific Investigations (DSI) Summary Review by Khairy Malek dated June 30, 2010
(10) Labeling Reviews and Proprietary Name Reviews by Irene Chen (DMEPA):
    - Labeling Review dated October 18, 2010
    - Proprietary Name Review dated October 18, 2010
    - Proprietary Name Review dated June 23, 2010
    - Proprietary Name Review dated January 22, 2010
(11) DDMAC Labeling Review by Sheetal Patel dated June 29, 2010

The reviews should be consulted for more specific details of the application.

3. CMC

The reader is referred to the CMC Review of Drug Product by Wei Guo dated September 24, 2010, the Secondary CMC Review by Emanuela Lacana dated November 23, 2010, the CMC Review of Drug Substance Non-Viral Issues dated September 24, 2010, Microbiology Memo by Denise Miller dated November 10, 2010, Microbiology Review by Denise Miller dated June 21, 2010, and the Microbiology Review (DMF (b) (4) by Stephen Langille dated June 9, 2010.

3.1 Overview

An overview of the drug substance (DS), drug substance viral issues, and drug product (DP) and packaging is provided below.

3.1.1 Overview of Drug Substance (DS)

The DS is manufactured by (b) (4) the drug substance Drug Master File (DMF) holder (DMF (b) (4)). DS is derived from porcine pancreas glands harvested from healthy pigs raised in (b) (4) as human food. The glands are obtained from slaughterhouses, which are under the inspection of the (b) (4) (b) (4) The glands (b) (4) until they are processed by the manufacturer. The glands go through a number of processing steps, including such things as (b) (4) (among others), which results in pancrelipase DS. The resulting pancrelipase DS is used for manufacture of drug product (DP).

(b) (4) is the DS DMF Holder for Ultresa (NDA 22-222) and Pertzye (NDA 22-175) as well as for Viokace. Thus, although the NDA for Viokace is an original submission, there is an extensive regulatory history with the DS DMF Holder because the other NDA's (for Ultresa and Pertzye) were originally submitted in July 2007 and October 2008, respectively, and there have been re-submissions of those NDA's.

The DS used in Viokace is DS 1252, (b) (4) DS 1206. The DS used in Ultresa is DS 1286, (b) (4) DS 1208. The DS used in Pertzye is DS 1206 and DS 1208.

3.1.2 Overview of DS Viral Issues

Given the source of the material, the possibility of contamination of the starting material with viruses relevant to swine has to be considered. The viruses known to be present in swine include enveloped, non-enveloped, and emerging viruses listed and considered in detail in the review of drug substance viral issues. (b) (4) viral inactivation steps are involved in the DS manufacturing process, including (b) (4)

To mitigate the risk from adventitious agents, the manufacturer performed an evaluation of the capacity of the manufacturing process to remove viruses (viral clearance and

clearance/inactivation studies and viral load testing). The viral clearance studies include the selection of model viruses for viral clearance and validation.

3.1.3 Overview of Drug Product (DP) and Packaging

The DP is manufactured by Confab Laboratories; it should be noted that pertinent information related to the DP and packaging has been submitted to NDA 22-542.

The DP manufacturing process entails: (b) (4) Viokace tablets are presented in two strengths based on lipase activity (10,440 USP units lipase, and 20,880 USP units lipase). The bulk tablets are stored in (b) (4).

The tablets are packaged in high density polyethylene (HDPE) bottles. Each bottle contains a desiccant packet. The tablet count is 100 tablets per bottle.

3.2 Issues

Deficiencies identified in the Drug Substance Review, the Drug Product Review, and the Microbiology Review are provided below:

3.2.1 DS Viral Issues

Many of the DS viral issues have been addressed in the reviews of other NDA's (i.e., Ultresa and Pertzye NDA's) that used the same DS DMF (see Section 3.1.1). In the most recent review of DS viral issues (dated April 28, 2010; filed under NDA 22-222), the DS Viral Issues Reviewer (Howard Anderson) concluded that deficiencies exist, but did not preclude approval of that application since these could be addressed as postmarketing commitments (PMC's) (see CDTL Review of Ultresa NDA dated May 5, 2010 for complete information). It should be noted that another DS Viral Issues Review has not been conducted since the time of the last review because updates regarding DS viral issues have not been provided in the DMF for (b) (4)

PMC's: The PMC's recommended by the DS Viral Issues reviewer are provided below. These PMC's will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle (see also Section 13.6).

PMC #1: Submit the final study reports of the cleaning agents effectiveness for viral inactivation for protocols # 09-VV-17-020 & 09-VV-12-121 to the FDA. (Final Report Submission date to be determined as per review.)

PMC #2: Submit the validation report for the PCV1 (Porcine Circovirus 1) infectivity release assay to the FDA. (Final Report Submission date to be determined as per review.)

PMC #3: Establish lot release specifications for the PCV1 infectivity assay. (Final Report Submission date to be determined as per review.)

PMC #4: Establish lot release specifications for the PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) infectivity assay. (Final Report Submission date to be determined as per review.)

PMC #5: Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide better assurance that released drug substance will not contain EMCV (Encephalomyocarditis Virus), HEV (Swine Hepatitis E Virus), SVDV (Swine Vesicular Disease Virus), Reo (Reo Virus), Rota (Rota Virus), PTV (Porcine Teschovirus) viruses. Revise the assays, and submit assay validation data, together with acceptance criteria. (Final Report Submission date to be determined as per review.)

PMC #6: Submit the plan to assess the risk to product quality associated with porcine hokovirus and the control strategy to the FDA. (Final Report Submission date to be determined as per review.)

3.2.2 DS Non-Viral Issues

Deficiency Items: The deficiency items identified by the DS Non-Viral Issues Reviewer and the Secondary CMC Reviewer are shown below. The wording of the items below is taken from the secondary (summary) review. (See DS Non-Viral Issues Review by Wei Guo dated September 24, 2010, and Secondary CMC Review by Emanuela Lacana dated November 23, 2010 for complete information.)

(1) During inspection of (b) (4), inspectors noted that changes to the drug substance intermediate container were introduced in the process, and the DMF holder was cited for lack of extractable leachable data. The DMF holder had not reported the change to the Agency or to the NDA holder. The Agency requested the change to be reported, however (b) (4) did not provide validation data or extractable/leachable studies for the new container. (Dr. Lacana noted that this issue was discovered after the primary review was completed and for this reason is not discussed in Wei Guo's review.) See **Item #6** in the Deficiency Letter sent to (b) (4) on October 27, 2010 (in Section 13.1.2 of this CDTL review).

(2) Both FDA field laboratories and CFSAN laboratories have analyzed samples of pancrelipase from (b) (4) for the presence of Bacillus cereus diarrheal enterotoxin and detected the toxin in several samples. (b) (4) claims that the results are false positive and that the false positive results are due to (b) (4). However, the DMF holder has provided no data to support this contention. See **Items #7 to #14** in the Deficiency Letter sent to (b) (4) on October 27, 2010 (in Section 13.1.2 of this CDTL review).

3.2.3 DP and Packaging Issues

PMC's: The PMC's recommended by the DP Reviewer and the Secondary CMC Reviewer are provided below. (See DP Review by Wei Guo dated September 24, 2010, and Secondary CMC Review by Emanuela Lacana dated November 23, 2010 for complete information.) These PMC's will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle (see also Section 13.6).

PMC #1: Evaluate stability of drug product manufactured using drug substance at the end of the shelf-life.

PMC #2: Revise release and stability specifications after 30 lots of drug product have been manufactured.

PMC #3: Include accelerated and/or stressed stability conditions in the annual stability protocol.

3.2.4 Microbiology Issues

Earlier reviews of microbiology issues of DMF (b) (4) were conducted for another NDA, Ultresa (NDA 22-222) that used the same DS DMF.

3.2.4.1 Initial Review

DMF (b) (4) was initially reviewed by the Microbiology Reviewer as a result of a facility inspection that revealed abnormally high counts of spore forming bacteria in the drug substance. The Microbiology Reviewer reviewed the DS manufacturing process for flaws that could lead to increased numbers of microorganisms.

The Microbiology Reviewer recommended that (b) (4) provide information on selected manufacturing processes. These items were included in a Deficiency Letter to (b) (4) dated September 15, 2009, and were related to (see final wording of Items #22 and #23 in Deficiency Letter to (b) (4) in Appendix 2): (22) washing, processing, and microbiological acceptance criteria for pancreas glands; and (23) information about manufacturing process (including storage time, temperature, and data showing effect of storage on microbial growth).

3.2.4.2 Second Review

Since the completion of the first review, results of testing done by the FDA's Southwest Regional Lab were available that showed that one of seven drug substance samples obtained from (b) (4) was positive for Bacillus cereus enterotoxin; the Microbiology Reviewer also assessed the adequacy of (b) (4) response to items that were identified during the initial review (see above).

Deficiency items for DS microbiology issues that were sent to (b) (4) in a Deficiency Letter dated May 3, 2010, were related to (see final wording of Items #1 through #6 in Appendix 3): (1) justification for in-process holding times (especially prior to (b) (4)); (2) in-process total aerobic microbial count (TAMC) alert and action levels (for 1206 and 1208); (3) explanation for wide range of TAMC prior to (b) (4) (for 1206 lots) and corrective actions; (4) rationale for selection of one of two 1206 activation processes (b) (4); (5) request to provide the maximum storage time for the 1208 (b) (4); and (6) commitment to test Bacillus cereus enterotoxin prior to release including description of methods and validation.

3.2.4.2 Current Review

The Microbiology Review filed under DMF (b) (4) by Stephen Langille dated June 9, 2010 notes that the responses to each of the deficiency items in the letter sent to (b) (4) on May 3, 2010 (see Appendix 3) were satisfactory. See Appendix 4 of this CDTL Review for the Microbiology Reviewer's assessment of the adequacy of (b) (4) response to Items #1 through #6 in that Letter. (See the Microbiology Review by Stephen Langille dated June 9, 2010 filed under Master File (b) (4) for complete information.)

Although the initial Microbiology Review filed under NDA 22-542 by Denise Miller dated June 21, 2010, recommended an Approval action, the review dated November 10, 2010 recommends a Complete Response action. The Microbiology Reviewer states in the November 10, 2010 review that additional information and subsequent review of DMF (b) (4) resulted in a request for quality microbiology information (on October 27, 2010), that a response has not been received to that request, and thus DMF (b) (4) is not supportive of NDA 22-542. See the Letter sent to (b) (4) with deficiency items dated October 27, 2010 in Section 13.1.2 of this CDTL review. (See the Microbiology Reviews by Denise Miller dated June 21, 2010, and November 10, 2010, for complete information.)

3.2.5 Facility Inspections

3.2.5.1 Earlier Facility Inspections (before Viokace NDA submitted)

A facility inspection of (b) (4) was conducted in April to May 2009, and a FDA Form 483 with (b) (4) observations was issued. The findings of abnormally high counts of spore forming bacteria in the drug substance prompted the initial review by Microbiology as described above (see Section 3.2.4 of this review). The findings also led to a consult with the Division of Anti-infective and Ophthalmology Products (DAIOP). The conclusions of the DAIOP Reviewer, Dr. Benjamin Lorenz were as follows (see Consult Review dated June 5, 2009):

> "The contamination by these (b) (4) organisms varied by lot and stage of processing. The consequence of ingesting this drug product orally with the levels of contamination found is difficult to predict. Since most of these organisms are likely (b) (4), it is not surprising the array of organisms that were found. These organisms are also typically found endogenously in the oral cavity, upper respiratory and gastrointestinal tracts of humans, so it may not

> necessarily constitute a significant risk for most immunocompetent individuals. Of the organisms found, the most concerning are the *Bacillus* spp., the effects of which might only predictably produce mild diarrhea. However, in patients with neutropenia, other major immunocompromise or anatomic derangements (as may be the case in patients with cancer or chronic pancreatitis), the risk could entail systemic illness. Since manufacturing levels exist for these particular organisms, and potentially immunocompromised patients may be exposed, the appropriate measures should be instituted to rectify this. Consider testing the final product for microbial and toxin contamination as well."

Upon further discussion at a meeting that included Dr. Lorenz, it was determined that it would not be feasible to test the final product for microbial and toxin contamination.

Based on the Establishment Evaluation System (EES) report, there was a "Withhold" recommendation for (b) (4) dated August 4, 2009.

3.2.5.2 Recent Facility Inspections (after Viokace NDA submitted)

A HHE Review was conducted by Anil Rajpal (see HHE dated February 23, 2010) because of findings from the (b) (4) inspection (described in Section 3.2.4.2 above) related to microbial contamination. The request for the HHE consult (from the Office of Compliance, Division of Manufacturing and Product Quality) stated that during the recent FDA inspection and analysis of samples from (b) (4), Bacillus cereus was found in seven samples, and the Bacillus cereus enterotoxin was found in one sample. Preliminary microbiological results from the Pacific Regional Laboratory were provided; the highest levels measured were 240 Most Probable Number [MPN]/g in one sample, and 93 MPN/g in another sample; the remainder of the samples had levels of 43 MPN/g or less. (Levels of Bacillus cereus measured in MPN/g can be considered interchangeable with levels measured in Colony Forming Units [CFU]/g.) The key conclusions of the HHE Review were as follows:

> "…the levels found on inspection are considerably lower than the cutoff for causing illness (10^6 CFU/g) as per the draft guidance *[draft guidance for FDA staff entitled "Sec 527.300 Dairy Products-Microbial Contaminants and Alkaline Phosphatase Activity"]*. However, there still exists a small but potential risk with the levels that were measured. *[reference to e-mail from Dr. Benjamin Lorenz dated February 12, 2010]* In addition, presence of the enterotoxin if present even in minute quantities in the final drug product could produce or worsen symptoms of diarrhea. *[reference to e-mail from Dr. Benjamin Lorenz dated February 12, 2010]* There is a plan to evaluate drug product for detectable enterotoxin and to assess whether the amount of enterotoxin present can be measured in the drug substance and/or drug product."

Confab Inspection: Based on the Establishment Evaluation System (EES) report, there is an "Acceptable" recommendation from the Office of Compliance for Confab dated January 5, 2010. The OAI Status for Confab in the Summary Report for NDA 22,542 is "None."

(b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is an "Acceptable" recommendation from the Office of Compliance for (b) (4) (contract testing

laboratory) dated July 16, 2010. The OAI Status for (b) (4) in the Summary Report for NDA 22,542 is "None."

(b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation from the Office of Compliance for (b) (4) dated November 18, 2010. The reason stated in the Summary Report for NDA 22,542 is "EIR REV-NONCONCUR W/ DISTRICT" (EIR stands for Establishment Inspection Report). In addition, the OAI Status for (b) (4) in the Summary Report for NDA 22,542 is "Potential OAI" (OAI stands for "Official Action Indicated").

(b) (4) Inspection: Based on the Establishment Evaluation System (EES) report, there is a "Withhold" recommendation from the Office of Compliance for (b) (4) (contract testing laboratory for (b) (4)) dated September 22, 2010. The reason stated in the Summary Report for NDA 22,542 is "EIR REV-CONCUR W/ DISTRICT" (EIR stands for Establishment Inspection Report). In addition, the OAI Status for (b) (4) in the Summary Report for NDA 22,542 is "None."

An overview of each of the observations cited in FDA Form 483 issued to (b) (4) is provided below.

(b) (4)

An overview of each of the observations cited in FDA Form 483 issued to (b) (4) (contract testing laboratory for (b) (4)) is provided below.

(b) (4)

3.3 Final Recommendation

A Complete Response Action is the final recommendation by CMC.

Deficiency items to be communicated to the Applicant (NDA 22-542) and to the drug substance DMF holder (b) (4) are provided in Sections 13.1.1 and 13.1.2, respectively.

4. Nonclinical Pharmacology/Toxicology

4.1 Issues

The reader is referred to the Nonclinical Pharmacology/Toxicology Reviews by Niraj Mehta dated June 29, 2010, and by David Joseph dated June 30, 2010, for complete information.

Per the Exocrine Pancreatic Insufficiency Drug Products Guidance[6], given the long history of clinical use with the PEPs, the performance of new animal pharmacology studies with the active ingredient (pancrelipase) is not needed to support the Viokace clinical development program. However, toxicology studies are needed if the excipients in the Viokace DP are not classified as GRAS, and the toxicology program for the excipients should supply data from long-term studies in both rodent and non-rodent mammalian species, plus standard reproductive toxicity and genotoxicity information. Consistent with the Guidance, no new pharmacology or toxicology studies were conducted with Viokace and no new non-clinical studies were submitted in the NDA submission. The non-clinical information provided by the Applicant in the submission was from the published literature for the excipients in the clinical formulation of Viokace.

The non-clinical information provided by the Applicant in the submission was mostly related to the excipients (colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, stearic acid, microcrystalline cellulose, and talc) because the daily intake for these excipients could exceed the maximum daily oral dose among all approved drugs products, as determined from the maximum daily dose of Viokace, and from information from the FDA Inactive Ingredients Database.

The overall conclusion from Dr. Mehta and Dr. Joseph from the nonclinical review of the information submitted in the NDA was that the submitted toxicology information provides a reasonable assurance of safety for the estimated maximum daily dose of any excipient that could result from Viokace administration, and that an approval of the Viokace NDA is recommended.

Dr. Mehta and Dr. Joseph additionally recommended that the proposed labeling be revised as follows:

- Indications and Usage section of Highlights: (b) (4) should be changed to "VIOKACE is a combination of porcine-derived lipases, proteases, and amylases."
- Use in Specific Populations section (Pregnancy subsection): Wording should be revised to:

  "Teratogenic Effects

  Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The risks and benefits 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. (b) (4)

[6] U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs." <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf> April 2006.

- Use in Specific Populations section (Nursing Mothers subsection): Wording should be revised to:
  "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."
- Nonclinical Toxicology section (Carcinogenesis, Mutagenesis, Impairment of Fertility subsection): Wording should be revised to: "Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase."

Dr. Mehta and Dr. Joseph also noted in their reviews that since Viokace administration may result in a substantial intake of lactose monohydrate (up to (b) (4) /day in a 60-kg patient), there appears to be a potential for adverse reactions in lactose intolerant patients. Dr. Mehta noted the following in his review: "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." This issue was discussed internally in meetings that included Dr. Mehta and Dr. Joseph after their reviews had been written. The current proposal based on those discussions is an addition to the Warnings and Precautions section of a subsection titled "Potential for Exacerbation of Symptoms of Lactose Intolerance" that has the following wording: "VIOKACE tablets contain lactose monohydrate. Patients who have lactose intolerance may not be able to tolerate VIOKACE."

Since Viokace is not recommended for Approval during this review cycle, the proposed labeling changes will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle.

4.2 Final Recommendation

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the labeling revisions described above are made.

5. Clinical Pharmacology/Biopharmaceutics

5.1 Issues

The reader is referred to the Clinical Pharmacology Review by Lanyan Fang dated June 17, 2010 for complete information.

The Applicant conducted an *in vivo* intubation study (bioavailability study; VIO16IP07-01). This was reviewed by Dr. Fang and her conclusions are described below:

This was a single-dose, open-label, crossover study to evaluate the intraduodenal delivery of Viokace (20,880 lipase units tablet) in 14 patients with EPI due to chronic pancreatitis. Patients were randomized to receive three tablets of Viokace (20,880 lipase units tablet) with or without Ensure Plus. Duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease. Twelve patients were in the per-protocol 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 Viokace as compared to administration of Ensure Plus alone. The clinical pharmacology reviewer provided a summary of the enzyme activity ratios and the percent recovery (see table below).

Table 3. 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

The clinical pharmacology reviewer noted that the bioavailability study using the intubation procedure is considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum because of many challenges in the study design, study conduct, and assay methodology. The bioavailability study is not a required study for the NDA approval.

The reader is also referred to the Biopharmaceutics Review by Albert Chen dated September 28, 2010 and addendum dated October 12, 2010. The Biopharmaceutics reviewer found the proposed dissolution methodology and specifications acceptable. The biowaiver for the lower strength (Viokace 10,440 units of lipase) was granted.

5.2 Final Recommendation

An Approval Action is the final recommendation by the Clinical Pharmacology discipline.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Viokace is not an antimicrobial agent.

7. Clinical/Statistical-Efficacy

7.1 Issues

The reader is referred to the Clinical Review by Marjorie Dannis dated November 10, 2010, and the Statistical Review by Shahla Farr dated November 3, 2010 for complete information.

The pivotal study (VIO16EPI07-01) was reviewed in depth by the Clinical Reviewer.

This was a multi-center, randomized, double-blind, placebo-controlled, parallel study in 50 patients, ages 24 to 70 years, with a confirmed diagnosis of EPI and CP or pancreatectomy.

Pertinent features of the study design are summarized in the table below.

Table 4. Pertinent Features of Study Design (VIO16EPI07-01)

Period		Treatment*
Screening Phase (up to 10 days)		Usual PEP[#]
Washout Phase (6 to 7 days)	• Outpatient (2 days) • Inpatient (4 to 5 days)[†]	No PEP treatment
Randomization Phase (up to 10 days)		Usual PEP[#]
Treatment Phase (6 to 7 days)	• Outpatient (2 days) • Inpatient (4 to 5 days)[†]	Viokace or Placebo

* Patients are on a PPI throughout the study. At screening, patients already on a PPI will continue to use the same PPI whereas patients not already on PPI will start omeprazole.
[#] Patients continue their current PEP during the screening period.
[†] 72-hour stool collection during the inpatient periods of the washout phase and the treatment phase
Viokace 20,880 lipase units tablets were administered in the study
(The table above is modified from a figure and supporting text found in the Clinical Review by Marjorie Dannis.)

The dose of Viokace during the treatment phase was 125,280 lipase units per meal (3 meals) and 41,760 lipase units per snack (2 snacks). The total daily dose was 459,360 lipase units/day. This corresponds to 7,656 lipase units/kg/day for a 60 kg person.

Patients received a proton pump inhibitor throughout the study. Patients were maintained on a controlled high fat diet of 100 grams fat per day during the inpatient periods of the washout and treatment phases.

Patients with CFA <80% in the Washout Phase were randomized to Viokace or placebo for six to seven days of treatment.

The primary efficacy endpoint was the coefficient of fat absorption (CFA) during the treatment phase. CFA is determined from a 72-hour stool collection while the patient is consuming a high-fat diet. The formula for Coefficient of Fat Absorption (CFA) is provided below:

$$CFA\ [\%] = \{[\text{Fat intake (g/day)} - \text{Fat excretion (g/day)}] / \text{Fat intake (g/day)}\} \times 100$$

Of the 218 patients who enrolled, 50 entered the treatment phase, and 49 completed the study. (One patient in Viokace group discontinued after randomization because of a failure of inclusion/exclusion criteria.) Of the 168 patients who failed screening, the majority (88

patients) had clinically-documented chronic pancreatitis and steatorrhea but did not meet the criterion for fecal elastase-1 (FE-1 < 100 μg/g stool); an additional 50 clinically documented patients who met the FE-1 criterion did not have a sufficiently low Washout Phase CFA (CFA < 80%) for randomization into the treatment phase.

The demographics and selected baseline characteristics of the study are summarized in the table below.

Table 5. Demographics of Study (VIO16EPI07-01)

	Viokace (n=30)	Placebo (n=20)
Age (years)		
Mean (SD)	51 (9.9)	51 (7.6)
Min, Max	24, 70	37, 63
Gender, n(%)		
Male	22 (73%)	19 (95%)
Female	8 (27%)	1 (5%)
Race, n(%)		
White	29 (97%)	19 (95%)
Black	1 (3%)	0
Other		1 (5%)
Pancreatectomy Status		
No Pancreatectomy History	18 (60%)	10 (50%)
Post-Pancreatectomy	12 (40%)	10 (50%)

(Table above is modified from a table and supporting text found in the Clinical Review by Marjorie Dannis.)

CFA in the washout phase, CFA in the treatment phase, and change in CFA are summarized in the table below.

Table 6. Washout Phase CFA, Treatment Phase CFA, and Change in CFA (VIO16EPI07-01)

Parameter Phase / Analysis Type	Statistic	Treatment Group Viokase®16 (N=30)	 Placebo (N=20)
CFA%			
Wash-Out Phase	n	30	20
	Mean	47.56	56.64
	SD	24.112	22.192
	Median	53.96	63.02
	Min., Max.	-29.1, 74.5	-9.5, 93.3
Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	85.52	58.02
	SD	8.902	24.249
	Median	88.34	64.87
	Min., Max.	52.6, 95.5	3.5, 93.0
	LSMean (SE)	87.8 (2.6)	58.4 (3.2)
	p-value [a]	<0.0001**	
Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	37.95	1.37
	SD	25.409	13.330
	Median	35.69	-1.65
	Min., Max.	1.6, 119.8	-21.4, 30.5
Percent Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	616.83	-5.78
	SD	2940.244	43.813
	Median	60.59	-2.79
	Min., Max.	-411.5, 16162.5	-136.6, 90.4

* Indicates statistical significance at the 0.050 level; ** Indicates statistical significance at the 0.010 level.

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase CFA% value as covariate

Notes:

1. LS Mean= Least Square Mean; PI= Percentile Imputation; SE= Standard Error.
2. Coefficient of Fat Absorption (CFA%) is defined as: {[Total fat intake during the stool collection period (g) – Total fat excretion during the stool collection period (g)]/ Total fat intake during the stool collection period (g)} x 100%.

Taken from Clinical Review by Marjorie Dannis (Source: VIO16EPI107-01 Study Report (Page 91)

At baseline (i.e., during the washout period), CFA was similar in both the Viokace and placebo groups. During the treatment phase, the mean CFA for patients receiving Creon was 85.5%; the mean CFA for patients receiving placebo was 58.0%. The difference in CFA was 27.5% ($p<0.0001$; 95% CI: 17.8%, 37.2%). The FDA Statistician confirmed the results and was in agreement with the Applicant.

The clinical reviewer performed a subgroup analysis based on washout phase CFA. In the subgroup of patients with washout phase CFA ≤ 40%, the mean change in CFA was 65% in patients administered Viokace (n=10), and 4% in patients administered placebo (n=4). In the subgroup of patients with washout phase CFA > 40%, the mean change in CFA was 25% in patients administered Viokace (n=20), and 1% in patients administered placebo (n=16). The clinical reviewer commented that the results suggest that patients with a washout CFA ≤ 40% had a greater response to Viokace treatment than those with higher baseline CFA values.

The clinical reviewer also performed a subgroup analysis based on pancreatectomy status. In the subgroup of patients with a history of pancreatectomy, the mean treatment phase CFA was 86% in patients administered Viokace (n=12), and 64% in patients administered placebo (n=10). In the subgroup of patients with no history of pancreatectomy, the mean treatment phase CFA was 85% in patients administered Viokace (n=18), and 52% in patients administered placebo (n=10). The clinical reviewer commented that the greater difference in CFA observed in the subgroup with a history of pancreatectomy may be due to a lower washout phase CFA in that subgroup compared to the subgroup with no history of pancreatectomy.

The statistical reviewer conducted an analysis of the change in CFA from the washout phase by gender (see table below).

Table 7. Analysis of Change in CFA by Gender - Mean (SD)

Gender	Change in CFA Mean (SD)		Difference (95% CI)
	Viokace	Placebo	
Female (n=9)	63.0 (33.5) (n=8)	-19.0 (0) (n=1)	82.0 (-1.9, 166.0)
Male (n=41)	28.8 (13.9) (n=22)	2.4 (12.8) (n=19)	26.4 (17.9, 34.9)

(Table above is taken from the Statistical Review by Shahla Farr.)

The statistical reviewer commented that there was a significant treatment by gender interaction effect ($p<0.001$). The statistical reviewer pointed out that the small sample size for females precludes interpretation of a possible difference in gender effects.

The statistical reviewer also conducted an analysis of the change in CFA from the washout phase by age (see table below).

Table 8. Analysis of Change in CFA by Age Category - Mean (SD)

Age Category	Change in CFA Mean (SD)		Difference (95% CI)
	Viokace	Placebo	
≤ 50 Years (n=25)	44.6 (30.7) (n=14)	6.1 (14.2) (n=11)	38.5 (17.7, 59.3)
> 50 Years (n=25)	32.1 (18.8) (n=16)	-4.4 (9.9) (n=9)	36.6 (22.5, 50.6)

(Table above is taken from the Statistical Review by Shahla Farr.)

The statistical reviewer noted that there was no treatment by age interaction. The results appeared similar by age category (≤50 years old vs. <50 years old).

The Clinical Reviewer commented that there were too few non-Caucasian patients to assess the results by race.

Since Viokace is not recommended for Approval during this review cycle, labeling changes will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle.

7.2 Final Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical Efficacy standpoint.

8. Safety

The reader is referred to the Clinical Review by Marjorie Dannis dated November 10, 2010 for complete information.

There is extensive clinical experience with porcine-derived PEPs in patients, as these have been in clinical use since prior to 1938. The AE profile of PEPs has been well described in the clinical literature; the long-term safety experience has demonstrated that the PEPs are relatively safe.

The PEP Guidance states that it is not necessary to conduct long-term safety evaluations of PEPs in support of PEP NDAs; this is largely because of the long and extensive safety experience with PEPs. The PEP Guidance however does state that a short-term safety evaluation is required during the clinical efficacy studies. Since PEPs act locally in the gastrointestinal tract and are not absorbed, the Guidance further recommends that the safety variables assessed should focus predominantly on the monitoring of clinical signs and symptoms during these clinical trials.

A key exception to the relative safety of PEPS is fibrosing colonopathy (FC):

- Fibrosing Colonopathy: FC is a rare but serious condition that may result in colonic stricture. Most of the cases of FC have been reported in younger children with CF. Although the etiology of FC is not known with certainty, FC has been associated with high dose exposure to PEPs. Consensus guidelines have been established by the Cystic Fibrosis Foundation (CFF) in order to limit the maximum daily dose; the guidelines recommend that PEP doses not exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.[7,8,9] (See also Appendix 1.) Continued monitoring for fibrosing

[7] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.

colonopathy that is associated with PEP use is likely to best be performed through global safety surveillance.

Other safety concerns with PEPs are described in the literature, and include the following:

- Hyperuricemia/Hyperuricosuria: Hyperuricemia/hyperuricosuria is thought to occur due to absorption in the gastrointestinal tract of porcine purines; this is particularly of concern in patients with renal impairment, gout or hyperuricemia.

- Hypersensitivity: Hypersensitivity reactions including skin reactions (e.g., pruritus, urticaria) and respiratory reactions (e.g., dyspnea, wheezing) are thought to occur due to inhalation of the PEP powder that may occur when the capsules are opened.

- Irritation to Oral Mucosa: Disruption of the protective enteric coating, and early release of the enzymes may lead to the irritation of the oral mucosa as well as loss of enzyme activity.

The theoretical risk of viral transmission is summarized below:

- Theoretical Risk of Viral Transmission: There is a concern that because PEPS are porcine-derived products, there may be a risk of porcine viruses being transmitted to humans although no such case has been documented, and there are procedures in place to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases). This was also the subject of an Anti-Viral Advisory Committee that took place on December 2, 2008 for Creon; the Committee generally agreed that physicians and patients should be informed of the theoretical risk of viral transmission but the overall risk/benefit profile should not be considered unfavorable so as to preclude patients from receiving the drug.[10,11] (See also Section 2.2.1 of this review, and the Drug Product and Drug Substance Reviews.)

8.1 Issues

The reader is referred to Clinical Review by Marjorie Dannis dated November 10, 2010 for complete information.

[8] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[9] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.
[10] Antiviral Drugs Advisory Committee (December 2, 2008);
<http://www.fda.gov/ohrms/dockets/ac/cder08 html#AntiviralDrugs>
[11] Ku, Joanna. CDTL Review of NDA 20-725, April 30, 2009.

8.1.1 Exposure

Clinical Studies (VIO16IP07-01, STEA-VK00-US01, and VIO16EPI07-01):

A total of 61 patients received at least one dose of Viokace in the three clinical studies. The number of patients exposed to Viokace by dosage in the Viokace clinical program is summarized in the table below.

Table 9. Number of Patients Exposed to VIOKASE®16 by Dosage in the VIOKASE® Clinical Program

Study	VIO16IP07-01	STEA-VK00-US01		VIO16EPI07-01		TOTAL
VIOKASE® Dose	3 tablets, single dose	8 tablets per day for 3 weeks	16 tablets per day for 3 weeks	Placebo	22 tablets per day for 6 days	
Safety Population	20	9	8	20	30	87
Patients receiving VIOKASE®	14	9	8	0	30	61

Notes:
1. Patients in study VIO16IP07-01 received omeprazole 20 mg per day, and in study VIO16EPI07-01 patients took their usual PPI or omeprazole 20 mg per day.
2. For patients enrolled under protocol STEA-VK00-US01, the number of units of lipase per tablet is 16,000 USP, while for patients enrolled under the Viokase®16 22-tablets treatment group of protocol VIO16EPI07-01, the number of units of lipase per tablet is 20,880 USP
3. Number of patients in the Safety Population is as defined in the corresponding Clinical Study Report. In study VIO16IP07-01, all patients who received at least one dose of omeprazole were included in the Safety Population. In studies STEA-VK00-US01 and VIO16EPI07-01, all patients who received at least one dose of VIOKASE®16 or corresponding placebo were included in the Safety Population.
4. Patients receiving VIOKASE indicates the number of patients who received at least one dose of VIOKASE®16.

(Table above is modified from the Clinical Review by Marjorie Dannis.)

Single dose study (VIO16IP07-01): In the single dose study (VIO16IP07-01),14 patients received a single dose of Viokace.

Phase 2b Study (STEA-VK00-US01): In the Phase 2b Study (STEA-VK00-US01), 2 of the 9 patients randomized to the 8 tablets per day group discontinued early (one patient withdrew because of an AE and the other discontinued after 14 days due to poor compliance (63%)). Taking into account the early discontinuations of 2 patients and using the assumption that one Viokace tablet corresponds to 16,000 USP units of lipase, the mean daily dose of lipase intake (lipase units/kg body weight/day) was as follows:

- Eight tablets per day group (n=9): 2021.5 lipase units/kg body weight/day
- Sixteen tablets per day group (n=8): 4130.4 lipase units/kg body weight/day

Pivotal Study (VIO16EPI07-01): In the Pivotal Study (VIO16EPI07-01), one patient in the Viokace group was discontinued from the study for not satisfying the inclusion/exclusion criteria and terminated early due to screening failure. Taking into account the early discontinuation of 1 patient from the Viokace group (i.e., the 22 tablets per day group) and using the assumption that one Viokace tablet corresponds to 20,880 USP units of lipase, the mean daily dose of lipase intake (lipase units/kg body weight/day) was as follows:

- 22 tablets per day group (n=30): 7205.5 lipase units/kg body weight/day

Postmarketing Exposure: The manufacturer does not have specific data on the number of patients treated with Viokace. However, based on sales data (total sales of (b) (4) Viokase 8 tablets and (b) (4) Viokase 16 tablets; from October 2001 to August 2009), and assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day, , the estimated exposure to Viokace is 20,915 patient treatment years.

8.1.2 Safety Findings

Deaths: No deaths were reported during the treatment phases of any of the three studies supporting this submission. The clinical reviewer noted that a 70 year old male patient in the Viokace treatment group of the Pivotal Study (VIO16EPI07-01) experienced a progression of his chronic pancreatitis to inoperable malignant tumor of the head of the pancreas after the study period was completed; this patient subsequently died approximately one month after the end of treatment, and the death was not considered to be related to study treatment.

SAEs: There were a total of four SAEs that were treatment-emergent and occurred during the Treatment Phase of the study

- Pivotal Study (VIO16EPI07-01): The same patient that developed the malignant tumor of the head of the pancreas (see Deaths section above) experienced cholelithiasis during the course of the study; the Clinical Reviewer commented that the event was moderate in intensity and was not considered related to study treatment.
- Phase 2b Study (STEA-VK00-US01): There were three treatment emergent SAEs that occurred in the same patient from the eight-tablet (low dose) treatment group. This patient was hospitalized due to possible hepato-renal syndrome, bacterial peritonitis and ascites. While hospitalized, the following procedures were performed on the patient: paracentesis and culture of ascites fluid, and antibiotic treatment. The Clinical Reviewer commented that the investigator deemed these events to be a result of complications of alcoholic cirrhosis and unrelated to the study medication.
- Single Dose Study (VIO16IP07-01): No treatment emergent SAEs were reported in the Single Dose study.

Dropouts and/or Discontinuations: Across the three studies, there were four cases of study discontinuation due to an AE; three of these cases involved events that occurred prior to the initiation of Viokace therapy.

- Pivotal Study (VIO16EPI07-01): No patients withdrew from the Pivotal Study (VIO16EPI07-01) due to an AE.
- Phase 2b Study (STEA-VK00-US01): One patient from the Phase 2b Study (STEA-VK00-US01) in the Viokace 8-tablet group experienced three SAEs and was withdrawn from the study; this patient is described above under SAEs.

- Single Dose Study (VIO16IP07-01): Three patients discontinued from Study VIO16IP07-01 due to AEs; however, each of these patients was discontinued prior to receiving either Viokace or the liquid meal.

Hypersensitivity Reactions: No hypersensitivity reactions were reported in any of the three studies supporting this submission.

Common Adverse Events:

- Pivotal Study (VIO16EPI07-01): In the randomized double-blind period of Study VIO16EPI07-01 (n=30 in the Viokace group; n=20 in the placebo group), the incidence of any AE's (regardless of causality) was numerically higher during Viokace treatment (23%) than during Placebo treatment (10%). The most common AE's reported were gastrointestinal complaints, which were reported more commonly during Viokace treatment (10%) than during Placebo treatment (0%). The most common gastrointestinal AE's in the Viokace group were biliary tract stones (7%), anal pruritus (7%), abdominal pain (3%), ascites (3%), and flatulence (3%).
- Phase 2b Study (STEA-VK00-US01): Study STEA-VK00-US01 consisted of an eight tablet per day group (low dose group; n=9) and a sixteen tablet per day group (high dose group; n=8). The incidence of any AE's (regardless of causality) was 67% in the low dose group and 50% in the high dose group. The most common AE's reported were gastrointestinal complaints; the incidence was 33% in the low dose group and 25% in the high dose group. There was no obvious effect of dose of Viokace on the pattern of AEs that were observed.
- Single Dose Study (VIO16IP07-01): There were a total of nine subjects who experienced at least one AE. The only AEs reported by more than one subject were dizziness and pharyngolaryngeal pain, which were reported by two subjects each.

Postmarketing Experience: Based on a cumulative review of postmarketing spontaneous data reported for Viokace and other pancrelipase formulations in Axcan Pharma Inc.'s database, most of the AEs reported with pancreatic enzymes preparations during post-marketing experience were gastrointestinal in nature; also, cases of skin disorders and drug ineffective have also been reported with a higher frequency. Most of the events reported during post-marketing experience were assessed as nonserious. Axcan Pharma Inc. and its subsidiaries received 24 individual reports assessed as serious (see Appendix 5 for a listing of these events).

Conclusion: The Clinical Reviewer concluded that the AE profile of Viokace as described in the individual studies was consistent with the currently described AE profile of PEPs in the medical literature. In general, AEs tended to reflect underlying disease, and were most commonly reported in the gastrointestinal (GI) and respiratory systems.

8.2 Final Recommendation

Should Viokace receive an Approval action during a subsequent review cycle, a Risk Evaluation and Mitigation Strategy (REMS) is recommended to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients (see Section 13.1

Recommended Regulatory Action, and see Section 13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements).

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Pediatric Research Committee (PeRC)

A Pediatric Research Committee (PeRC) meeting occurred on July 7, 2010. The PeRC agreed with the Division and the PMHS that pediatric studies for Viokace should be fully waived. The PeRC noted that PMHS should advise the Division on appropriate pediatric labeling text for this NDA.

Consult with Pediatric and Maternal Health Staff (PMHS)

The Pediatric and Maternal Health Staff (PMHS) was consulted prior to the PeRC meeting. The PMHS Consult Review recommended that pediatric studies for Viokace should be fully waived because the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and because the drug is not likely to be used in a substantial number of pediatric patients. (See Consult Review by Elizabeth Durmowicz dated February 16, 2010 for complete information.)

Dr. Durmowicz also provided labeling recommendations (see Consult Review by Elizabeth Durmowicz dated August 17, 2010 for complete information.). The currently proposed labeling language that was agreed upon in labeling meetings that included Dr. Durmowicz for the "Use in Specific Populations" section of Highlights and for the "Use in Specific Populations" section ("Pediatric Use" subsection) of the FPI is shown below:

- "Use in Specific Populations" section of Highlights:

  "Pediatric Patients
  - The safety and effectiveness of VIOKACE have not been established in pediatric patients. (8.4)
  - VIOKACE use in pediatric patients may result in suboptimal growth due to tablet degradation in the gastric environment. (8.4)

- "Use in Specific Populations" section ("Pediatric Use" subsection) of FPI:

  "8.4 Pediatric Use

  The safety and effectiveness of VIOKACE in pediatric patients have not been established. Delayed-release (enteric-coated) capsules (b) (4) for pediatric patients. Due to greater degradation in the gastric environment, VIOKACE, a non-enteric-coated, pancreatic enzyme replacement product, may have decreased bioavailability and therefore may be less efficacious than enteric-coated formulations.7, 8 Thus, use of VIOKACE in pediatric patients may increase the risk

> of inadequate treatment of pancreatic insufficiency and result in suboptimal weight gain, malnutrition and/or need for larger doses of pancreatic enzyme replacement [See Warnings and Precautions (5.1)] The efficacy of VIOKACE was established in adult patients with concomitant proton pump inhibitor (PPI) therapy. The long-term safety of PPI use in pediatric patients has not been established."

Since Viokace is not recommended for Approval during this review cycle, the proposed labeling changes will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Viokace is not systemically absorbed.

11.2 Division of Scientific Investigations (DSI) audits

The reader is referred to the DSI Summary Review by Khairy Malek, dated June 30, 2010 for complete information.

DSI inspections of two clinical sites of the Pivotal Study (VIO16EPI07-01) were performed; these were Site 35 (Dr. Rydewska; Warsaw, Poland; n=8) and Site 42 (Dr. Toskes; Gainesville, Florida; n=6). These sites were selected by the Division based on the number of patients enrolled (Site 35 was the largest international site; Site 42 was the largest domestic site).

Site 35:
The DSI Inspector commented that for Site 35, review of the records revealed no significant discrepancies/regulatory violations.

Site 42:
Site 42 was initially given a classification of "OAI" (Official Action Indicated) by the field investigator because four out of six patients used prohibited concomitant medications (Methadone in Subject 4205, Duragesic Patch in Subject 4201, Oscal [Calcium Carbonate] in Subject 4206, and Calcitrate in Subject 4210). The site was reclassified as "VAI" (Voluntary Action Indicated); the reason for the reclassification to VAI as per the DSI Reviewer (Dr. Malek) was that the identified issues were not considered important enough to impact data integrity. The DSI Reviewer stated in the review "The data are considered reliable in support of the application; however, the review division may choose to consider the clinical impact, if any, of the use of concomitant medications at Dr. Toskes' site in their assessment of the application."

The Clinical Reviewer agreed with the DSI Reviewer that the data obtained from these particular patients may be used in support of this application. The Clinical Reviewer stated that the effect on CFA results was minimal from allowing prohibited concomitant medications. Both the patients using narcotics (the patient using methadone and the patient using the Duragesic Patch) were using these medications chronically. In addition, the doses of each of the narcotics were relatively low; the Duragesic Patch dose was 50 μg/hr and the daily methadone dose was 30 mg. Regarding the patient using Oscal, the Clinical Reviewer

believes that CFA results were not likely to have been affected because the dose (1 gram daily) was considerably lower than the dose described by Saunders et al. as having an effect on fat excretion; that report describes an increase of fat excretion from a daily dose of 6 grams of calcium carbonate and appears to be the basis for the exclusion of calcium carbonate in the protocol (see Clinical Review). Finally, review of the CFA results (for each of the patients that used prohibited concomitant medications) reveals that the results are similar to those of other patients in the same treatment group with similar baseline CFA values (see Tables 7, 9, and 10 in Section 5.3.1.11.6.2 of the Clinical Review); this further supports the conclusion that the effect on CFA results are minimal from the use of prohibited concomitant medications.

The final recommendation is that the data generated by the clinical sites of Drs. Rydewska and Toskes and appear acceptable in support of the application.

11.3 Drug Shortage

Currently, Creon, Zenpep, and Pancreaze are the only PEPs that are available on the market that have undergone the NDA review process. Other PEPs that have not undergone the NDA review process will not be able to be marketed after April 28, 2010; as per the FR Notice (see Section 2.2.1), all PEPs must have an open IND by April 28, 2008, an NDA submitted by April 28, 2009, and an approved NDA by April 28, 2010.

Discussions took place with the manufacturers of Creon, Zenpep, and Pancreaze regarding the inventory and production capability of each of the firms after April 28, 2010, in case no other PEPs are approved by that time. Based on the information obtained from each of the calls, it appears that there would be enough PEPs on the market to meet the needs of patients. Thus, even with a Complete Response action for Viokace, a drug shortage does not appear to be likely.

11.4 Facility Inspections

During recent inspections of the [redacted] (b) (4) manufacturing facility for this application and of [redacted] (b) (4) (contract testing laboratory for [redacted] (b) (4)), the field investigator conveyed deficiencies to the representative of the facilities; based on the Establishment Evaluation System (EES) report, there are "Withhold" recommendations from the Office of Compliance for both [redacted] (b) (4) and for [redacted] (b) (4). Satisfactory resolution of these deficiencies is required before this application may be approved. (See also Sections 3.2.4 and 3.2.5.) [redacted] (b) (4)

12. Labeling

12.1 Proprietary name

A review of the trade name "Viokace" was performed by Irene Chan in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and

Epidemiology (OSE) (see DMEPA Tradename Review dated January 22, 2010). DMEPA's evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Viokace conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. The DMEPA reviewer noted that search of the FDA AERS database was conducted and identified one case where the name Viokase was identified as a cause for error; the case specified the suffix "8" in the name "Viokase 8" as the cause for error. The DMEPA Reviewer stated that because the Applicant has submitted a new name, Viokace, which does not contain a suffix, DMEPA does not believe this case is relevant to their review.

It should be noted that a previously proposed proprietary name for this product, "Viokase" was found to be unacceptable (b) (4)

A Label and Labeling Review was also performed by Irene Chen in the Division of Medication Errors Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) (see DMEPA Label and Labeling Review dated October 18, 2010). Using Failure Mode and Effects Analysis and lessons learned from post-marketing experience with the pancrelipase products, DMEPA evaluated the container labels, carton labeling and insert labeling. DMEPA's findings indicate that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. Detailed reasons and recommendations are provided in the DMEPA Label and Labeling Review. These recommendations will be communicated to the Applicant in the CR Letter (see Section 13.1.1).

Since Viokace is not recommended for Approval during this review cycle, additional labeling changes will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle.

12.2 Physician Labeling / Medication Guide / Carton and Container Labeling

Since Viokace is not recommended for Approval during this review cycle, labeling changes (to Physician Labeling, Medication Guide, and Carton and Container Labeling) will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended action is Complete Response (CR).

The Primary CMC Reviewer (of Drug Product, and of Non-Viral Drug Substance Issues) and the Secondary CMC Reviewer recommend this NDA for CR Action; all of the deficiency items are drug substance deficiencies and were communicated to the drug substance DMF Holder, (b) (4) (DMF (b) (4)), in a separate letter dated October 27, 2010.

The Microbiology Reviewer concluded that this NDA can not be recommended for approval until the microbiology deficiencies cited in the October 27, 2010 letter to (b) (4) have been adequately addressed.

GMP deficiencies noted in a recent inspection of (b) (4) and in a recent inspection of (b) (4) (contract testing laboratory for (b) (4)) resulted in Withhold recommendations from the Office of Compliance for both (b) (4) and (b) (4); in addition, (b) (4)

The Clinical Pharmacology Reviewer, Nonclinical Pharmacology/Toxicology Reviewer, and Clinical Reviewer recommended this NDA for approval. In addition, the Clinical Reviewer recommended that the Risk Evaluation and Mitigation Strategy (REMS) be required as part of approval should Viokace receive an Approval action during a subsequent review cycle.

13.1.1 CR Letter to Axcan Pharma US, Inc. (NDA 22-542)

PRODUCT QUALITY

1. The (b) (4) DMF (b) (4) has been reviewed in support of NDA 022542 and found to contain deficiencies. A letter dated October 27, 2010, was sent to (b) (4) listing several deficiencies regarding the drug substance manufacturing process. FDA conveyed additional information requests at a face-to-face meeting held on November 15, 2010, with you and representatives from (b) (4) (b) (4) should address all deficiencies by directly submitting information to their DMF, or, if the information was previously submitted, then by specific reference to the appropriate submissions. Please notify us when (b) (4) has submitted the requested information. Satisfactory resolution of the deficiencies identified is required before this application may be approved.

FACILITY INSPECTIONS

2. During an inspection of a manufacturing facility referenced in this application, (b) (4) conducted between (b) (4) and

(b) (4), the FDA investigator conveyed deficiencies to a representative of the facility. (b) (4) response dated (b) (4), addressing the deficiencies listed on FDA form 483 dated (b) (4), was not adequate. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

3. Please submit draft labeling revised as follows:

   A. Package Insert

      i. Per the insert labeling, you have proposed imprinting the (b) (4) on the 10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease strength tablets. However, we note that (b) . We recommend that you remove the imprinted (b) (4) replace it with an imprint code.

   Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

   To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

4. Please submit draft carton and container labeling revised as follows:

   A. RETAIL CONTAINER LABELS (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

      i. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please remove the statement, (b) (4) which follows the established name. (b) (4) does not appear in the Official USP monograph title for this product.

      ii. As currently presented, the font utilized for the established name appears to be too thin. Revise the established name to be in accordance with 21 CFR 201.10 (g)(2) so that the established name is printed in letters that are at least half as large as the letters comprising

the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

B. RETAIL CARTON LABELING (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

i. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please revise the established name from (b) (4) to (pancrelipase) Tablets. (b) (4) does not comply with the official USP monograph title for Pancrelipase Tablets per the United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27 and 10/1/10-2/1/11, USP 33/NF 28.

ii. As currently presented, the "Axcan Pharma" logo on the principle display panel appears large and is more prominent than the strength presentation. Minimize or remove this logo.

iii. See comment 3(A)(ii) above.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS will be necessary for Viokace (pancrelipase), if it is approved, to ensure that the benefits of the drug outweigh the possible risks of fibrosing colonopathy and transmission of viral disease to patients. The REMS, should it be approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS, included in your submission dated October 29, 2009, amended on August 20, 2010 and September 17, 2010, which contains a Medication Guide, and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 22542**."

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

13.1.2 Deficiency Letter to (b) (4) (DMF (b) (4))

The deficiencies below were sent to (b) (4) (DMF (b) (4)) in a letter dated October 27, 2010.

1. Provide a list of all contract laboratories that will be used in support of manufacturing your products. Include the specific tests that will be performed by each laboratory, the company name, and address where testing is to be conducted. For each laboratory provide a point of contact including name, phone, fax, and email address.

2. For any contract laboratory used in support of manufacturing your products, provide a copy of the quality agreement between the contract laboratory and the associated manufacturing site.

3. For NDA 022222, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.

4. For NDA 022542, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.

5. For NDA 022175, provide copies of your quality agreements with the NDA holder and with the drug product manufacturer.

6. The establishment inspection report indicates that you have implemented a change in the drug substance intermediate storage container, from (b) (4) white drums to (b) (4) blue drums. Provide the results of studies conducted to demonstrate that the change in storage container will not adversely impact product quality. Specifically, submit the following information:
    a. Extractable/leachable studies and risk analysis performed on the (b) (4) storage container.
    b. Evaluation of the quality of pancrelipase manufactured using the (b) (4) containers.
    c. Available stability data on lots of pancrelipase manufactured using the (b) (4) containers.
    d. Since your process provides for re-use of the drug substance intermediate storage container, provide the results of validation studies performed to support re-use of the (b) (4) container.

    Additionally, review your manufacturing process and verify that the information provided in the DMF accurately reflects your current manufacturing process for drug substances 1206, 1208, 1252, and 1286. If changes were incorporated in the process, provide a list of changes and all relevant data to demonstrate that the changes do not adversely impact product quality.

7. Provide an update on efforts to reduce the bioburden on incoming pancreas glands.

8. Provide the microbial limits specification for pancreatin drug substance manufactured using the 1206 and 1208 processes.

9. Update the manufacturing procedures for the 1208 and 1206 processes with clearly defined time limits for each manufacturing step and the points at which samples for microbiological testing will be collected.

10. Update the information regarding microbiological monitoring of the (b) (4) with the following:
    a. The bioburden alert and action levels from the (b) (4) manufactured using the 1206 and 1208 manufacturing processes.
    b. A commitment to test the bioburden of the (b) (4) from each drum immediately prior to (b) (4)

11. Reaffirm your actions provided previously in the May 4, 2010 amendment to DMF (b) (4) (response to item 2) regarding exceeded microbiological alert and action levels.

12. Provide a commitment to clean all processing equipment between individual batches.

13. Section 3.2.S.7.1.2.4.1 in the August 12, 2010 submission lists the total aerobic microbial count (TAMC) limits for stability batches of drug substance at (b) (4) CFU/g (1206) and (b) (4) CFU/g (1252). The microbial limits for all pancrelipase stability batches should be at or below the levels established for release testing. Provide updated stability batch acceptance criteria for each of the pancreatin products.

14. As a condition of NDA approval:
    a. Develop and implement a release test procedure that monitors for the presence of *Bacillus cereus* diarrheal enterotoxin in pancrelipase samples.
    b. Provide a commitment to test each batch of drug substance for *Bacillus cereus* diarrheal enterotoxin prior to release.

13.2 Risk Benefit Assessment

The benefit characteristics appear similar to those of already marketed PEPs for treatment of EPI. The outstanding risk issues with this application are concerns about the ability of the drug substance manufacturer to adequately ensure the microbial quality of the drug substance (see Items #7 to #14 in Section 13.1.2 of this review), and concerns about adverse effects on product quality from a change in the drug substance intermediate storage container (see Item #6 in Section 13.1.2 of this review).

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

See Section 13.1 of this review.

13.4 Recommendation for Postmarketing Required Pediatric Studies

No postmarketing required pediatric studies are recommended for this Application.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

PMR studies are recommended, with the following language for the Complete Response Letter:

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

An unexpected serious risk of pancreatic enzyme products (PEPs) including Viokace (pancrelipase) Tablets in patients with chronic pancreatitis or pancreatectomy is fibrosing colonopathy (a stricture process of the colon); the magnitude of this risk in these patients is unknown. In addition, there is an unexpected serious risk of transmission of viral disease to patients from porcine-derived PEPs such as Viokace (pancrelipase) Tablets.

Based on the above, FDA has determined that if NDA 022542 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the unexpected serious risks of fibrosing colonopathy and transmission of viral disease to patients taking Viokace (pancrelipase) Tablets.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 022542 is approved, you will be required to conduct the following:

1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with chronic pancreatitis or pancreatectomy treated with Viokace (pancrelipase) Tablets in the US and to assess potential risk factors for the event.

2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Viokace (pancrelipase) Tablets.

Any additional specific details of these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete one or both of these studies prior to re-submitting your application, you may include the final report(s) and relevant data sets in your Complete Response submission to facilitate review of the information.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

Since Viokace is not recommended for Approval during this review cycle, postmarketing commitments will be planned for negotiation with the Applicant should Viokace receive an Approval action during a subsequent review cycle.

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: CFF Dosing Guidelines

The CFF Dosing Guidelines (from Borowitz et al., 1995[12]) are provided below:

> "Infants may be given 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding. Although it makes physiologic sense to express doses as lipase units per gram of fat ingested, a weight-based calculation is a practical substitute beyond infancy. Enzyme dosing should begin with 1000 lipase units/kg per meal for children less than age four years, and at 500 lipase units/kg per meal for those older than age 4 years. Enzyme doses expressed as lipase units per kilogram per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two or three snacks per day.
>
> If symptoms and signs of malabsorption persist, the dosage may be increased by the CF center staff. Patients should be instructed not to increase the dosage on their own. There is great interindividual variation in response to enzymes; thus a range of doses is recommended. Changes in dosage or product may require an adjustment period of several days. If doses exceed 2500 lipase units/kg per meal, further investigation is warranted (see discussion of management of CF, below). It is unknown whether doses between 2500 and 6000 lipase units/kg per meal are safe; doses greater than 2500 lipase units/kg per meal should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of absorption.
>
> Doses greater than 6000 lipase units/kg per meal have been associated with colonic strictures in children less than 12 years of age, whether standard-strength enzymes or high-strength pancreatic enzymes were taken. Patients currently receiving higher doses should be examined and the dosage either immediately decreased or titrated downward to a lower range."

Borowitz et al. 2002[13] states:

> "To avoid fibrosing colonopathy, it is recommended that enzyme doses should be less than 2500 lipase units/kg per meal or less than 4000 lipase units/gram fat per day."

Fitzsimmons et al. 1997[14] states:

> "A 1995 consensus conference on the use of pancreatic-enzyme supplements sponsored by the U.S. Cystic Fibrosis Foundation recommended that the daily dose of pancreatic enzymes for most patients remain below 2500 units of lipase per kilogram

[12] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[13] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.
[14] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

per meal (10,000 units per kilogram per day) and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment. Our finding of a pronounced dose-response relation between high daily doses of pancreatic enzymes and the development of fibrosing colonopathy in young patients with cystic fibrosis provides support for these recommendations."

APPENDIX 2: Microbiology Deficiency Items (September 15, 2009)

Microbiology Deficiency Items (from DMF Deficiency Letter sent to (b) (4) dated September 15, 2009; Master File (b) (4)):

22) Provide the following information regarding the handling and testing of the intact pancreas glands prior to (b) (4):

    a. Are the glands washed or processed in any way prior to (b) (4)?

    b. Are microbiological acceptance criteria in place for the pancreas glands?

23) Section 3.2.S.2.1.2.2 of DMF (b) (4) states that the maximum length of the pancreatin/pancrelipase manufacturing process is (b) (4) Please provide the following information regarding the manufacturing process:

    a. A justification for this extended processing time

    b. The maximum storage time and storage temperature of the (b) (4) stored in (b) (4) drums

    c. Data showing that the (b) (4) stored in the (b) (4) drums does not support microbial growth

APPENDIX 3: Microbiology Deficiency Items (May 3, 2010)

Deficiencies in Drug Substance Microbiology (from DMF Deficiency Letter sent to (b) (4) dated May 3, 2010; Master File (b) (4)):

1. Provide a justification for all in-process holding times associated with the manufacture of Pancreatin using the 1206 and 1208 manufacturing processes. The processing times and holding conditions prior to the "(b) (4) step" are of particular importance since most of the microbial proliferation occurs during that stage of the manufacturing process.

2. Provide the following information regarding in-process microbial alert and action levels for the 1206 and 1208 Pancreatin manufacturing processes:
   a. The total aerobic microbial count (TAMC) alert and action levels for (b) (4) samples collected following activation but immediately before the addition of (b) (4) to the (b) (4) TAMC alert and action levels should be commensurate with those obtained from (b) (4) gland samples as reported in the 16 April 2010 submission to the agency.
   b. TAMC alert and action levels for samples of the (b) (4) collected immediately prior to (b) (4)
   c. A summary of the actions taken when alert and action levels are exceeded

3. Provide an explanation for the wide range of TAMC prior to the addition of (b) (4) for 1206 pancreatin lots (< (b) (4) CFU/g in 39 lots as compared to > (b) (4) /g in 11 lots) in the data provided in attachment 5 of the 16 April 2010 submission. Provide a list of corrective actions to be taken to ensure that acceptable bioburden levels are achieved prior to the addition of (b) (4) to the (b) (4)

4. According to the manufacturing procedure listed on pages 790-791 of volume 24.14 of DMF (b) (4), the 1206 (b) (4) process can take place for (b) (4) Explain the rationale for determining which process to use and correlate the TAMC counts obtained in the 1206 process samples (attachment 5 of the 16-April-2010 document) with the holding times and temperatures used for each batch.

5. Step f) (1) of the 1208 process description states that (b) (4) Provide the maximum storage time for the 1208 (b) (4) prior to (b) (4)

6. Provide the following information regarding testing for the diarrheal form of *Bacillus cereus* enterotoxin:
   a. A commitment to test each batch of Pancreatin drug substance for *Bacillus cereus* enterotoxin prior to release
   b. A description of the *Bacillus cereus* enterotoxin test method, the validation procedure, and a summary of the supporting validation data.

APPENDIX 4: Microbiology Reviewer's Assessment of [(b) (4)] Response

The Microbiology Reviewer's assessment of [(b) (4)] response to Deficiency Items in the May 3, 2010 Letter is summarized below. (This is taken from the CDTL Review for Ultresa dated November 24, 2010.)

The Microbiology Reviewer deemed the responses to each of the deficiency items in the letter sent to [(b) (4)] satisfactory. (See Microbiology Review by Stephen Langille dated June 9, 2010 filed under Master File [(b) (4)] for complete information.)

Response to Deficiency Items #1 to #6: A summary of the Microbiology reviewer's assessment of the adequacy of [(b) (4)] response to Items #1 through #6 in the Letter to [(b) (4)] dated May 3, 2010 (see Appendix 2) is presented below.

(1) Justification for in-process holding times (especially prior to [(b) (4)] response to this item was deemed satisfactory by the Microbiology Reviewer. [(b) (4)] provided the processing and holding times and conditions for the 1206 and 1208 manufacturing processes.

(2) In-process total aerobic microbial count (TAMC) alert and action levels (for 1206 and 1208). [(b) (4)] response to each of the parts of this item was deemed satisfactory by the Microbiology Reviewer. (a) The [(b) (4)] samples alert level proposed was [(b) (4)] CFU/g and the action level proposed was [(b) (4)] CFU/g. The Microbiology Reviewer noted that an incoming gland microbial limit acceptance criterion has not been established, but the DMF holder has committed to [(b) (4)] The Microbiology Reviewer also noted that [(b) (4)] will track the microbial counts of incoming glands to determine which practices and slaughterhouses provide the greatest control of gland bioburden. (b) The action limit proposed for [(b) (4)] pancreatin and for the finished drug substance was no more than [(b) (4)] CFU/g . (c) Exceeded in-process alert levels of [(b) (4)] CFU/g will result in a Bacillus diarrheal enterotoxin (BDE) test; a positive BDE test will result in an out of specification (OOS) investigation confirmation of the test results, corrective action, and rejection of the batch. An exceeded in-process action limit of [(b) (4)] CFU/g TAMC will also result in an OOS investigation and rejection of the batch following confirmation of the results.

(3) Explanation for wide range of TAMC prior to [(b) (4)] (for 1206 lots) and corrective actions. [(b) (4)] response to this item was deemed satisfactory by the Microbiology Reviewer. [(b) (4)] stated that the wide range of TAMC is due to the [(b) (4)] The following corrective actions were provided to ensure acceptable bioburden levels prior to the addition of [(b) (4)]: (a) removal of the [(b) (4)] for the 1206 process (see item #4 below); (b) addition of an in-process specification for the [(b) (4)] samples for the 1206 and 1208 process; and (c) use of [(b) (4)] (1206 manufacturing

process) and [(b) (4)] (1208 manufacturing process). The Microbiology Reviewer commented that although it is possible that [(b) (4)] could account for the wide fluctuations in TAMC observed in different lots of 1206 Pancreatin, it is not the only possible explanation since the 1208 manufacturing process, which uses a [(b) (4)], also showed varying microbial counts. However, the Microbiology Reviewer concluded that implementation of a new sampling [(b) (4)] and tighter microbial limits do represent significant improvements to the manufacturing process.

(4) Rationale for selection of one of two 1206 [(b) (4)] processes [(b) (4)] [(b) (4)] response to this item was deemed satisfactory by the Microbiology Reviewer. [(b) (4)] agreed to cease production using the extended holding time for the 1206 manufacturing process, and provided a revised 1206 manufacturing protocol.

(5) Request to provide the maximum storage time for the 1208 [(b) (4)] response to this item was deemed satisfactory by the Microbiology Reviewer. [(b) (4)] stated that the maximum storage time for the 1208 process is [(b) (4)], and provided a summary of the microbiological studies to support the proposed [(b) (4)] hold time. The Microbiology Reviewer commented that although a maximum holding time of [(b) (4)] is not considered ideal, the [(b) (4)] is stored in the presence of the [(b) (4)] and is unlikely to support microbial growth; he further noted that the [(b) (4)] will be tested for TAMC prior to [(b) (4)], and that the action level is no more than [(b) (4)] CFU TAMC/g.

(6) Commitment to test Bacillus cereus enterotoxin prior to release including description of methods and validation. [(b) (4)] response to each of the parts of this item was deemed satisfactory by the Microbiology Reviewer. (a) [(b) (4)] stated in an amendment dated June 6, 2010, that the Bacillus cereus enterotoxin test will be a finished active pharmaceutical ingredient (API) release test for the 1206 and 1208 product. (b) A [(b) (4)] algorithm for enterotoxin testing was provided in the June 6, 2010 amendment. The initial test will be done using the 3M TECRA BDE test. If this test is positive, an OXOID-RPLA test will be used to confirm the results of the TECRA test. A positive OXOID-RPLA test will result in a "Positive" report for the sample. A negative OXOID-RPLA test will result in verification of the negative results with a Western blot assay. A positive Western blot will be reported as a "positive" sample result. A negative Western blot will be reported as a "negative" sample result [(b) (4)] states that this test algorithm was implemented due to the high incidence of false positive results normally obtained using the TECRA and OXOID-RPLA tests. The Microbiology Reviewer noted that the proposed BDE testing algorithm was judged to be acceptable by food safety experts from CFSAN. The Microbiology Reviewer further noted that as of June 6, 2010, the OXOID test and Western blot assay have not been validated to test for the presence of the BDE toxin. Therefore, it was agreed upon in a meeting with Axcan held May 20, 2010 (that included members of both Axcan and [(b) (4)]) that the TECRA will be used as the release test until the OXOID and Western blot tests have been validated and the validation studies submitted to the FDA (see Response to Question 15 in Memo by Stephen Langille dated May 26, 2010 filed under NDA 22-222; also see Meeting Minutes dated June 18,

2010). A summary of the validation studies supporting the TECRA test was provided in a submission from (b) (4) dated May 28, 2010.

APPENDIX 5: Summary of 24 Individual Postmarketing Reports Assessed As Serious

[The following is taken from Module 2 of the submission (Summary of Clinical Safety). These are 24 individual reports that Axcan Pharma Inc. and its subsidiaries received and that were assessed as serious.]

- Eleven (11) cases of fibrosing colonopathy were reported from spontaneous notification (10 cases) and literature (1 case).

- Three (3) reports involving an unspecified formulation of pancreatic enzymes were received from the World Health Organization (WHO) Vigibase database and were assessed as serious by the initial reporter. A causal relationship has not been provided and minimal information is available. These cases include diarrhea, abdominal distension and weight increase in one patient, weight decreased, pain and malabsorption in another patient as well as stomach discomfort, diarrhea, abdominal pain, pain, nausea, malaise, frequent bowel movements, dizziness and dehydration in the third patient.

- One (1) case of 3 episodes intestinal obstruction requiring hospitalization was reported in a pediatric patient who was treated with ULTRASE®. This was not medically confirmed.

- One (1) case of intussusception was reported in a 15-year-old patient treated with ULTRASE® as well as another pancreatic enzyme formulation (Pancrease®). The patient was switched to ULTRASE®, used it for 9 days and was switched back to his previous pancreatic enzyme formulation. One (1) week later, the patient was diagnosed with intussusception. The patient was treated with ileostomy, received total parenteral nutrition (TPN) and was recovering from the event at the time of the report.

- One (1) case of fatal intestinal perforation was reported in a 4-year-old patient who was treated with generic formulation of pancrelipase as well as ULTRASE®. This report was received from the father of the patient and was not medically confirmed (no causality assessment provided).

- One (1) case of nausea requiring hospitalization was reported in a 62-year-old female subject enrolled in a Pfizer-sponsored study entitled "A phase I study of Bevacizumab in combination with SU011248" who was taking VIOKASE® (non-study medication). The investigator assessed the nausea as possibly related to VIOKASE®. Co-suspected medications included SU-011-248 (sunitinab malate), bevacizumab, Celebrex (celecoxib) as well as ibuprofen. Confounding factors included the patient's underlying solid tumor and infection. The patient also experienced abdominal pain/cramp, cough, dehydration, dyspnea and body aches but they were judged as unlikely related or not related to VIOKASE®. The patient had recovered from nausea at the time of reporting.

- One (1) case of diarrhea and abdominal discomfort was reported in an 18-month-old patient treated with ULTRASE® MS for an unknown indication. The case was assessed as medically relevant. The patient was given a new bottle of ULTRASE® from a different lot and she recovered from the events.

- One (1) fatal case of dispensing error with subsequent overdose, aspiration, atelectasis and death was reported in a 3-week-old male infant who was treated for pancreatic insufficiency with VIOKASE® powder through a naso-gastric (ng) tube. VIOKASE® is not approved for administration through ng tubes.

- One (1) case of severe abdominal pain (cramps) was reported in a 71-year-old male patient treated with ULTRASE® MT for an unknown indication. The patient was hospitalized for 9 days. ULTRASE® was discontinued, but the outcome was not reported.

- Two (2) cases of diarrhea leading to hospitalization were reported in patients treated with pancreatin (PANZYTRAT®). One of the patients recovered from the event (action taken not reported).

- One (1) case of product commingling, feeling abnormal, loss of consciousness, cardio-respiratory arrest and drug screen positive for methadone was reported in a 47 year-old female patient treated with VIOKASE®16 (pancrelipase) for chronic pancreatitis. This report has not been medically confirmed. The patient has been taking VIOKASE® for many years without any problem and experienced the above mentioned adverse events after taking one pill found in VIOKASE® bottle with different appearance which was clarithromycin. The patient recovered and continued taking VIOKASE® without any adverse event. A potential product commingling (clarithromycin pills in VIOKASE® bottle) at the manufacturing, packaging and dispensing (pharmacy) levels was ruled out.

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

/s/

ANIL K RAJPAL
11/24/2010

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-542
Submission Code	N
Letter Date	October 29, 2009
Stamp Date	October 30, 2009
PDUFA Goal Date	November 30, 2010
Reviewer Name	Marjorie F. Dannis, MD
Through	Anil Rajpal, MD
Review Completion Date	November 8, 2010
Established Name	Pancrelipase Tablets
(Proposed) Trade Name	Viokace
Therapeutic Class	Pancreatic Enzyme Product (PEP)
Applicant	Axcan Pharma Inc
Priority Designation	Standard
Formulation	For oral administration
Dosing Regimen	In combination with a proton pump inhibitor, not to exceed 2,500 USP lipase units/kg/meal or 10,000 USP lipase units/kg/day
Indication	Exocrine pancreatic insufficiency secondary to chronic pancreatitis or pancreatectomy
Intended Population	Adults with exocrine pancreatic insufficiency

TABLE OF CONTENTS

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Reviewer recommends a Complete Response (CR) action based upon manufacturing and product deficiencies.

From a solely clinical perspective, the safety and efficacy of Viokace have been established for the treatment of adults with exocrine pancreatic insufficiency (EPI) secondary to chronic pancreatitis (CP) or partial/total resection of the pancreas. The pivotal study VIO16EPI07-01 demonstrated the short-term efficacy and safety of Viokace (with concomitant proton pump inhibitor [PPI]) in adults with EPI secondary to CP or partial/total resection of the pancreas. The safety and effectiveness of Viokace have not been established in pediatric patients, thus this non-enteric coated pancreatic enzyme product (PEP) should not be indicated for use in the pediatric population.

1.2 Risk Benefit Assessment

The efficacy and safety of Viokace were demonstrated by the results of one short-term Phase 3 trial (Study VIO16EPI07-01). The pivotal study, VIO16EPI07-01 was a multicenter, randomized, double-blind, placebo-controlled, parallel study evaluating the efficacy and safety of Viokace in 50 patients, ages 24 to 70 years, with a diagnosis of EPI secondary to CP or partial/total resection of the pancreas. Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Viokace and placebo. The results showed that there was a clinically meaningful and statistically significant increase in CFA in Viokace treated patients versus patients treated with placebo. In addition, the patients who were the most severely affected (had the lowest baseline CFA level), gained the most benefit by having the largest increase in CFA.

Exposure to Viokace during the clinical studies was similar to what is currently encountered for PEP treatment of CP patients in clinical practice. One death occurred during the VIOKACE development program, but was thought by the investigators and by this Reviewer to be related to the patient's serious underlying disease and not to be related to the study drug. The Serious Adverse Events (SAEs) that occurred were also thought by the investigators and by this Reviewer not to be related to Viokace treatment. The Adverse Events (AEs) observed during the studies (mostly in the gastrointestinal organ system) were consistent with the underlying diseases of the patients, and most AEs were mild or moderate in severity. In general, the AE profile reported in these studies was similar to the side-effect profile of PEPs as reported in the medical literature.

Overall, the clinical information obtained from the short-term efficacy and safety studies is adequate to support approval of Viokace for the treatment of adults with EPI secondary to CP or partial/total resection of the pancreas.

1.3 Recommendations for Postmarketing Risk Management Activities

1.3.1 Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

In accordance with section 505-1 of the FDCA, a REMS is necessary for Viokace to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

The proposed REMS must include a Medication Guide and a Timetable for Submission of Assessments. The timetable for submission of assessments shall be no less frequent than by 18 months, three years, and in the seventh year after the REMS is initially approved. Each assessment must assess the extent to which the elements of the REMS are meeting the goals of the REMS and whether the goals or elements should be modified.

1.3.2 Postmarketing Study Requirements (PMRs)

The Agency has determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients taking Viokace.

Therefore, based on appropriate scientific data, the Agency has determined that, if this application is approved in a subsequent review cycle, pursuant to section 505(o)(3) of the FDCA, The following studies will be required:

1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with chronic pancreatitis or pancreatectomy treated with Viokace in the US and to assess potential risk factors for the event.

2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Viokace.

The specific details of these required post-marketing studies will be described more fully in the approval letter for this application, should it be approved.

1.3.3 Recommendations for other Postmarketing Study Commitments

Postmarketing Commitments will be negotiated should Viokace receive an approval action during a subsequent review cycle.

2 Introduction and Regulatory Background

2.1 Product Information

Viokace is the investigational agent studied in this application. Viokace is an immediate release pancreatic enzyme product for oral administration. The active ingredient, pancrelipase, is a concentrated porcine extract comprised of the pancreatic enzymes: lipase, amylase, and protease. Viokace consists of pancrelipase formulated in two dosage strengths:

- 10,440 USP units of lipase; 39,150 USP units of protease; 39,150 USP units of amylase
- 20,880 USP units of lipase; 78,300 USP units of protease; 78,300 USP units of amylase

"Viokace" has been accepted as the trade name for this application.

Currently, the mutually agreed upon (Division and Applicant) indication that Viokace will receive is the following (in Indications and Usage section of Highlights of Prescribing Information):

"VIOKACE is a combination of porcine-derived lipases, proteases, and amylases. VIOKACE, in combination with a proton pump inhibitor, is indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy."

Currently, the mutually agreed upon dosing regimen for Viokace is the following (in Dosage and Administration section of Highlights of Prescribing Information):

"Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.

- Begin with 500 lipase units/kg of body weight per meal 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.
- Individualize dosage based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet."

2.2 Treatments for Proposed Indications

PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). PEPs have been widely available in the US and throughout the world as nutritional supplements, and as over-the-counter (OTC) and prescription therapies; however, in the US, PEPs were never evaluated for safety and efficacy under NDA until recently when the FDA required that all PEPs be marketed under an approved NDA by April 28, 2010. Cotazym (NDA 20-580) was approved in 1996, but is not currently marketed. On April 30, 2009, Creon (pancrelipase) was approved for the treatment of EPI due to CF or other conditions; on April 30, 2010, an efficacy supplement for Creon was approved so that the current indication for Creon is for the treatment of EPI due to CF, chronic pancreatitis, pancreatectomy, or other conditions. In addition, Zenpep (pancrelipase) was approved for the treatment of EPI due to CF or other conditions on August 27, 2009, and Pancreaze (pancrelipase) are approved for the treatment of EPI due to CF or other conditions on April 12, 2010.

2.3 Availability of Proposed Active Ingredient in the United States

Previous formulations of Viokace had been marketed in the US (under the trade name "Viokase"); however, these formulations are not currently marketed in the US because of requirements that all PEPs be marketed under an approved NDA by April 28, 2010. The manufacturer does not have specific data on the number of patients treated with Viokace. However, an estimate of the patient exposure to "Viokase" was calculated for the period of September 1, 2009 to January 31, 2010 from the number of product units distributed in the US. Since dosing of pancrelipase products is weight-based (for children and adults), the calculation of patient exposure required the following assumptions:

- The majority of patients taking Viokace for the treatment of EPI are adult patients.
- The average weight of adult males and females is 60 kg.
- A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzymes supplementation has been recommended by the FDA in conjunction with the CFF in the Guidance for Industry "Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." Therefore, an average dose of 1,500 USP lipase units/kg/meal from Viokace supplementation was assumed for calculation purposes.
- Patients would be consuming a total of four meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the average dose administered is 360,000 USP lipase units/day. Table A below (electronically scanned and copied from Applicant) displays the US Unit Sales of "Viokase" and the patient exposure from September 1, 2009 to January 31, 2010.

Table A: US Unit Sales and Patient Exposure from Sept. 1, 2009 - Jan. 31, 2010

	VIOKASE® 8	VIOKASE® 16
Number of tablets	(b) (4)	
Number of lipase units		
Number of days of treatment	262,560	60,596
Number of years of treatment	719	166
Total number of patient treatment years	885	

In addition, the active ingredient in Viokace (i.e., pancrelipase) is presently available as enteric-coated (EC) formulations in three approved products (Creon, Zenpep, and Pancreaze). However, there is not currently a non-EC formulation available. If Viokace was to be approved, it would be the first approved non-EC formulation.

Secondary to concerns about variability in potency and safety of PEPs, the FDA has required that all PEPs be marketed under an approved NDA effective April 28, 2010. Thus, PEPs are no longer available without a prescription. Please see Section 2.5 for a complete description of regulatory history.

2.4 Important Safety Issues with Consideration to Related Drugs

PEPs were first marketed in the US prior to the Food Drug and Cosmetic Act of 1938; thus, they had never been evaluated for safety and efficacy under an NDA. In the 1990's, concerns about variability in potency and safety (such as fibrosing colonopathy) led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective (GRAS and GRAE, respectively). There were substantial irregularities in potency resulting in patients being both under dosed, as well as over dosed, each presenting a different safety and efficacy concern.

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). Fibrosing colonopathy (FC) is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs.[1] There was also a concern that the enteric-coating or excipients in the delayed-release PEP formulations could lead to FC. As a result of these potential efficacy and safety concerns, the CFF and FDA published weight-based dosing guidelines for PEP administration (see Section 2.1). Thus, monitoring for FC should be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products, as should the CFF/FDA weight-based dosing guidelines.

[1] FitzSimmons, SC, Burkhart, GA, Borowitz, D et al. High Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Cystic Fibrosis. New England Journal of Medicine. May 1997; 336 Number 18; 1283-9.

Hyperuricemia and hyperuricosuria have been reported in patients with EPI treated with PEPs. Caution should be exercised when prescribing PEPs to patients with gout, renal impairment, or hyperuricemia. Porcine-derived PEPs contain purines that may increase blood uric acid levels.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is the initial NDA submission for Viokace. Relevant clinical pre-submission regulatory activity for Viokace was notable for the following:

A Special Protocol Assessment was submitted by the Applicant on November 13, 2006. The protocol (VIO16EPI07-01) was entitled "A Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled, Phase III Study to Assess the Safety and Efficacy of Viokase for the Correction of Steatorrhea in Patients with Exocrine Pancreatic Insufficiency." The Division and the Applicant reached agreement on the following points:

- The overall design of the study which appeared to meet the criteria for demonstrating efficacy and safety set forth in the "Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs."
- The acceptability of the proposed concomitant use of PPIs provided that the dose is to be standardized during the study.
- In addition, the FDA clarified that the proposed pivotal study design appeared adequate to support the limited indication of adult patients with chronic pancreatitis or pancreatectomy. However, the proposed protocol would not support the use of Viokace in patients with cystic fibrosis or in a pediatric population.

The regulatory background of the PEPs is as follows:

PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). PEPs have been widely available in the US and throughout the world as nutritional supplements, and as OTC and prescription therapies; however, PEPs had never been evaluated for safety and efficacy under an NDA.

Due to concerns about variability in potency, the Agency published a Notice of Proposed Rule in the Federal Register (FR) on 15-July-1991 establishing that PEPs are not considered GRAS and GRAE, and the PEPs were considered misbranded. Concurrently, the Agency declared its intention to consider all PEPs to be new drugs requiring an approved NDA for continued marketing. This position was reaffirmed on 25-April-1995 with the publication of a Final Rule calling for all PEPs to be marketed drug products under approved NDAs in order to remain on the market. In April 2004, the Agency published in the FR a Notice of Requirement for NDA Approval of all PEPs within the next four years, with a deadline of 28-April-2008. In October 2007, enforcement discretion was extended until 28-April-2010, but all PEPs must have an open IND by 28-April-2008, and an NDA submitted by 28-April-2009.

In April 2006, The Guidance for Industry; Exocrine Pancreatic Insufficiency Drug Products was published[2] (the Guidance). In this document, the FDA stated its expectation that animal (porcine and bovine) derived PEP NDA applications would be submitted as 505(b)(2) applications. In these submissions, Applicants were allowed to have a limited clinical development program, which could include short-term studies to establish efficacy and safety. These abbreviated clinical development programs are acceptable for PEP applications because assumptions were made about the efficacy and safety of these drugs based on a large body of efficacy and safety information available in the medical literature. The PEPs are also considered to be the standard of care for EPI due to CF and other causes, as described in the current CFF consensus statement.

2.6 Other Relevant Background Information

PEPs are currently used by adult patients as well as pediatric patients for the treatment of EPI due to a variety of causes. To date, there are three PEPs approved for the treatment of EPI due to CF and other conditions. These are Creon, Zenpep and Pancreaze, all of which are enteric-coated pancreatic enzyme products. There is a substantial body of literature to support dosing, safety and efficacy of the enteric-coated PEPs in pediatric patients with EPI due to CF. Most experts acknowledge that the enteric-coated products represent an advance over non-enteric coated products.[3]

CP is an inflammatory disorder with loss of exocrine and endocrine functions. One of the most common causes of CP in adults is alcoholism. In children, CP is rare and the condition behaves differently.[4]

The Viokace development program consisted of three clinical studies, each with an exclusively adult patient population with EPI secondary to CP. No clinical studies were done in pediatric patients; also, no clinical studies were done in patients with CF.

In contrast to the substantial body of literature to support dosing, safety and efficacy of the enteric-coated PEPs in pediatric patients with EPI due to CF, data from the literature are inadequate to support safety, efficacy or dosing for PEP products in pediatric patients for the treatment of EPI due to CP or EPI due to conditions other than CF. Because pediatric patients should be growing and are therefore likely to be at greater risk for poor weight gain and/or malnutrition than adults, to claim a pediatric indication for the treatment of EPI due to CP, demonstration of adequate growth and nutrition in pediatric patients is required. Thus, safety and efficacy of Viokace use in children has not yet been established.

CP is a rare condition in pediatric patients and given the safety and efficacy concerns of the non-enteric coated products, Viokace would not represent a therapeutic benefit over the enteric-

[2] U.S. Department of Health and Human Services. Food and Drug Administration .Center for Drug Evaluation and Research (CDER). "Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products –Submitting NDAs."(http://www.fda.gov/Cder/guidance/6275fnl.pdf). April 2006.

[3] Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep.* 2007;9(2):116-22.

[4] Mischler EH, Parrell S, Farrell PM, Odell GB. Comparison of effectiveness of pancreatic enzyme preparations in cystic fibrosis. *Am J Dis Child.* 1982;136(12):1060-3. (Abstract only)

coated products. Based on the preferred use of enteric-coated products, Viokace is not likely to be used in a substantial number of pediatric patients. In addition, the approved indication for Viokace is likely to include concomitant use of a PPI and the safety of chronic PPI use in children has not been established. Therefore, the Division, in association with The Pediatric and Maternal Health Staff (PMHS) has recommended a full waiver of PREA required studies based on the following criteria: (i) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (ii) is not likely to be used in a substantial number of pediatric patients. (See also PMHS Consult Memo by Dr. Elizabeth Durmowicz dated February 16, 2010.)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

3.2 Compliance with Good Clinical Practices

DSI inspections of selected clinical sites were performed, and included the inspection of Sites 42 in Gainesville, Florida and 35 in Warsaw, Poland (Drs. Toskes and Rydewska, respectively). These sites were selected by the Division based on the number of patients enrolled (Site 42 had 6 patients; Site 35 had 8 patients). Site 42 was the largest domestic site; Site 35 was the largest international site.

Site 35:

For Site 35, the DSI Staff Letter states "The study appears to have been conducted adequately, and the data generated by this site can be used in support of the respective indication" (see DSI Staff Letter by Dr. Jean Mulinde dated August 19, 2010). The Clinical Inspection Summary states "The data generated from this site can be used in support of the NDA" (see Clinical Inspection Summary by Dr. Khairy Malek dated June 30, 2010).

Site 42:

Site 42 was initially given a classification of "OAI" (Official Action Indicated) by the field investigator because four out of six patients used prohibited concomitant medications (Methadone in Subject 4205, Duragesic Patch in Subject 4201, Oscal [Calcium Carbonate] in Subject 4206, and Calcitrate in Subject 4210); the Clinical Inspection Summary states in the key to classifications that OAI indicates "Significant deviations from regulations. Data unreliable." (See DSI Staff Letter by Tejashri Purohit-Sheth dated June 1, 2010, and Clinical Inspection Summary by Dr. Khairy Malek dated June 30, 2010.)

The site was reclassified as "VAI" (Voluntary Action Indicated); the Clinical Inspection Summary states in the key to classifications that VAI indicates "Deviation(s) from regulations" (see Clinical Inspection Summary by Dr. Khairy Malek dated June 30, 2010). The reason for the reclassification to VAI as per the DSI Reviewer (Dr. Malek) was that the identified issues were not considered important enough to impact data integrity. The DSI Reviewer noted that there was no evidence that the subject identified to have taken Calcitrate (Subject 4210) actually took Calcitrate; the DSI Reviewer added that the Clinical Investigator (Dr. Toskes) provided assurance that this subject did not use Calcitrate. Regarding the subject identified to have used the Duragesic Patch (Subject 4201), the DSI Reviewer pointed out that the Clinical Investigator stated that the effect of the patch on gut motility is less than that of oral or parenteral administration. For the subject identified to have used Oscal (Subject 4206), the DSI Reviewer commented that calcium was not absolutely prohibited by the protocol; the DSI Reviewer pointed out that calcium was allowed in multivitamin preparations.

The DSI Reviewer stated (in the overall assessment of findings and recommendations of the Clinical Inspection Summary dated June 30, 2010) that "The data are considered reliable in support of the application; however, the review division may choose to consider the clinical impact, if any, of the use of concomitant medications at Dr. Toskes' site in their assessment of the application."

This Reviewer agrees with the DSI Reviewer that the data obtained from these particular patients may be used in support of this application. This Reviewer believes that the effect on CFA results was minimal from allowing prohibited concomitant medications. Both the patients using narcotics (the patient using methadone and the patient using the Duragesic Patch) were using these medications chronically. In addition, the doses of each of the narcotics were relatively low; the Duragesic Patch dose was 50 μg/hr and the daily methadone dose was 30 mg. Regarding the patient using Oscal, this Reviewer believes that CFA results were not likely to have been affected because the dose (1 gram daily) was considerably lower than the dose described by Saunders et al.[5] as having an effect on fat excretion; that report describes an increase of fat excretion from a daily dose of 6 grams of calcium carbonate and appears to be the basis for the exclusion of calcium carbonate in the protocol (see also Section 5.3.1.4). Finally, review of the CFA results (for each of the patients that used prohibited concomitant medications) reveals that the results are similar to those of other patients in the same treatment group with similar baseline CFA values (see Tables 7, 9, and 10 in Section 5.3.1.11.6.2); this further supports the conclusion that the effect on CFA results are minimal from the use of prohibited concomitant medications.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. The Applicant states that they did not enter into a financial agreement with any of the clinical investigators which would affect the outcome of the study.

[5] Saunders et al., 1988, "Effect of Calcium Carbonate and Aluminum Hydroxide on Human Intestinal Function," Digestive Diseases and Sciences, 33(4):409-413.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC data have been extensively reviewed by the CMC Reviewers. The Drug Product Reviewer, Wei Guo, Ph.D. states, "I do not recommend approval of this submission. At this time (9/23/10) the compliance status of the (b) (4) facility is still under evaluation and there are issues with the presence of Bacillus cereus diarrheal enterotoxin in the drug substance. The approvability of this NDA is pending on the successful resolution of these issues." Please see the CMC reviews for more detailed information.

4.2 Clinical Microbiology

According to the Microbiology Reviewer, Denise A. Miller, the drug product is a non-sterile immediate release tablet for oral administration with microbial limit specifications and no microbiology deficiencies preventing approval identified. Of note, the Microbiology Review was completed on June 21, 2010 when, according to the Reviewer, there were "no deficiencies noted based on the microbiology information submitted."

Thus, NDA 22-542 was recommended for approval on the basis of a satisfactory product quality microbiology review. Please see the Microbiology Review for more detailed information on the microbiology data.

4.3 Preclinical Pharmacology/Toxicology

Since extensive human experience exists with the PEPs, and consistent with recommendations in the Guidance, no non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA. As outlined in the FDA Guidance for exocrine pancreatic insufficiency products, no toxicology studies were needed if excipients were classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. The Applicant did not conduct any nonclinical studies with Viokace.

According to the Nonclinical Pharmacology Reviewer, Niraj Mehta, Ph.D. "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." Please see the Nonclinical Pharmacology Review for more detailed information on the nonclinical information relevant to this NDA submission.

4.4 Clinical Pharmacology

Clinical pharmacology data have been reviewed by the Clinical Pharmacology Reviewer, Lanyan Fang, Ph.D. Her recommendation is: "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." Please see Clinical Pharmacology Review for complete details.

4.4.1 Mechanism of Action

Viokace acts locally in the gastrointestinal (GI) tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates; it is not systemically absorbed.

4.4.2 Pharmacodynamics

Lipase, amylase, and protease act locally in the GI tract and are not systemically absorbed; therefore, pharmacodynamic studies are not applicable.

4.4.3 Pharmacokinetics

PEPs act locally in the GI tract and are not absorbed; therefore, pharmacokinetic studies are not applicable.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

There were a total of three clinical studies (including one bioavailability study) conducted in the Viokace clinical development program; these clinical studies included a number of different designs (e.g., randomized, placebo-controlled, active-controlled, crossover, parallel, and open-label). See Table 1 for a listing and summary of these studies.

Table 1: Clinical Studies for Viokace

Study Number	Design	Primary Endpoint/ Objective	Product/Dose	Number of Patients per Arm Entered/Completed
VIO16EPI07-01	R, DB, PC, MC, P	Changes in percent absorption of dietary fat (CFA %)	Viokace 16 and placebo 22 tabs/day with PPI	Viokace (30/30) placebo (20/20
STEA-VK00-US01	R, OL, P	Change from Baseline of Fecal Fat Excretion (g/24 h)	Viokace 16 (8 or 16 tabs/ day)	16 tabs -8/8 8 tabs -9/6
VIO16IP07-01	OL, C, Bioavailability	Evaluate the intra-duodenal delivery of lipase, protease and amylase from administration of Viokace 16	Viokace 16 3 tabs/single dose	20/14

R-randomized
DB-double blind
PC-placebo controlled
MC-multi-center
P-parallel
OL-open label
C-cross-over

5.2 Review Strategy

There were three studies submitted with this NDA. They include one controlled clinical study, one uncontrolled clinical study and one bioavailability study. This review focuses on the controlled clinical study: the pivotal study (VIO16EPI07-01). In addition, a brief efficacy analysis was done for Study STEA-VK00-US01 (a randomized, open label, parallel study) comparing two different Viokace doses (see Section 6.1.10).

The majority of time was spent reviewing the pivotal study, VIO16EPI07-01. The efficacy of Viokace was established from this randomized, double-blind, placebo-controlled study. STEA-VK00-US01 was a randomized, open-label, parallel study, which compared two doses of Viokace (8 tablets/16 tablets) for the treatment of steatorrhea in patients with EPI.

A pooled safety analysis was performed when appropriate given the three distinct study designs. Additionally, safety was assessed separately for Study VIO16EPI07-001 and Study STEA-VK00-US01.

This NDA was submitted as a 505(b)(2) application. To obtain approval, PEP NDAs must meet the requirements for clinical studies described in 21 CFR 314.50. The Agency determined that there was a considerable body of evidence that replacement of pancreatic enzymes has clinical benefit for patients with cystic fibrosis and chronic pancreatitis (44 FR 75666, 50 FR 46594, and 69 FR 23410). Thus, the limited clinical development program of Viokace (one small pivotal study) was acceptable.

5.3 Discussion of Individual Studies

5.3.1 Study VIO16EPI07-01

5.3.1.1 Study Design

The pivotal study, VIO16EPI07-01, was a multicenter, randomized, double-blind, placebo-controlled, parallel study evaluating the efficacy and safety of Viokace in 50 patients, ages 24 to 70 years, with a diagnosis of exocrine pancreatic insufficiency (EPI) secondary to chronic pancreatitis (CP) or partial/total resection of the pancreas. Efficacy was assessed by the comparison of the coefficient of fat absorption (CFA) following oral administration of Viokace and placebo.

The study consisted of five phases defined as: a Screening Phase (up to 10 days) to determine eligibility; a Wash-out Phase (no PEP), comprised of a 2-day Outpatient Period and a 4- to 5-day Inpatient Period; a Randomization Phase (up to 10 days) in which patients resumed their usual PEP; a Treatment Phase, comprised of a 2-day Outpatient Period and a 4- or 5-day Inpatient Period, in which patients took double-blind drug treatment (Viokace or placebo); a Follow-up Phase in which patients who received at least one dose of the study medication were followed up whether or not they completed the Treatment Phase. See Figure 1 below.

Figure 1: Overall Study Design

- **Screening Phase**
  - Up to10 days: determine eligibility
- **Washout Phase - No PEP**
  - Outpatient (1-2 day)
  - Inpatient (4-5 day with stool collection)
- **Randomization Phase - Usual PEP**
  - Up to 10 days
- **Treatment Phase - (Viokace or placebo)**
  - Outpatient (1-2 day)
  - Inpatient (4-5 day with stool collection)
- **Follow-up Phase**
  - 7-10 days after discharge

5.3.1.2 Study Objectives

The primary objective of the study was to determine the efficacy and safety of Viokace versus placebo in reducing steatorrhea (as measured by 72-hour stool fat determinations) in adults with EPI.

5.3.1.3 Patient Population

5.3.1.3.1 Key Inclusion Criteria

Patients were eligible for study participation if they were males or females 18 years of age and older and had:

- A medical condition compatible with EPI such as CP or partial or total resection of the pancreas. Patients with CP had to have at least one of the following:
  - *An abnormal secretin test,*
  - *Diffuse calcification of the pancreas on plain film of the abdomen,*
  - *An abnormal endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound,*
  - *An abnormal computed tomography (CT) such as dilated main pancreatic duct, atrophy or calcification of the pancreas,*
  - *A serum trypsin concentration below 20 ng/mL*
- Evidence of EPI as demonstrated by a fecal elastase equal to or below 100 μg/g (≤100 μg/g) of stools (FE-1 ScheBo test) at screening
- Evidence of EPI as manifested by a CFA% below 80% (< 80%) during the Wash-out Phase

5.3.1.3.2 Key Exclusion Criteria:

Patients were excluded from study participation if they met any of the following exclusion criteria:

- History of fibrosing colonopathy, cirrhosis of the liver or portal hypertension
- History of malignant pancreatic tumor or significant bowel resection
- Causes for EPI other than CP and partial/total pancreas resection; e.g., cystic fibrosis, primary sclerosing cholangitis, hemochromatosis, isolated enzyme deficiency, deficiency in activation of enzymes in the small intestine, etc.
- Acute pancreatitis, or acute exacerbation of CP at screening or within last 2 weeks
- Had a condition known to increase fecal fat loss including: celiac disease, Crohn's disease, tropical Sprue, Whipple's disease, lactose intolerance, biliary cancer, biliary stricture, cholelithiasis, pseudomembranous colitis
- A dysmotility disorder

5.3.1.4 Concomitant Medications

All medications taken in the 3 months prior to entry into the study had to be documented in the CRF. All reasonable efforts had to be made to keep the current concomitant medication used by the patient as stable as possible. If a new drug was introduced to treat a medical condition during

the study, the Investigator had to review the inclusion/exclusion criteria to make sure that the patient continued to meet these criteria. Patients already on PPI therapy were able to continue their usual treatment; patients who were not on PPI therapy at Screening started omeprazole (20 mg QD) for the duration of the study.

Concomitant administration of the following medications was prohibited during the study: drugs or products that affect fat absorption, including enemas, all laxatives including natural products (with exception of bisacodyl if required and prescribed by the investigator at any time during the study), mineral oil and castor oil, olestra (fat substitute), all fat blocking nutritional supplements, narcotics, gastrointestinal motility modifiers, barium, potassium chloride, calcium carbonate (except in multivitamins), magnesium hydroxide, GI motility modifiers, and Orlistat.

In response to an Information Request from the Division, the Applicant stated that calcium carbonate was prohibited during the study because it has been demonstrated to form insoluble salts with both fatty acids and bile salt, with measurable increases in fecal excretion of both; this is based on a reference by Saunders et al. that the Applicant provided.[6]

5.3.1.5 Study Visits and Procedures

The majority of study visits were in the outpatient setting (study Visits 1, 3 and 5). During Visits 2 and 4, patients were hospitalized for four to six days wherein they were fed a controlled diet (high-fat 100 g/day) and were monitored. The two, 72-hour stool collections were performed during the inpatient stays for Visits 2 and 4. The study visits and procedures are summarized in Table 2 (electronically copied and reproduced from the Applicant's submission).

[6]Saunders et al., 1988, "Effect of Calcium Carbonate and Aluminum Hydroxide on Human Intestinal Function," Digestive Diseases and Sciences, 33(4):409-413.

Table 2: Schedule of Study Assessments

Phase	Screening Phase	Wash-Out Phase						
		Outpatient Period		Inpatient Period				
Visit	V1	(2 days)		V2 (4 to 5 days)				
Duration	Up to 10 days	D1	D2	D1 [b]	D2	D3	D4 [d] (last day)	D5 [d] (last day)
Informed consent	X							
Demographic data	X							
Relevant Medical / Surgical History	X							
Physical Examination	X						X	X
Vital Signs	X			X	X	X	X	X
Weight (W) / Height (H)	X (W/H)			X(W)	X(W)	X(W)	X(W)	X(W)
Inclusion/Exclusion Criteria	X							
Fecal Elastase 1 Test	X							
Clinical Laboratory Tests and Urinalysis	X						X	X
Serum (S) / Urine (U) Pregnancy Test	X (S)			X (U)				
Patient's Usual Pancreatic Enzymes Treatment	X	Off	Off	Off	Off	Off	Off	Off
PPI	X	X	X	X	X	X	X	X
Dietician Instructions	X							
Diary Dispensing [a]	X							
High-fat Diet		X	X	X	X	X	X	X
Diary Completion /Collection [c]		X	X	X				
Stool Collection				X	X	X	X	X
FD&C Blue No. 2 Dye (stool marker) [d]				X			X	X
Double-Blind Study Drug (VIOKASE® 16 or Placebo)								
Recording Adverse Events	X	X	X	X	X	X	X	X
Recording Concomitant Medication	X							
Compliance Check								
Drug Accountability								

[a] Patient diaries dispensed to patients will include food records, stool frequency, characteristics of stools and use of PPI.
[b] Patients will arrive at the facility on the previous evening or in the morning of Day 1 of the Inpatient Period of the Wash-Out Phase (D1 IWO).
[c] Diary completed to include food records, stool frequency and stool characteristic recordings. Diaries will be collected on Day 1 of the Inpatient Period (D1 IWO).
[d] The dye marker is to be administered with breakfast on Day 1 (D1 IWO) and Day 4 (D4 IWO) of the Inpatient Period. If stool transit time should be delayed and the dye marker has not passed within 36 hours after first administration (by Day 2 of the Inpatient Period), administer the second dye on Day 5 (D5 IWO) of the Inpatient Period.

Source: Applicant's VIO16EPI07-01 Study Report (Page 38, Section 9.5.1, Table 9.5-1)

Table 2: Schedule of Study Assessments (Cont'd)

Phase	Randomization Phase	Treatment Phase							Follow-Up Phase
		Outpatient Period		Inpatient Period					
Visit	V3	(2 days)		V4 (4 to 5 days)					V5
Duration	Up to 10 days	D1	D2	D1 [b]	D2	D3	D4 [e] (last day)	D5 [e] (last day)	After Discharge
Informed consent									
Demographic data									
Relevant Medical / Surgical History									
Physical Examination							X	X	
Vital Signs				X	X	X	X	X	
Weight (W) / Height (H)	X (W)			X (W)	X (W)	X (W)	X (W)	X (W)	
Inclusion/Exclusion Criteria									
Fecal Elastase 1 Test									
Clinical Laboratory Tests and Urinalysis							X	X	
Serum (S) / Urine (U) Pregnancy Test				X(U)			X (S)	X (S)	
Patient's Usual Pancreatic Enzymes Treatment	X	Off	Off	Off	Off	Off	Off	Off	
PPI	X	X	X	X	X	X	X	X	
Dietician Instructions	X								
Diary Dispensing [a]	X								
High-fat Diet		X	X	X	X	X	X	X	
Diary Completion /Collection [d]		X	X	X					
Stool Collection				X	X	X	X	X	
FD&C Blue No. 2 Dye (stool marker) [e]				X			X	X	
Double-Blind Study Drug (VIOKASE® 16 or Placebo)	X [c]	X	X	X	X	X	X	X	
Recording Adverse Events	X	X	X	X	X	X	X	X	X
Recording Concomitant Medications	X	X	X	X	X	X	X	X	X
Compliance Check							X	X	
Drug Accountability							X	X	

[a] Patient diaries dispensed to patients will include food records, stool frequency and stool characteristic recordings.

[b] Patients will arrive at the facility on the previous evening or in the morning of Day 1 of the Inpatient Period of the Treatment Phase (D1 IT).

[c] Randomization number assigned and double blind study medication dispensed to patients.

[d] Diary completed to include food records, stool frequency and stool characteristic recordings. Diaries will be collected on Day 1 of the Inpatient Period (D1 IT).

[e] The dye marker is to be administered with breakfast on Day 1 (D1 IT) and Day 4 (D4 IT) of the Inpatient Period. If stool transit time should be delayed and the dye marker has not passed within 36 hours after first administration (by Day 2 of the Inpatient Period), administer the second dye on Day 5 (D5 IT) of the Inpatient Period.

Source: Applicant's VIO16EPI07-01 Study Report (Page 39, Section 9.5.1,Table 9.5-1)

5.3.1.6 Randomization and Controls

Upon confirmation of the CFA% at the end of the Wash-Out Phase, patients who qualified for the Treatment Phase (i.e., CFA% below 80) were contacted via telephone and returned to the facility (Visit 3) to receive either Viokace or placebo according to the double-blind treatment assignment.

The double-blind study medication was packaged in kits numbered from 001 to 645. Each kit assigned to a unique patient was comprised of one box containing two bottles of 100 tablets of Viokace or placebo. The study medication was to be taken as six tablets with each meal and two tablets with two of three snacks for a total of 22 tablets per day.

5.3.1.7 Study Medication Dose Selection and Dispensing

A standard dose of Viokace was used for each patient in the study. According to the Applicant, this dose was selected based upon several factors. One contributing factor was the information that was available on FDA-approved enteric-coated pancrelipase products indicated for treatment of EPI due to cystic fibrosis and other conditions. The FDA, in conjunction with the CFF, has recommended a starting dose of 500 to 1,000 USP lipase units/kg/meal with titration up to 2,500 USP lipase units/kg/meal and a maximum of 10,000 USP lipase units/kg/day. This dosing recommendation is in place to reduce the risk of fibrosing colonopathy and colonic strictures in patient with cystic fibrosis. Clinical studies conducted on various enteric-coated products have demonstrated that these dosing recommendations result in acceptable safety and efficacy profiles.

Another factor which affected the dose selection for this study was the failure of a previous study (STEA-VK00-US01) which used smaller doses (8 or 16 tablets of Viokace) to demonstrate a statistically significant difference in reducing steatorrhea between Viokace and Baseline. The analysis of this study suggested that the failure to demonstrate a statistically significant difference between Viokace and Baseline was attributable in part to the dose administered (2 or 4 tablets per meal and 16 tablets daily for the higher dose).

In the current study, Viokace tablets was administered as 6 tablets per meal and 2 tablets with two of three snacks (total of 22 tablets daily). Six tablets of Viokace per meal administered to a 60-70 kg adult would result in a dose of 125,280 USP lipase units per meal or 1,790-2,088 USP lipase units/kg/meal, which is within the therapeutic range, but less than the maximum recommended dose of 2,500 USP lipase units/kg/meal. Based on the daily maximum of 22 Viokace tablets per day, a 60-70 kg patient would be exposed to 6,562-7,656 USP lipase units/kg/day, which again is within the therapeutic range but less than the maximum recommended dose of 10,000 USP lipase units/kg/day.

Doses in this study were not to exceed a maximum lipase dose of 2,500 lipase units/kg/meal, which is in agreement with the recommendation in the Guidance for Industry (FDA, 2006) of titration to less than 2,500 lipase units/kg/meal.

A selected fixed dosing regimen was assigned to all patients participating in the study. Study drug was administered with meals and two out of three snacks to compensate for the lack of endogenous enzyme secretion in patients with EPI.

This study was double-blinded only during the Treatment Phase, at which time patients received either Viokace or Placebo. Blinding was achieved using identical tablets for the two treatments and identical packaging, created in accordance with the randomization list.

The randomization list was produced by a qualified statistician that was working under the responsibility of Axcan Pharma Inc.'s Quality Assurance department. The randomization list was maintained under secure conditions at Axcan Pharma Inc.'s Quality Assurance department. The randomization list was not available to study sites, CRAs, or Axcan Pharma Inc. clinical research personnel.

Drug Accountability forms were supplied to Investigators at the beginning of the study. The pharmacist, Investigator or authorized personnel maintained a record of all medication received from Axcan Pharma Inc. All study medication dispensed to the patients was also recorded on the Drug Accountability form, throughout the study.

5.3.1.8 Efficacy and Endpoint Measures

5.3.1.8.1 Primary Efficacy Endpoint

This study included a single primary endpoint: the CFA% during the Treatment Phase in patients with EPI treated with Viokace compared to placebo.

The primary efficacy parameter was the Coefficient of Fat Absorption (CFA%) during the Treatment Phase defined as:

$$\frac{\textit{fat intake} - \textit{fat excretion}}{\textit{fat intake}} \times 100$$

This primary efficacy parameter was evaluated at the end of the Wash-Out Phase and the Treatment Phase (Inpatient Period). Fat intake (g) was defined as the sum of fat ingested beginning with breakfast on the day the first blue dye marker was administered up to the last meal on the day preceding the administration of the second blue dye marker. Fat excretion (g) was defined as the sum of fat excreted beginning with the stool following the appearance of the first blue tinted stool (after the administration of the first blue dye marker) up to the first tinted stool following the administration of the second blue dye marker. In other words, it was the sum of fat excreted after the first blue tinted stool up to the second blue tinted stool, excluding the first blue tinted stool but including the second blue tinted stool. Fat intake and fat excretion were derived for both the Wash-Out and the Treatment Phases respectively.

The primary efficacy endpoint was the comparison of the coefficient of fat absorption (CFA) after administration of Viokace versus placebo. CFA was determined from the fat intake (calculated from the 72-hour dietary records) and fat excretion (from the 72-hour stool

collection) during the efficacy evaluation period of each inpatient phase of the study. Food intake was strictly controlled and recorded for 72 hours by qualified site personnel. The fecal fat measurements were obtained during a 72-hour in hospital stool collection.

5.3.1.8.2 Secondary Endpoints

The secondary endpoints were to investigate the effect of Viokace on stool frequency (number of bowel movements) and stool characteristics (hard, formed/normal, soft, watery). The efficacy was based on a comparison between Viokace and placebo.

5.3.1.8.3 Safety Endpoints

Safety endpoints included assessments of or changes in, frequency, duration, and severity of treatment-emergent AEs, clinical laboratory parameters, physical examination findings, and vital sign measurements in the safety population. The safety analysis population was defined as all patients who were randomized and received at least one dose of study drug.

5.3.1.9 Statistical Considerations

This was a placebo-controlled study intended to show superiority of Viokace over placebo. The study included a single primary endpoint: the CFA% during the Treatment Phase in patients with EPI treated with Viokace compared to placebo.

Dropouts were not replaced during the study, but were included in the data analysis to the extent that data were available. Statistical comparisons were two-sided and carried out at the 0.05 level, except for interaction effects which were tested at a 0.10 level. Safety analyses were conducted on an observed case basis. Missing safety observations were not imputed. The sample size of this study was too small to enable any meaningful statistical subgroup analyses.

Missing Treatment Phase CFA% were to be imputed using the median (50^{th} percentile) Treatment Phase CFA% within each treatment group. However, there were no missing data. The main test for efficacy (H0) was an overall mean comparison comparing Viokace with placebo. This was done through a two-way Analysis of Covariance (ANCOVA) model, with fixed effect for pooled site and treatment group as well as Wash-Out Phase CFA% as a covariate. These parameters were analyzed by using the main effect ANCOVA model (see below):

Treatment Phase CFA% = Wash-Out Phase CFA% + treatment group + pooled site

At the time of this Review, additional statistical considerations are not yet available. (*Updated November 8, 2010: please see Statistical Review by Shahla Farr)

5.3.1.10 Protocol Amendments

Changes in the conduct of the study were instituted as defined in the amended protocol dated July 27, 2007. Changes in the planned statistical analyses were carried out as described in the amended SAP (Version 2.0) dated July 8, 2009 and according to Statistical reviewer, Shahla Farr, "Although the date of the amendment is close to the date of their submission, there is

nothing in it to change the analyses of the primary or secondary endpoints." (email dated October 14, 2010.

Additionally, changes in the definition of Wash-Out Phase Concomitant Medications, Treatment Phase Concomitant Medications, Wash-Out Phase AEs and Treatment Emergent AEs were instated after the study unblinding, but before the clinical study report finalization:

"Medications taken during the Wash-Out Phase (i.e., from the first day of the Wash-Out Phase up to the Wash-Out Phase discharge day), and during the Treatment Phase (i.e., from the first dose of study medication date up to the last dose of study medication) will be considered as Wash-Out Phase concomitant medications and Treatment Phase concomitant medications respectively. Medications that started during the Randomization Phase (i.e., from the day after the Wash-Out Phase discharge day up to the day that preceded the day of the first dose of study medication) and after the last dose of study medication will not be reported in tables, but will be presented in patient data listings."

"A Wash-Out Phase adverse event (WOPAE) is defined as any event that started on or after the first day of the Wash-Out Phase up to the Wash-Out Phase discharge day. A treatment emergent adverse event (TEAE) is defined as any event that started on or after the first dose of study medication up to the last dose of study medication or has an unknown/not reported onset date. Adverse events that started during the Randomization Phase (i.e., from the day after the Wash-Out Phase discharge day up to the day that preceded the day of the first dose of study medication) and after the last dose of study medication will not be reported in tables, but will be presented in patient data listings."

Other changes to the amended protocol included:
A change to the exclusion criteria whereby patients were permitted to take enzyme therapy up to the day before the Wash-Out Phase and after the Wash-Out Phase until the beginning of the Treatment Phase. In addition, patients were provided with a second diary at V3 (Randomization Phase), not at V2 (Wash-Out Phase).

These changes in the protocol do not appear to have had a considerable effect on the overall results of the study.

5.3.1.11 Study Results

5.3.1.11.1 Demographics

There were 50 patients between the ages of 24 and 70 years enrolled in Study VIO16EPI07-01. The mean age was 51 for both the Viokace and placebo groups. There were more males than females in both groups with the placebo group having a higher percent of males. The patients were mostly homogeneous in terms of race with the majority of patients being Caucasian. This homogeneity is also seen in most PEP studies with predominant CF populations. All patients had CP with about 44% of patients also having a pancreatectomy.

The demographics of patients enrolled in Study VIO16EPI07-01 are summarized below in Table 3.

Table 3: Demographics of Study VIO16EPI07-01

	Viokace (n=30)	Placebo (n=20)
Age (years)		
Mean (SD)	51 (9.9)	51 (7.6)
Min, Max	24, 70	37, 63
Gender, n(%)		
Male	22 (73%)	19 (95%)
Female	8 (27%)	1 (5%)
Race, n(%)		
White	29 (97%)	19 (95%)
Black	1 (3%)	0
Other		1 (5%)
EPI etiology		
Chronic Pancreatitis	30 (100%)	20 (100)
Pancreatectomy	12 (55%)	10 (45%)

5.3.1.11.2 Patient Disposition

There were 218 patients who enrolled in Study VIO16EPI07-01. Of this number, 168 patients failed screening: 88 patients with clinically documented chronic pancreatitis and steatorrhea did not meet the criterion for FE-1 (FE-1 < 100 µg/g stool), while an additional 50 clinically documented patients who did meet the FE-1 criterion did not have a sufficiently low Wash-Out Phase CFA% (CFA% < 80%) for randomization into study entry. Thus, 50 patients were randomized and 49 completed the study. A summary of patient disposition is presented in Table 4 below.

Table 4: Patient Disposition

Parameter	Viokace n (%)	Placebo n (%)
Enrolled	218	
Randomized	30 (14%)	20 (9%)
Completed Study	29 (97%)	20 (100%)
Discontinued Study After Randomization (Inclusion/Exclusion Criteria Failure)	1 (3%)	0
Per Protocol	20 (67%)	15 (75%)

The Wash-Out Phase mean CFA% values for the Viokace and placebo groups of the ITT population were comparable at 47.6 ± 24.1 and 56.6 ± 22.2, respectively.

There were 14 study sites with between one and eight patients completing the study at each site. Enrollment by site is summarized below in Table 5.

Table 5: Completed Patients per Study Site

Site Number	14	18	21	22	23	29	32	33	35	36	38	42	44	46
	1406	1801	2101	2202	2301	2905	3203	3301	3506	3601	3802	4201	4404	4617
	1414	1810	2103	2203	2308	2906	3211	3304	3507	3604	3805	4204		
	1418		2105	2205	2309		3213	3306	3514			4205		
	1422		2106		2312			3307	3524			4206		
			2109		2314				3527			4210		
			2110						3533			4211		
									3538					
									3542					
Total Patients	**4**	**2**	**6**	**3**	**5**	**2**	**3**	**4**	**8**	**2**	**2**	**6**	**1**	**1**

5.3.1.11.3 Concomitant Medications

All study patients were to be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. All concomitant medication and concurrent therapies were documented at the Screening Visit and at all study visits and at early termination when applicable. Dose, route, frequency of administration, indication for administration, and dates of medication were captured.

5.3.1.11.4 Compliance with Study Medication

Compliance to the required treatment regimen was high and very consistent in the Safety population. Average overall compliance during the Treatment Phase was 99 ± 2.7% and 99 ± 2.5% for the Viokace and placebo groups, respectively. Overall compliance values during the Treatment Phase were similar between the Viokace and placebo groups, with 97% and 90% of patients respectively in the 80-100% compliance category. Compliance during the Inpatient and Outpatient Periods of the Treatment Phase was also very similar.

Compliance with PPI treatment in the Safety population was very high at 100% for both the Viokace and placebo groups during both the Wash-Out and Treatment Phases Compliance was 100% irrespective of whether PPI was provided by Axcan Pharma Inc. or whether PPI was concomitant medication maintained by the patient throughout the course of the study.

5.3.1.11.5 Protocol Deviations and Violations

Protocol deviations that were considered major and that were not authorized by the study sponsor were reported for ten patients in the Viokace group and five patients in the placebo group. In the Viokace group, the majority of protocol deviations were reported for non-compliance with the high-fat diet (four patients; 40% of all patients excluded from PP population) and for other reasons as per Axcan Pharma Inc.'s request (four patients; 40% of all patients excluded from PP population). In the Placebo group, the majority of protocol deviations were reported for other reasons as per Axcan Pharma Inc.'s request (three patients; 60% of all patients excluded from PP

population). The reasons considered by Axcan Pharma Inc. as major protocol violations included ICF being signed after the Screening visit, aberrant Wash-Out Phase CFA% and medical history.

5.3.1.11.6 Efficacy Results

5.3.1.11.6.1 Primary Efficacy Analysis

The primary endpoint in Study VIO16EPI07-01 was the CFA during the Treatment Phase. The CFA measured during treatment with Viokace was compared with the CFA measured during treatment with placebo. Fifty patients were included in the efficacy analysis population.

The Applicant's results show that the mean CFA during the Treatment Phase for patients receiving Viokace was 86%; the mean CFA during the Treatment Phase for patients receiving placebo (no treatment) was 58%. The difference in CFA was 28% (95% CI: 17.8, 37.2). The efficacy results showed a difference in CFA that was statistically significant ($p < 0.0001$). This reviewer and the FDA Statistician confirmed the results and were in agreement with the Applicant. The results are summarized in Table 6 (electronically copied and reproduced from the Applicant's submission)

Table 6: Coefficient of Fat Absorption (CFA%) (Intent-to-Treat Population)

Parameter Phase / Analysis Type	Statistic	Treatment Group Viokase®16 (N=30)	 Placebo (N=20)
CFA%			
Wash-Out Phase	n	30	20
	Mean	47.56	56.64
	SD	24.112	22.192
	Median	53.96	63.02
	Min., Max.	-29.1, 74.5	-9.5, 93.3
Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	85.52	58.02
	SD	8.902	24.249
	Median	88.34	64.87
	Min., Max.	52.6, 95.5	3.5, 93.0
	LSMean (SE)	87.8 (2.6)	58.4 (3.2)
	p-value [a]	<0.0001**	
Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	37.95	1.37
	SD	25.409	13.330
	Median	35.69	-1.65
	Min., Max.	1.6, 119.8	-21.4, 30.5
Percent Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	616.83	-5.78
	SD	2940.244	43.813
	Median	60.59	-2.79
	Min., Max.	-411.5, 16162.5	-136.6, 90.4

* Indicates statistical significance at the 0.050 level; ** Indicates statistical significance at the 0.010 level.

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase CFA% value as covariate

Notes:

1. LS Mean= Least Square Mean; PI= Percentile Imputation; SE= Standard Error.
2. Coefficient of Fat Absorption (CFA%) is defined as: {[Total fat intake during the stool collection period (g) – Total fat excretion during the stool collection period (g)]/ Total fat intake during the stool collection period (g)} x 100%.

Source: VIO16EPI107-01 Study Report (Page 91, Section 11, Table11.4-1)

The results of the primary endpoint show a statistically significant difference in the mean values in CFA of patients treated with Viokace as compared to patients on placebo. In the Viokace clinical development program, the primary endpoint results were analyzed in conjunction with the changes in CFA for individual patients (see Section 5.3.1.11.6.2 below)

The variability of the mean CFA% was much greater with placebo treatment, as represented by a standard deviation approximately 3-fold greater with the placebo treatment versus Viokace treatment (see Table 6 above). Additionally, the low end of the range in CFA% was 52.6% for Viokace compared to 3.5% for placebo treatment, indicating that the treatment effect was consistent across patients while on Viokace.

Moreover, in the ITT population, CFA% during the Wash-Out Phase was 47.6 ± 24.2 with minimum and maximum values of 29.1 and 74.5 in Viokace treated patients and 56.6 ± 22.2 with minimum and maximum values of -9.5 and 93.3, respectively, in placebo treated patients. Under the 50th percentile imputation analyses, the change in CFA% from Wash-Out Phase to Treatment Phase for patients on Viokace was 38.0 ± 25.4% compared to 1.4 ± 13.3% for patients taking placebo.

5.3.1.11.6.2 Additional Analyses of the Primary Endpoint

This Reviewer performed additional analyses of the primary endpoint, including analyses of the change in CFA by no-treatment CFA, by gender, and by age. Also, an analysis was performed comparing patients who had pancreatic surgery to those who did not.

Analysis by No-Treatment CFA

A widely accepted definition of severe EPI is patients who have a CFA less than or equal to 40% on no treatment. In addition, treatment effect has been reported to be more pronounced in patients with lower no-treatment CFA. . The medical literature notes that in the most severely affected patients an increase from baseline in CFA of 30% represents a clinically meaningful change, thus, this subgroup of patients was analyzed separately.

There were fourteen patients in the severe category, ten in the Viokace treatment group and four the placebo group. The mean change in CFA for the Viokace treatment group was 65% and 4% for the placebo group. All of the most severely affected patients in the Viokace treatment group had an increase in CFA greater than or equal to 40%, with seven patients having an increase in CFA of greater than 50%. Thus, the most severely affected patients in the Viokace treatment group demonstrated the greatest response to treatment with Viokace. The magnitude of the change (mean change 65% in this group, and $\geq$40% in most of the patients) was a clinically meaningful result. Individual results for patients with Wash-Out Phase CFA<40 on Viokace and placebo are tabulated below in Table 7 and 8.

Table 7: Patients on *Viokace* with Washout Phase CFA< 40

Patient Number	Washout Phase CFA*	Treatment Phase CFA*	Change in CFA[#]
3802	-29	91	120
2313	0.5	85	84
2106	12	90	78
4206	22	96	74
1418	23	76	53
2205	28	73	45
3304	36	91	56
4211	37	92	55
3524	37	80	43
2314	38	77	40

Mean change CFA (< 40 subgroup) = 65

*Wash-out phase CFA and Treatment Phase CFA values shown are rounded to two significant figures

[#] Values in the Change in CFA column are rounded to the nearest integer (Change in CFA = Treatment Phase CFA – Washout Phase CFA)

Table 8: Patients on *Placebo* with Washout Phase CFA< 40

Patient Number	Washout Phase CFA*	Treatment Phase CFA*	Change in CFA[#]
3203	-9.5	3.5	13
1810	33.2	11.8	-21
2906	33.7	64.2	30
2203	35.6	30.7	-5

Mean change CFA (< 40 subgroup) = 4

*Wash-out phase CFA and Treatment Phase CFA values shown are rounded to one decimal place

[#] Values in the Change in CFA column are rounded to the nearest integer (Change in CFA = Treatment Phase CFA – Washout Phase CFA)

For the subgroup of patients who had mild or moderate EPI (N=36) (defined by this Reviewer as a wash-out phase CFA greater than 40), the mean change in CFA for the Viokace treatment group (n=20) was 25% and for the placebo group (n=16) was 1%. The increase in CFA following Viokace treatment was not as pronounced as seen in the patients with severe EPI. This result is not unexpected as these moderately affected patients have less of a capacity to respond, since they started at a higher wash-out phase level. Individual results for patients with CFA>40 on Viokace and placebo are tabulated below in Tables 9 and 10. In general, there was a gradation in treatment responses with larger increases in CFA for patients with wash-out phase CFAs at the low end, and smaller increases for higher wash-out phase CFA levels.

Table 9: Patients on *Viokace* with Wash-Out Phase CFA>40

Patient Number	Washout Phase CFA*	Treatment Phase CFA*	Change in CFA[#]
2109	42.2	80.0	38
3533	48.7	89.6	41
2202	50.9	85.0	34
1801	50.9	52.6	2
1414	53.9	79.0	25
2308	54.0	91.8	38
4617	54.1	84.4	30
4201	56.0	93.2	37
3211	57.3	94.8	37
3506	58.6	91.3	33
2309	65.0	87.4	22
2110	65.3	84.4	19
4210	66.0	91.5	26
3542	67.0	91.6	25
3805	70.1	72.0	2
3507	71.6	91.9	20
2905	71.8	86.2	15
3307	72.2	91.2	19
4404	72.5	87.9	15
2101	74.5	88.8	14

Mean change CFA (> 40 subgroup) = 25

*Wash-out Phase CFA and Treatment Phase CFA values shown are rounded to one decimal place

[#] Values in the Change in CFA column are rounded to the nearest integer (Change in CFA = Treatment Phase CFA – Washout Phase CFA)

Table 10: Patients on *Placebo* with Wash-Out Phase CFA>40

Patient Number	Washout Phase CFA*	Treatment Phase CFA*	Change in CFA[#]
3604	42.1	24.3	-18
3601	46.5	42.1	-4
1406	54.7	52.9	-2
2103	54.9	65.2	10
2105	55.2	80.4	25
3527	62.0	64.6	3
4205	64.0	73.7	10
3306	65.0	62.1	-3
1422	67.8	48.8	-19
2312	69.6	85.5	16
3538	70.2	67.8	-2
3213	71.5	69.9	-2
2301	73.1	75.0	2
3514	74.1	72.4	-2
3301	75.9	72.5	-3
4204	93.3	93.0	0

Mean change CFA (> 40 subgroup) = 1

*Wash-out phase CFA and Treatment Phase CFA values shown are rounded to one decimal place

[#] Values in the Change in CFA column are rounded to the nearest integer (Change in CFA = Treatment Phase CFA – Washout Phase CFA)

Overall, the additional efficacy analysis of change in CFA by wash-out phase CFA in Study VIO16EPI07-01 showed that the increase in CFA on Viokace treatment is greatest in the most

severely affected patients. The patients who had a higher wash-out phase CFA showed smaller increases in CFA after treatment with Viokace.

The inverse relationship between low wash-out phase CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. The mean change in CFA for all patients on Viokace with a wash-out phase CFA<40 was 65%. Each of the patients who were the most severely affected (wash-out phase CFA<40) had an increase in CFA of at least 40%. This percentage increase was defined by the medical literature as a clinically meaningful result. Most other patients also had increases in CFA following treatment with Viokace.

These results above support the approval of Viokace for the treatment of EPI due to chronic pancreatitis or pancreatectomy; treatment with Viokace is beneficial to most patients. The treatment effect is variable; however, it follows a trend that the greatest change in CFA is observed in the patients with the lowest wash-out phase CFA.

Analysis by Post-Pancreatectomy versus No Pancreatectomy

The efficacy results were analyzed by whether the patient had had a pancreatectomy or did not. For the subgroup of patients who had pancreatectomies, during the Treatment Phase, the mean placebo CFA and Viokace CFA were 64 and 86 respectively; therefore, the difference between treatment groups was 22. The same analysis for the subgroup without pancreatic surgery showed that during the Treatment Phase, the mean placebo CFA and Viokace CFA were 52 and 85 respectively; therefore, the difference between treatment groups was 33. See Tables 11 and 12 below. The difference in CFA's of 33 in patients without pancreatic surgery is slightly greater than the corresponding difference in the post-pancreatectomy patients. This difference could possibly be explained by the difference seen in the Washout Phase CFAs for each treatment group. Both treatment group values in the no pancreatectomy group were about ten less than the corresponding values in the post- pancreatectomy group.

Table 11: Post-Pancreatectomy Patients (N=22)

Treatment Phase	Mean ± SD (Min-Max)
Placebo CFA (n=10)	64 ± 21.6 (24, 93)
Viokace CFA (n=12)	86 ± 5.5 (77, 92)
Difference in CFA	22

Table 12: No Pancreatectomy Patients (N=28)

Treatment Phase	Mean ± SD (Min, Max)
Placebo CFA (n=10)	52 ± 26.2 (3.5, 72.5)
Viokace CFA (n=18)	85 ± 10.8 (52.3, 95.5)
Difference in CFA	33

Analysis by Gender and Age

The efficacy results were also analyzed by gender and by age. The majority of the patients were Caucasian (96%) and male (82%). There was only one female subject in the placebo arm. Age ranged between 24 to 70 years. To create an age category, the patients were divided into two age groups, less than or equal to 50 and older than 50. Referenced from Statistical Reviewer, Shahla Farr, Tables 13 and 14 show the results of the subgroup analyses of Change in CFA from wash-out period by gender and by age category, respectively.

Table 13: Reviewer's Analysis of Efficacy (CFA) by Gender

Gender	Mean (±SD) Change in CFA from Washout Period		p-value
	Viokace	Placebo	
Female (n=9)	63.0 ± 33.5 (n=8)	-19 (n=1)	--
Male (n=41)	28.8 ± 13.9 (n=22)	2.4 ± 12.8 (n=19)	<0.001

Table 14: Reviewer's Analysis of Efficacy (CFA), by Age Category

Age Category	Mean (±SD) Change in CFA from Washout Period		p-Value
	Viokace	Placebo	
50 Years and Younger (n=25)	44.6 ± 30.7 (n=14)	6.1 ± 14.2 (n=11)	<0.001
Older than 50 (n=25)	32.1 ± 18.8 (n=16)	-4.4 ± 9.9 (n=9)	<0.001

It was difficult to assess mean changes in CFA with respect to gender as there were greater than four times as many males in the study as females (nine females were included in the efficacy analysis population).

The difference in Mean Change in CFA of 36 (between Viokace and placebo) for the subgroup of patients 50 years and younger, was similar to the difference in Mean Change in CFA for the subgroup of patients older than 50.

The primary endpoint in Study VIO16EPI07-01 was the change in the CFA during the Treatment Phase in patients treated with Viokace compared to placebo. The overall results showed that a clinically meaningful and statistically significant change in the CFA during the Treatment Phase was demonstrated in patients treated with Viokace compared to placebo. The difference in CFA was 28% (95% CI: 17.8, 37.2) which was statistically significant ($p < 0.0001$). Unplanned additional and subgroup analyses showed that factors such as gender and age did not appear to considerably affect clinical efficacy; however, patients with lower wash-out phase CFAs tended to have a better response to treatment with Viokace.

As expected from the published medical literature with treatment with other PEPs, the patients in this study who were the most severely affected gained the most benefit by having had an increase

in CFA of at least 40%; this percentage increase was defined by the medical literature as a clinically meaningful result. Conversely, patients with higher baseline CFA had a lesser responses to Viokace treatment.

5.3.1.11.6.3 Secondary Efficacy Analysis

There were several secondary efficacy endpoints in this study. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; however, these endpoints are not suitable for labeling. The secondary efficacy endpoints analyzed had no clinically definable change that was clinically meaningful.

Stool Frequency

The mean average total daily number of bowel movements during the Wash-Out Phase for the ITT population was 2.95 in patients assigned to Viokace treatment and 2.40 in patients assigned to placebo. The mean average total daily number of bowel movements decreased during the Treatment Phase to 1.93 in patients taking Viokace and 2.33 in patients on placebo. The difference in the mean values between Wash-out and Treatment Phase was -1.01 for Viokace and -0.07 for placebo. (See Table 15 electronically scanned and copied from Applicant)

Table 15: Mean Number of Stools Per Day (Intent-To-Treat Population)

Phase / Analysis Type	Statistic	Treatment Group	
		Viokase®16 (N=30)	Placebo (N=20)
Wash-Out Phase	n	30	20
	Mean	2.95	2.40
	SD	1.176	0.824
	Median	2.71	2.29
	Min., Max.	1.0, 5.3	1.0, 4.0
Treatment Phase / OC	n	30	20
	Mean	1.93	2.33
	SD	0.989	0.950
	Median	1.75	2.33
	Min., Max.	0.8, 5.3	0.8, 4.3
	LS Mean (SE)	1.8 (0.2)	2.5 (0.2)
	p-value [a]	0.0083**	
Change from Wash-Out Phase to Treatment Phase / OC	n	30	20
	Mean	-1.01	-0.07
	SD	1.053	0.738
	Median	-0.98	0.00
	Min., Max.	-3.0, 0.8	-1.3, 1.5
Percent Change from Wash-Out Phase to Treatment Phase / OC	n	30	20
	Mean	-28.97	1.11
	SD	33.079	36.838
	Median	-33.33	0.00
	Min., Max.	-75.0, 75.0	-62.5, 100.0

* Indicates statistical significance at the 0.0500 level; ** Indicates statistical significance at the 0.0100 level.

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase mean number of stools per day as a covariate.

Notes:

1. LSMean= Least Squares Mean; SE= Standard Error.
2. Mean number of stools per day is defined as: Total number of stools during the completed days in the Inpatient Period/Total number of completed days in the Inpatient Period.
3. Since there are no missing Treatment Phase values, only the 'Observed Case' analysis type is displayed.

Source: VIO16EPI107-01 Study Report (Pages 93-94, Section 11, Table 11.4-3)

The difference in the mean values was statistically significant (p = 0.0083); however, the clinical significance of this very small change in number of bowel movements over a 72 hour period is not clear.

Stool Characteristics

Another secondary endpoint was the comparison of stool characteristics between Viokace and placebo recorded over the 72-hour stool collection period. The proportion of hard, formed/normal, soft and watery stools was evaluated during the Inpatient Periods of both the

Wash-Out and Treatment Phases. Although a higher mean average daily proportion of normal/formed stools was observed during the Treatment Phases for patients on Viokace (45.9%) compared to those on placebo (37.2%) no statistically significant difference between the treatment groups was detected. (See Table 1 in Appendix 9.4.1 of this review electronically scanned and copied from Applicant.) In addition, a difference of less than 10% in mean average daily proportion of normal/formed stools is difficult to interpret clinically.

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and the nature of the underlying disease. The secondary endpoints were subjective and assessed without using validated endpoint measures. Thus overall, given the subjective nature of the analyses of the secondary efficacy variables, and the lack of clinical relevance, these results are not sufficient to support labeling.

5.3.1.11.7 Review of Safety

5.3.1.11.7.1 Deaths and Serious Adverse Events (SAEs)

5.3.1.11.7.1.1 Deaths

There were no deaths which occurred during the study period (Wash-Out Phase, Treatment Phase and Follow-up Phase) After the Treatment Phase and follow-up period, one patient from the Viokace treatment group (Patient 4617) experienced a progression of his chronic pancreatitis to inoperable malignant tumor of the head of the pancreas; he died on June 28, 2009, one month after the last dose of study drug. Following is a brief narrative for this patient:

Patient 4617 was a 70 year-old male who experienced choledocholithiasis, cholelithiasis, hydrops of gallbladder, ascites, renal cyst, coagulation factor decreased, postoperative wound complication, anemia and progression of CP to inoperable malignant tumor of the head of pancreas leading to his death. (See Appendix 9.5.1 of this review for a full narrative description of events.)

The Applicant considered that the high fat diet (study procedure) may have played a role in the occurrence of cholelithiasis, choledocholithiasis and hydrops of gallbladder by stimulating the gallbladder leading to the migration of the preexisting calculi. All other reported events were considered to be part of chronic illness and/or represent outcomes of disease progression occurring in a patient with heavy medical and surgical history.

5.3.1.11.7.1.2 Other SAEs

There was one patient in the Viokace treatment group who experienced a treatment-emergent Serious Adverse Event *during* the Treatment Phase of the study. Patient 4617 experienced cholelithiasis. (See Appendix 9.5.1 of this review for a full narrative description of the events.) The Applicant did not consider this SAE to be related to study treatment. However, this Medical Reviewer agrees with the Investigator's assessment that the high fat diet may have played a role

in the occurrence of cholelithiasis, choledocholithiasis and hydrops of gallbladder by stimulating the gallbladder leading to the migration of the preexisting calculi.

After the end of the Treatment Phase, Patient 4617 experienced additional SAEs of decreased coagulation factor, and a progression of chronic pancreatitis to inoperable malignant tumor of the head of the pancreas leading to death. In addition, Patient 3307 from the Viokace group, experienced two SAEs (cardiac failure and pulmonary edema). Following is a narrative for Patient 3307:

Patient 3307 was a 61 year-old male patient who experienced pulmonary edema, heart insufficiency NYHA type IV/III, mitral valve insufficiency, ischemic heart disease, arterial hypertension and insomnia.

Patient 3307's relevant medical history included duodenitis in 1999, hepatic steatosis from 1999 to 2003, CP since 1999, nephrolithiasis since 1999, chronic cholecystitis in 2001, bronchopneumonia in 2002, inguinal hernia with operation from 2001 to 2002, diabetes mellitus since 2004 and appendicitis in 2006.

The patient started treatment with study drug on (b) (6) at a daily dosage of 22 tablets. The Treatment Phase was completed 7 days later on (b) (6). On (b) (6), the patient suddenly started to experience severe dyspnea and was admitted to the hospital with a diagnosis of pulmonary edema. Clinical workup performed during hospitalization revealed heart insufficiency IV/III (NHHA type), mitral valve insufficiency, ischemic heart disease and arterial hypertension. On (b) (6), the patient started treatment with Avedol (Carvedilol) and Spironol (spironolactone) for heart insufficiency, Tritace (ramipril), furosemide for hypertension and Zolpic (zolpidem). The patient was discharged from the hospital on an unspecified date in a stable condition (pulmonary edema resolved on (b) (6)). The events of cardiac failure, mitral valve disease, myocardial ischemia and hypertension were ongoing at the time of discharge.

The Investigator considered that there was no reasonable possibility for a causal relationship between the study drug and the pulmonary edema and that diabetes could have contributed to this event. This Reviewer agrees that there was no reasonable possibility for a causal relationship between study drug and heart insufficiency secondary to NYHA Class III/IV, mitral valve insufficiency, ischemic heart disease and arterial hypertension.

There were no patients from the placebo group who experienced an SAE.

5.3.1.11.7.2 Common Adverse Events

Of the 50 patients included in the safety population that were randomized, a total of nine patients experienced Treatment-Emergent Adverse Events. Seven patients in the Viokace treatment group experienced 16 AEs, and two patients in the placebo group experienced four AEs. Table 16 below provides an overview of Treatment-Emergent Adverse Events which occurred in the safety population.

Table 16: Treatment-Emergent Adverse Events Overview (Safety Population)

Parameter	Viokace (N=30)	Placebo (N=20)
Total Number of TEAEs	16	4
Total Number of Serious TEAEs	1	0
Patients with TEAEs	7 (23%)	2 (10%)
Patients with Serious TEAEs	1 (3%)	0
Patients with Possibly, Probably or Definitely Related TEAEs	3 (10%)	0
Patients Discontinued due to TEAEs	0	0

Source: Applicant's Summary of Clinical Safety: page 17; Table 2.7.4.2.1-1

In the Viokace group, the most frequently represented organ system was gastrointestinal disorders. There were 5 patients in the Viokace group that had gastrointestinal AEs, including anal pruritus (2 patients), abdominal pain, ascites, and flatulence. In addition, two patients had biliary tract stones. There were no gastrointestinal AEs reported in the placebo group. All of the other adverse events occurred in only one patient. See Table 17 below for the complete list of Treatment-Emergent Adverse Events.

Table 17: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

MedDRA Primary System Organ Class/ Preferred Term	Viokace (N=30)	Placebo (N=20)
Total Number of TEAEs	16	4
Total Number of Patients with any TEAEs	7 (23.3%)	2 (10.0%)
Blood And Lymphatic System Disorders		
Anemia	1 (3.3%)	0
Gastrointestinal Disorders		
Anal pruritus	2 (6.7%)	0
Abdominal pain	1 (3.3%)	0
Ascites	1 (3.3%)	0
Flatulence	1 (3.3%)	0
General Disorders and Administration Site Conditions		
Edema peripheral	1 (3.3%)	0
Hepatobiliary Disorders		
Biliary tract stones	2 (6.7%)	0
Hydrocholecystis	1 (3.3%)	0
Infections and Infestations		
Viral infection	1 (3.3%)	0
Nervous System Disorders		
Headache	1 (3.3%)	0
Renal and Urinary Disorders		
Renal cyst	1 (3.3%)	0
Skin and Subcutaneous Tissue Disorders		
Rash	1 (3.3%)	0
Musculoskeletal and Connective Tissue Disorders		
Myalgia	0	1 (5.0%)
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1 (3.3%)	1 (5.0%)

Source: Adapted from Applicant's Summary of Clinical Safety: page 17; Table 2.7.4.7-1

In general, there were few AEs reported during the treatment period of Study VIO16EPI 07-01, with most only occurring in one patient. This was in contrast to other pivotal studies of PEPs which were performed with a majority of cystic fibrosis patients. Since most patients with cystic fibrosis are affected with the disease from birth, and thus have other organ systems chronically affected (e.g. respiratory system), more AEs would be expected in a patient population which included them. Since, by entry criteria, the patient population for this EPI study did not include any CF patients, it is not unexpected that fewer AEs occurred.

Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals. However, with such a small number of TEAEs occurring, it is difficult to draw any clinical conclusions.

5.3.1.11.7.3 Safety Summary

Exposure to Viokace (20,880 USP units of lipase per tablet) was standardized for Study VIO16EPI07-01; patients received 22 to 24 tablets per day which was administered as six

tablets with each meal and two tablets for each of two or three snacks. This was a total daily dose of 459,360 lipase units to a maximum of 501,120 lipase units or (assuming a 70 kg individual) approximately 7,142 lipase units per kilogram per day or about 1,800 lipase units per kilogram per meal. The dose used was higher than the average doses of enteric coated product used in other EPI studies, both with patient populations of cystic fibrosis and chronic pancreatitis. Typically, doses for the enteric coated enzyme products have been approximately 4,000 to 5,000 lipase units per kilogram per day. Although the doses used for Study VIO16EPI07-01 were higher than typically used in other PEP studies, they were still within the limits as specified by the CF Foundation as below:

- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy. Total daily dose (3 meals plus 2 or 3 snacks) should not exceed 10,000 lipase units/kg/day.[7]

The dose used during this study was similar to what is currently encountered for PEP treatment of CF patients in clinical practice. However, there is less information available on the pancreatic enzyme doses used to treat other conditions associated with EPI. A recent randomized, single-blind, placebo controlled treatment study of Creon in patients with chronic pancreatitis used a fixed enzyme dose of 288,000 lipase units per day. This dose appeared to be efficacious in treating patients with chronic pancreatitis and pancreatectomy. This patient population may be more heterogeneous with regard to the severity of their EPI symptoms. Thus, in clinical practice, titration of dose is probably necessary to achieve optimal control of symptoms of EPI.

There were no deaths that occurred during the actual study; however, one patient died shortly after completion of the study. The death was assessed by the Investigator to be related to the patient's underlying diseases and all other reported events were considered to be part of chronic illness and/or represent outcomes of disease progression occurring in a patient with a heavy medical and surgical history. There were two patients who reported SAEs, one during the Treatment Phase of the study and one after the Treatment Phase. The SAE which occurred after the treatment period was in the same patient who expired after the study. During the treatment period, this patient developed cholelithiasis and related complications. It is possible that a high fat diet could have contributed to this condition. (See Appendix 9.5.1 of this review for a full narrative description of the event.)

In addition, another patient from the Viokace group, experienced two SAEs (cardiac failure and pulmonary edema). This Reviewer believes that there was no reasonable possibility for a causal relationship between study drug and the chronic heart disease that was diagnosed on hospitalization.

[7] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46. (PMID: 16782527)

No patients discontinued from the study secondary to AEs.

There were no clinically significant laboratory findings or changes in vital signs/physical exams associated with Viokace treatment. Most variations could be explained by the underlying chronic disease or by increased nutrition associated with the high fat diet and increased absorption. The remaining variations were of a small magnitude and were considered to be of no clinical consequence.

Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals. However, with such a small number of TEAEs occurring, it is difficult to draw any clinical conclusions.

The AEs observed during VIO16EPI07-01were few and most were mild or moderate in severity. The most commonly reported AEs during Viokace treatment were biliary stones and anal pruritis. Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals, and in general, the AE profile reported in this study was acceptable.

5.3.1.12 Summary and Conclusions for Study VIO16EPI07-01

The primary endpoint of the pivotal study, VIO16EPI07-01, was met. Treatment with Viokace resulted in a statistically significant increase in absorption of fat (increase in CFA) compared to placebo. The most severely affected patients (baseline CFA <40%) demonstrated the greatest response to treatment with Viokace (mean increase in CFA equal to 65), which was clinically meaningful. Subgroup analyses showed that factors such as age did not appear to affect efficacy. The efficacy of Viokace was demonstrated in adults with pancreatitis.

Exposure to Viokace during the study was higher than typically seen in other PEP studies; however, exposure was within the limits as specified by the CF Foundation. The safety profile of Viokace was acceptable.

Thus overall, the results of the pivotal trial demonstrate that CP patients who are treated with Viokace have objective and subjective improvement of their clinical symptoms of EPI, and that Viokace is reasonably well tolerated by this patient population. These results support the approval of Viokace for the treatment of EPI in patients with CP or pancreatectomy.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The Applicant is proposing that Viokace receive the following indication:

Viokace [redacted] in combination with a proton pump inhibitor, is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis [redacted].

Specific wording for labeling of Viokace is currently being negotiated with the Applicant. However, in the opinion of this Reviewer, the data submitted to the Viokace application support the specific statement that, [redacted] It is noted that all of the patients enrolled in the clinical studies submitted to the NDA were adults who had EPI due to CP or pancreatectomy. In the opinion of this Reviewer, the data submitted [redacted] are not robust enough to warrant other indications for Viokace. In addition, this Reviewer believes that Viokace should solely be indicated for adults.

6.1.1 Methods

The efficacy evaluation of the Viokace clinical program involved review of two clinical studies. The pivotal study, VIO16EPI07-01, was reviewed in depth and Study STEA-VK00-US01 (a randomized, open label, parallel study) was briefly reviewed to highlight several lessons learned from completion of this study.

The studies will be discussed separately as the differences in study design do not allow for the pooling of data. See Section 5.3 for a detailed review of Study VIO16EPI07-01. Study STEA-VK00-US01 will only be briefly reviewed in Section 6.1.10 as an additional efficacy issue.

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%).

There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products – Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, VIO16EPI07-0106-001, as reasonable and appropriate.

6.1.2 Demographics

The entire clinical development plan for Viokace included adult patients ages 24 years to 70.

6.1.2.1 Pivotal Study: VIO16EPI07-01

There were 50 patients between the ages of 24 and 70 years enrolled in Study VIO16EPI07-01. The mean age was 51 for both the Viokace and placebo groups. There were more males than females in both groups with the placebo group having a higher percent of males.
The patients were mostly homogeneous in terms of race with the majority of patients being Caucasian. This homogeneity is also seen in most PEP studies with predominant CF populations. All patients had CP with about 44% of patients also having a pancreatectomy.

The demographics of patients enrolled in Study VIO16EPI07-01 are summarized below in Table 18.

Table 18: Demographics of Study VIO16EPI07-01

	Viokace (n=30)	Placebo (n=20)
Age (years)		
Mean (SD)	51 (9.9)	51 (7.6)
Min, Max	24, 70	37, 63
Gender, n(%)		
Male	22 (73%)	19 (95%)
Female	8 (27%)	1 (5%)
Race, n(%)		
White	29 (97%)	19 (95%)
Black	1 (3%)	0
Other		1 (5%)
EPI etiology		
Chronic Pancreatitis	30 (100%)	20 (100)
Pancreatectomy	12 (55%)	10 (45%)

6.1.3 Patient Disposition

6.1.3.1 Pivotal Study VIO16EPI07-01

There were 218 patients who enrolled in Study VIO16EPI07-01. Of this number 168 patients failed screening: 88 patients with clinically-documented chronic pancreatitis and steatorrhea did not meet the criterion for FE-1 (FE-1 < 100 μg/g stool), while an additional 50 clinically documented patients who did meet the FE-1 criterion did not have a sufficiently low Wash-Out Phase CFA% (CFA% < 80%) for randomization into study entry. Thus, 50 patients were randomized and 49 completed the study. A summary of patient disposition is presented in Table 19 below.

Table 19: Patient Disposition

Parameter	Viokace n (%)	Placebo n (%)
Enrolled	218	
Randomized	30 (14%)	20 (9%)
Completed Study	29 (97%)	20 (100%)
Discontinued Study After Randomization (Inclusion/Exclusion Criteria Failure)	1 (3%)	0
Per Protocol	20 (67%)	15 (75%)

The Wash-Out Phase mean CFA% values for the Viokace® 16 and Placebo groups of the ITT population were comparable at 47.6 ± 24.1 and 56.6 ± 22.2, respectively. See Table 20 below.

Table 20: Wash-Out Phase Coefficient of Fat Absorption (CFA%) (ITT Population)

		Treatment Group	
Parameter	Statistic	Viokase®16 (N=30)	Placebo (N=20)
Wash-Out Phase CFA%	n	30	20
	Mean	47.56	56.64
	SD	24.112	22.192
	Median	53.96	63.02
	Min., Max.	-29.1, 74.5	-9.5, 93.3

Source: VIO16EPI07-01 Study Report (Page 76, Section 11.2.2, Table 11.2-5)

There were 14 study sites with between one and eight patients completing the study at each site. Enrollment by site is summarized in Table 21.

Table 21: Completed Patients per Study Site

Site Number	14	18	21	22	23	29	32	33	35	36	38	42	44	46
	1406	1801	2101	2202	2301	2905	3203	3301	3506	3601	3802	4201	4404	4617
	1414	1810	2103	2203	2308	2906	3211	3304	3507	3604	3805	4204		
	1418		2105	2205	2309		3213	3306	3514			4205		
	1422		2106		2312			3307	3524			4206		
			2109		2314				3527			4210		
			2110						3533			4211		
									3538					
									3542					
Total Patients	**4**	**2**	**6**	**3**	**5**	**2**	**3**	**4**	**8**	**2**	**2**	**6**	**1**	**1**

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for Study VIO16EPI07-01 was the coefficient of fat absorption (CFA). CFA following oral administration of Viokace and placebo were compared. The fecal fat measurements were obtained during a 72-hour in-hospital stool collection.

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted clinically meaningful increase in CFA that has been determined for patients with EPI due to causes other than CF; however, as EPI due to any cause has similar clinical findings, it would be reasonable to consider this degree of change as meaningful in EPI due to pancreatectomy and chronic pancreatitis. In addition, there is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. Patients with higher CFAs at baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Therefore, and in concert with the Agency's "Guidance for Industry Exocrine Pancreatic Drug Products – Submitting NDAs", the Division accepts the use of CFA as the primary efficacy measure in the pivotal study, VIO16EPI07-01, as reasonable and appropriate.

The Applicant's results show that the mean CFA during the Treatment Phase for patients receiving Viokace was 86%; the mean CFA during the Treatment Phase for patients receiving placebo (no treatment) was 58%. Therefore, the difference in CFA was 28% (95% CI of 17.8, 37.2). The efficacy results showed a difference in CFA that was statistically significant ($p < 0.0001$). This reviewer and the FDA Statistician confirmed the results and were in agreement with the Applicant. The results are summarized in Table 22 (electronically copied and reproduced from the Applicant's submission).

Table 22: Coefficient of Fat Absorption (CFA%) (Intent-to-Treat Population)

Parameter Phase / Analysis Type	Statistic	Treatment Group Viokase®16 (N=30)	 Placebo (N=20)
CFA%			
Wash-Out Phase	n	30	20
	Mean	47.56	56.64
	SD	24.112	22.192
	Median	53.96	63.02
	Min., Max.	-29.1, 74.5	-9.5, 93.3
Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	85.52	58.02
	SD	8.902	24.249
	Median	88.34	64.87
	Min., Max.	52.6, 95.5	3.5, 93.0
	LSMean (SE)	87.8 (2.6)	58.4 (3.2)
	p-value [a]	<0.0001**	
Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	37.95	1.37
	SD	25.409	13.330
	Median	35.69	-1.65
	Min., Max.	1.6, 119.8	-21.4, 30.5
Percent Change from Wash-Out Phase to Treatment Phase / PI Using the 50th Percentile	n	30	20
	Mean	616.83	-5.78
	SD	2940.244	43.813
	Median	60.59	-2.79
	Min., Max.	-411.5, 16162.5	-136.6, 90.4

* Indicates statistical significance at the 0.050 level; ** Indicates statistical significance at the 0.010 level.

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase CFA% value as covariate

Notes:

1. LS Mean= Least Square Mean; PI= Percentile Imputation; SE= Standard Error.
2. Coefficient of Fat Absorption (CFA%) is defined as: {[Total fat intake during the stool collection period (g) – Total fat excretion during the stool collection period (g)]/ Total fat intake during the stool collection period (g)} x 100%.

Source: VIO16EPI07-01, Study Report (Page 91, Section 11.4.1.1, Table 11.4-1)

The results of the primary endpoint show a statistically significant difference in CFA during the Treatment Phase in patients treated with Viokace as compared to patients on placebo. The clinical significance of a mean difference in CFA of 28% is challenging to interpret as this is an average of all of the patients, regardless of their baseline (no-treatment or Wash-out Phase) CFA values. Thus, the primary endpoint results should be examined in conjunction with the CFA for

individual patients. This was performed as a subgroup analysis by this Reviewer (see section 5.3.1.11.6.2 above).

Overall, the additional efficacy analysis of change in CFA by no treatment CFA showed that the increase in CFA on Viokace treatment is greatest in the most severely affected patients. There were 14 patients in the severe category (no treatment Phase CFA < 40), ten in the Viokace treatment group and four in the placebo group. The mean change in CFA for the Viokace treatment group was 65% and 4% for the placebo group. All of the most severely affected patients in the Viokace treatment group had an increase in CFA greater than or equal to 40%., with seven patients having an increase in CFA of greater than 50%. Thus, the most severely affected patients in the Viokace treatment group demonstrated the greatest response to treatment with Viokace. The magnitude of the change (mean change 65% in this group, and ≥40% in most of the patients) was a clinically meaningful result.

The patients who had a higher no-treatment CFA (≥40% during Wash-Out Phase) showed smaller increases in CFA after treatment with Viokace. The inverse relationship between low no-treatment CFA and change in CFA (the lower the value initially, the higher the increase) is critical to the efficacy of the study. These results support the approval of Viokace for the treatment of EPI; treatment with Viokace is beneficial to most patients. The treatment affect is variable; however, it follows a trend that the greatest change in CFA is observed in the patients with the lowest no-treatment CFA.

6.1.5 Analysis of Secondary Endpoint(s)

There were several secondary efficacy endpoints in this study. These endpoints evaluated other factors that may help to support the results of the primary efficacy analysis; however, these endpoints are not suitable for labeling. The secondary efficacy endpoints analyzed had no clinically definable change that was clinically meaningful.

Stool Frequency

The mean average total daily number of bowel movements during the Wash-Out Phase for the ITT population was 2.95 in patients assigned to Viokace treatment and 2.40 in patients assigned to placebo. The mean average total daily number of bowel movements decreased during the Treatment Phase to 1.93 in patients taking Viokace and 2.33 in patients on placebo. The difference in the mean values between Wash-out and Treatment Phase was -1.01 for Viokace and -0.07 for placebo. See Table 23 below (electronically scanned and copied from Applicant).

Table 23: Mean Number of Stools Per Day (Intent-To-Treat Population)

Phase / Analysis Type	Statistic	Treatment Group	
		Viokase®16 (N=30)	Placebo (N=20)
Wash-Out Phase	n	30	20
	Mean	2.95	2.40
	SD	1.176	0.824
	Median	2.71	2.29
	Min., Max.	1.0, 5.3	1.0, 4.0
Treatment Phase / OC	n	30	20
	Mean	1.93	2.33
	SD	0.989	0.950
	Median	1.75	2.33
	Min., Max.	0.8, 5.3	0.8, 4.3
	LS Mean (SE)	1.8 (0.2)	2.5 (0.2)
	p-value [a]	0.0083**	
Change from Wash-Out Phase to Treatment Phase / OC	n	30	20
	Mean	-1.01	-0.07
	SD	1.053	0.738
	Median	-0.98	0.00
	Min., Max.	-3.0, 0.8	-1.3, 1.5
Percent Change from Wash-Out Phase to Treatment Phase / OC	n	30	20
	Mean	-28.97	1.11
	SD	33.079	36.838
	Median	-33.33	0.00
	Min., Max.	-75.0, 75.0	-62.5, 100.0

* Indicates statistical significance at the 0.0500 level; ** Indicates statistical significance at the 0.0100 level.

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase mean number of stools per day as a covariate.

Notes:

1. LSMean= Least Squares Mean; SE= Standard Error.
2. Mean number of stools per day is defined as: Total number of stools during the completed days in the Inpatient Period/Total number of completed days in the Inpatient Period.
3. Since there are no missing Treatment Phase values, only the 'Observed Case' analysis type is displayed.

Source: VIO16EPI107-01 Study Report (Pages 93-94, Section 11, Table 11.4-3)

The difference in the mean values was statistically significant (p = 0.0083); however, the clinical significance of this very small change in number of bowel movements over a 72 hour period is not clear.

Stool Characteristics

Another secondary endpoint was the comparison of stool characteristics between Viokace and placebo recorded over the 72-hour stool collection period. The proportion of hard, formed/normal, soft and watery stools was evaluated during the Inpatient Periods of both the

Wash-Out and Treatment Phases. Although a higher mean average daily proportion of normal/formed stools was observed during the Treatment Phases for patients on Viokace (45.9%) compared to those on placebo (37.2%), no statistically significant difference between the treatment groups was detected. (See Table 24 below electronically scanned and copied from Applicant) In addition, a difference of less than 10% in mean average daily proportion of normal/formed stools is difficult to interpret clinically.

Table 24: Proportion of Stools by Characteristic during the Treatment Phase (Intent-to-Treat Population)

		Treatment Group	
Parameter	**Statistic**	**Viokase®16 (N=30)**	**Placebo (N=20)**
Proportion of Hard Stools (%)	n	30	20
	Mean	5.08	0.67
	SD	13.610	2.981
	Median	0.00	0.00
	Min., Max.	0.0, 50.0	0.0, 13.3
	LSMean (SE)	5.2 (2.1)	1.3 (2.6)
	p-value [a]	0.3108	
Proportion of Formed / Normal Stools (%)	n	30	20
	Mean	45.86	37.23
	SD	33.269	37.906
	Median	50.00	25.40
	Min., Max.	0.0, 100.0	0.0, 100.0
	LS Mean (SE)	45.6 (4.6)	34.3 (5.8)
	p-value [a]	0.1203	
Proportion of Soft Stools (%)	n	30	20
	Mean	47.80	55.48
	SD	33.305	39.457
	Median	46.43	64.17
	Min., Max.	0.0, 100.0	0.0, 100.0
	LS Mean (SE)	46.3 (5.2)	54.3 (6.5)
	p-value [a]	0.3229	
Proportion of Watery Stools (%)	n	30	20
	Mean	1.26	5.80
	SD	4.819	14.572
	Median	0.00	0.00
	Min., Max.	0.0, 21.1	0.0, 60.0
	LS Mean (SE)	2.7 (1.5)	8.7 (1.8)
	p-value [a]	0.0611	

Source: VIO16EPI107-01 Study Report (Page 96, Section 11, Table11.4-5)

These secondary efficacy variables were difficult to analyze accurately given the multiple variables involved and the nature of the underlying disease. The secondary endpoints were subjective and assessed without using validated endpoint measures. Thus overall, given the

subjective nature of the analyses of the secondary efficacy variables, and the lack of clinical relevance, these results are not sufficient to support labeling.

6.1.6 Other Endpoints

There are no other endpoints evaluated that are of clinical relevance.

6.1.7 Subpopulations

Subgroup analyses by gender and age were performed by this Reviewer. It was difficult to assess mean changes in CFA with respect to gender as there were greater than four times as many males in the study as females (nine females were included in the efficacy analysis population). The difference in mean change in CFA of 36 (between Viokace and placebo) for the subgroup of patients 50 years and younger, was similar to the difference in mean change in CFA for the subgroup of patients older than 50. (See also Tables 13 and 14 in Section 5.3.1.11.6.2.)

There were too few non-Caucasian patients to perform a meaningful analysis by race (see Table 3 in Section 5.3.1.11.1). Ideally, races other than Caucasian should have been represented in the pivotal study in higher proportions. However, given the plethora of knowledge available for porcine PEPs, there is no compelling evidence to suggest that non-Caucasian patients would respond differently to treatment with Viokace. Future studies of Viokace for the treatment of EPI secondary to CP and other conditions should be more heterogeneous regarding race.

Analysis of subgroups defined by baseline (no-treatment) CFA showed that the patients who were the most severely affected (lowest baseline CFA) gained the most benefit of Viokace treatment by having the largest increase in CFA (see above Section 6.1.4 Analysis of Primary Endpoint).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in the Viokace clinical development program were treated with doses that did not exceed the CFF guideline limits of 2,500 U lipase/kg/meal and 10,000 U lipase/kg/day. For the pivotal study, patients received a set dose of 22 tablets/day of Viokace (6 tablets per meal and two tablets for two or three snacks). Compliance was high in both treatment groups, with patients taking over 98% of their assigned medication (98.99% in the Viokace group and 98.90% in the placebo group). In the Viokace group, all patients took at least 19 tablets of Viokace per day for the treatment period (range of 19-23 tablets per day).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects was not assessed in the Viokace clinical development program since the clinical data obtained were from short-term studies. According to

the literature, there does not appear to be the development of tolerance to PEPs and patients remain on these medications for long periods of time (typically life-long treatment).

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 STEA-VK00-US01

This clinical study was a randomized, open label, parallel study comparing two doses of Viokace for the treatment of steatorrhea in patients with EPI. The primary endpoint was the comparison of Fecal Fat Excretion (FFE) levels at Baseline and at 3 weeks post-treatment. A secondary endpoint was the comparison of CFA at Baseline and at 3 weeks post-treatment. Fecal fat excretion is the amount of fat excreted in one's stool.

Primary efficacy results are shown below in Table 25 below (electronically scanned and copied from Applicant). There appears to be a trend toward decreasing fecal fat levels, but it is not statistically significant.

Table 25: Change in Fecal Fat Excretion (FFE) from Baseline to 3 Weeks Post-Treatment

		Treatment Group	
Parameter	**Statistic**	**VIOKASE® 16 8-tab**	**VIOKASE® 16 16-tab**
Change from Baseline to Day 42	N	7[*]	8
	Mean	-9.27	-9.98
	SD	18.6	13.6
	Median	-5.08	-4.13
	Min., Max.	-41.7, 10.9	-35.2, 3.24
	p-value [a]	0.193 [@]	0.077
	p-value [b]	0.297	0.109 [@]
	Correlation [c]	0.652	0.865

Source: STEA-VK00-US01 Study Report (Page 68, Section 11, Table 11.2.4.1)

Secondary efficacy results are shown below in Table 26 below (electronically scanned and copied from Applicant). The results of change in CFA (which is the primary endpoint usually used), were not statistically significant. Mean change in CFA of about 9 is not very impressive and probably does not represent a clinically meaningful change.

Table 26: Change in CFA from Baseline to 3 Weeks Post-Treatment

Parameter	Statistic	Treatment Group	
		VIOKASE® 16 8-tab	VIOKASE® 16 16-tab
Change from Baseline to 2nd Inpatient Phase	N	7[*]	8
	Mean	9.42	9.66
	SD	19.3	14.8
	Median	6.12	4.04
	Min., Max.	-11.6, 43.0	-5.00, 36.8
	p-value [a]	0.209 [@]	0.108
	p-value [b]	0.297	0.148 [@]
	Correlation [c]	0.624	0.817

Source: STEA-VK00-US01 Study Report (Page 68, Section 11, Table 11.2.4.1)

In summary, Study STEA-VK00-US01 was a failed study. However, there were some important lessons potentially learned by the Applicant. In the next study, the Applicant planned on making several changes to the study design:

- Increased sample size (30 patients on Viokace)
- Increased dose of Viokace (22 tablets per day)
- Revised inclusion criteria to include patients with confirmed EPI (CFA% <80% and Fecal elastase ≤ 100 μg/g stool)
- Included concomitant PPI therapy for the duration of the study

There were no other relevant efficacy analyses performed.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Safety data were reviewed from the three clinical studies performed in the Viokace clinical development program. These studies included a pivotal Phase 3 placebo-controlled study (VIO16EPI07-01), an open-label Phase 2b study (STEA-VK00-US01) and a bioactivity study (VIO16IP07-01). In all studies, the population was the same: patients with EPI secondary to chronic pancreatitis. Safety was assessed in these studies by the review of all of the AE data.

The most important study reviewed for safety was VIO16EPI07-01, which was the double blind, placebo-controlled study in CP patients; however, all of the safety data from the Viokace clinical studies were reviewed in their entirety.

7.1.2 Adequacy of Data

In the opinion of this Reviewer, the Applicant adequately categorized the adverse events using MedDRA classification.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

There was some pooling of safety data for this review. Although the study designs were different, all of the studies had a similar patient population (CP patients) and two had similar primary endpoints. In addition, the pivotal study was analyzed separately (see Section 5 above).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety of Viokace was evaluated in three clinical studies. In two individual studies, patients were treated for one to three weeks duration with Viokace.

A total of 61 patients received at least one dose of Viokace in the clinical studies; see Table 27 (electronically scanned and copied from Applicant). In studies VIO16IP07-01 and VIO16EPI07-01, all patients also received 20 mg omeprazole per day throughout the treatment period. In Study VIO16IP07-01, all patients who received at least one dose of omeprazole were included in the safety population.

Table 27: Number of Patients Exposed to Viokace by Dosage in the Viokace Clinical Program

Study	VIO16IP07-01	STEA-VK00-US01		VIO16EPI07-01		TOTAL
VIOKASE® Dose	3 tablets, single dose	8 tablets per day for 3 weeks	16 tablets per day for 3 weeks	Placebo	22 tablets per day for 6 days	
Safety Population	20	9	8	20	30	87
Patients receiving VIOKASE®	14	9	8	0	30	61

Notes:
1. Patients in study VIO16IP07-01 received omeprazole 20 mg per day, and in study VIO16EPI07-01 patients took their usual PPI or omeprazole 20 mg per day.
2. For patients enrolled under protocol STEA-VK00-US01, the number of units of lipase per tablet is 16,000 USP, while for patients enrolled under the Viokase®16 22-tablets treatment group of protocol VIO16EPI07-01, the number of units of lipase per tablet is 20,880 USP
3. Number of patients in the Safety Population is as defined in the corresponding Clinical Study Report. In study VIO16IP07-01, all patients who received at least one dose of omeprazole were included in the Safety Population. In studies STEA-VK00-US01 and VIO16EPI07-01, all patients who received at least one dose of VIOKASE®16 or corresponding placebo were included in the Safety Population.
4. Patients receiving VIOKASE indicates the number of patients who received at least one dose of VIOKASE®16.

Source: Integrated Summary of Safety (Page 13, Section 2.7.4, Table 2.7.4.1.2-1)

Table 28 below (electronically scanned and copied from Applicant) presents the dose as the mean daily lipase dose during the study treatment periods. These doses were within the limitations as specified by the CFF Foundation's guidelines (less than 2,500 U lipase/kg/meal and 10,000 U lipase/kg/day).

Table 28: Mean Lipase Dose During Treatment in the Viokace Clinical Program

		VIOKASE®16 Treatment Group			
Study Treatment Group	**Statistic**	**8 tablets per day**	**16 tablets per day**	**22 tablets per day**	**Overall Treatment Phase**
Mean daily dose of lipase intake (lipase units/kg body weight/day)	n Mean (SD) Min, Max	9 2021.5 (499.95) 1489, 2840	8 4130.4 (833.38) 3017, 5689	30 7205.5 (1376.27) 5083, 11484	47 5689.4 (2428.44) 1489, 11484
Mean dose of lipase intake per meal (lipase units/kg body weight/meal)	n Mean (SD) Min, Max	7 538.6 (98.36) 420, 719	8 1095.7 (253.36) 764, 1600	30 1320.3 (243.31) 995, 1914	45 1158.8 (360.93) 420, 1914

Notes:

1. In this table, the term "meal" refers to either a meal or a snack.
2. It is to be noted that lipase intake is null for the Placebo treatment group. Therefore, no descriptive statistics are presented for that treatment group.
3. Mean total daily dose of lipase intake (lipase unit/kg of body weight/day) is defined as: {[(Total number of tablets taken during the completed days of the Treatment Phase x Number of units of lipase per tablet) / patient's weight (kg)] / Number of completed days during the Treatment Phase). For patients enrolled under protocol STEA-VK00-US01, the number of units of lipase per tablet is 16,000 USP, while for patients enrolled under the Viokase®16 22-tablets treatment group of protocol VIO16EPI07-01, the number of units of lipase per tablet is 20,880 USP
4. Mean dose of lipase intake per meal (lipase unit/kg of body weight/meal) is defined as: {[(Total number of tablets taken during the completed days of the Inpatient Period of the Treatment Phase x Number of units of lipase per tablet) / patient's weight (kg)] / Number of meals eaten during the completed days of the Inpatient Period of the Treatment Phase). For patients enrolled under protocol STEA-VK00-US01, the number of units of lipase per tablet is 16,000 USP, while for patients enrolled under the Viokase®16 22-tablets treatment group of protocol VIO16EPI07-01, the number of units of lipase per tablet is 20,880 USP

Source: Integrated Summary of Safety (Page 14 Section 2.7.4, Table 2.7.4.1.2-2)

In the Phase 3 study VIO16EPI07-01, a total of 30 patients were randomized to the Viokace treatment arm, and 20 patients were randomized to receive placebo. All randomized patients received at least one dose of study medication (Viokace or placebo) and were therefore considered to be part of the safety population. A total of 29 patients in the Viokace group and 20 patients in the placebo group completed the study; one patient in the Viokace group was discontinued from the study for not satisfying the inclusion/exclusion criteria and terminated early due to screening failure.

In the Phase 2b study STEA-VK00-US01, a total of 17 patients were randomized to receive Viokace: Nine patients were randomized to receive 8 Viokace tablets per day (referred to herein

as "8-tablet"), and 8 patients were randomized to receive 16 Viokace tablets per day (referred to herein as "16-tablet"). All randomized patients received at least one dose of study medication (Viokace) and were therefore considered to be part of the safety population. A total of 7 patients in the 8-tablet group and 8 patients in the 16-tablet group completed the study. In the 8-tablet group, one patient withdrew from the study because of an AE, and one patient was discontinued from the study after 14 days of treatment due to poor compliance to study drug (63%).

In the bioactivity study VIO16IP07-01 (single dose study), a total of 20 patients were randomized to one of two treatment sequences. All 20 patients received at least one dose of omeprazole and were therefore included in the Safety Population. Of the 20 subjects, five discontinued prior to receiving either Viokace or Ensure Plus® (liquid meal), three due to AEs, and two because of screening failures. One patient received Ensure Plus® and withdrew consent prior to receiving any Viokace treatment because they could not tolerate the liquid meal. The remaining 14 patients completed the study. Therefore, of the 20 patients in the safety population, a total of 14 received the Viokace treatment.

According to the PEP Guidance, it was acceptable that the Viokace clinical program was limited to short-term efficacy and safety studies. The long-term safety of PEPs has been established over the many years of their use. This application relied on the published medical literature for full descriptions of AE profiles.

The data in the Viokace clinical development program were limited by several factors which included: small study size, use of only one pivotal study, a homogeneous study population, and short study duration. However, given the extensive knowledge of PEPs worldwide, the overall Viokace safety program was adequate and was consistent with the recommendations of the Guidance.

7.2.2 Explorations for Dose Response

No formal dose-response investigations were performed, but all patients received fixed doses of Viokace (per study) and these doses remained within CFF guidelines. The pivotal study used only one dosage strength, Viokace 16 (20,800 USP units of lipase); however, the other dosage strength, Viokace 8 (10,400 USP units of lipase) is (b) (4) According to the Biopharmaceutical Reviewer, Tien-Mien Chen, Ph.D., "the biowaiver for the lower strength (Viokace 8 tablet) is granted". Please refer to ONDQA Biopharmaceutics Review for further details.

7.2.3 Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs, the PEP Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not needed to support the Viokace clinical development program. In addition, this was a 505(b)(2) application, thus no special animal or in vitro testing was required.

7.2.4 Routine Clinical Testing

The schedule of clinical assessments performed for the pivotal study, VIO16EPI07-01, was adequate (see Table 2: Schedule of Study Assessments for Study VIO16EPI07-01 in Section 5.3.1.5), and consisted predominantly of monitoring for AEs during study drug treatment, and changes from baseline in physical examinations (including vital signs) and clinical laboratory assessments (chemistry, hematology and urinalysis). The efforts to elicit AEs were acceptable. Since PEPs are not absorbed, no ECGs were collected.

7.2.5 Metabolic, Clearance, and Interaction Workup

Viokace acts locally in the GI tract to improve the absorption of lipids, fat soluble vitamins, proteins, and to a lesser extent carbohydrates. It is not systemically absorbed thus absorption, distribution, metabolism, and elimination (ADME) assessments were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There is an extensive history of clinical use with the PEPs, and their safety profile is well described. The most serious safety concern with PEP administration is fibrosing colonopathy (FC). FC is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs. As a result of this potential safety (and efficacy) concern, the CFF and FDA published weight-based dosing guidelines for PEP administration (see Section 2.1).

The clinical development program for Viokace followed the current CFF recommendations on limiting the dosages (by lipase units). No cases of fibrosing colonopathy were reported in the clinical development program; however, it is noted that cases of FC are rare, and the finding of even a single case of FC in a safety population of this size was not expected.

PEP treatment has been associated with elevated serum and urine levels of uric acid (hyperuricemia and hyperuricosuria). Uric acid levels were adequately monitored throughout the pivotal clinical study. No clinically significant uric acid elevations were reported; however, given the short duration of treatment and the treatment of patients who were of adequate nutritional status only, most of whom were maintained on stable doses of PEPs prior to entry into these studies, clinically meaningful changes in uric acid levels were not expected.

Despite the negative findings for FC, hyperuricemia, and hyperuricosuria in the short-term clinical development program for Viokace in a small number of patients, given the concerns for these AEs with the administration of PEPs, caution should be exercised when prescribing PEPS to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels. In addition, monitoring for FC should be addressed in any future labeling for Viokace, and should be a component of ongoing safety monitoring/pharmacovigilance of Viokace.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths that occurred during the treatment phases of any of the three studies supporting this submission. In Study VIO16EPI07-01, one patient in the Viokace treatment group (Patient No. 4617, a 70 year old male) experienced a progression of his chronic pancreatitis to inoperable malignant tumor of the head of the pancreas after the study period was completed; this patient subsequently died on (b) (6). The death was not considered to be related to study treatment.

7.3.2 Nonfatal Serious Adverse Events

Overall in the Viokace clinical development program, there were a total of ten Serious Adverse Events (SAEs) in five patients across the three clinical studies. Nine of these SAEs were Treatment-Emergent, and of these, four occurred during the Treatment Phase of the study. None of these events were considered to be related to study treatment by the study investigator(s).

Study VIO16EPI07-01
One patient in the Viokace treatment group experienced one SAE during the Treatment Phase of this study. Patient No. 4617 experienced cholelithiasis; this event was moderate in intensity and was not considered related to study treatment. The same patient had two additional SAEs after the study was completed (coagulation factor decreased and disease progression) in addition to progression of his chronic pancreatitis to inoperable malignant tumor of the head of the pancreas, and subsequent death.

Patient No. 3307 experienced SAEs of cardiac failure and pulmonary edema after the treatment phase of the study. Clinical workup performed during hospitalization revealed heart insufficiency IV/III (NYHA type), mitral valve insufficiency, ischemic heart disease and arterial hypertension.

Study STEA-VK00-US01
There were four SAEs reported in this study. Three of these events were treatment emergent and occurred in the same patient from the 8-tablet treatment group. This patient (Patient No. 22) was hospitalized due to possible hepato-renal syndrome, bacterial peritonitis and ascites. While hospitalized, the following procedures were performed on the patient: paracentesis and culture of ascites fluid, and antibiotic treatment. The investigator deemed these events to be a result of complications of alcoholic cirrhosis and unrelated to the study medication. This patient was discontinued from further participation in the study. The outcome of the SAE was listed as unresolved because the patient moved to another state and follow-up could not be completed.

One additional SAE was reported in a patient during the Washout Phase of the study prior to initiation of Viokace treatment. This patient (Patient No. 07) experienced severe abdominal pain and was hospitalized for six days after a diagnosis of blockage of the small bowel and gas pocket. The SAE of intestinal obstruction was deemed unrelated to study drug since the patient had not yet started on treatment. The patient recovered from the event.

Study VIO16IP07-01

There was one SAE in this study. Patient No. 0115 was hospitalized approximately 1 week after completing the study with symptoms of infection including fever, chills, dizziness, tremors, shaking, weakness and nausea. The patient was diagnosed with a urinary tract infection and was treated with IV saline and a broad spectrum antibiotic. The infection resolved and the patient was discharged from the hospital 4 days later. This SAE was judged to be of moderate intensity and not related to the study treatment.

7.3.3 Dropouts and/or Discontinuations

Across the three studies, there were four cases of study discontinuation due to an AE; three of these cases involved events that occurred prior to the initiation of Viokace therapy.

There were no patients who withdrew from Study VIO16EPI07-01 due to an AE.

One patient from Study STEA-VK00-US01 in the Viokace 8-tablet group (Patient No. 22) experienced three SAEs and was withdrawn from the study. This patient is described above under Nonfatal Serious Adverse Events (Section 7.3.2).

Three patients discontinued from Study VIO16IP07-01 due to AEs; however, each of these patients was discontinued prior to receiving either Viokace or the liquid meal.

Patient No. 0105 was a 60 year old male who was experiencing atrial fibrillation upon admission to the research facility. This was a previously diagnosed condition. The patient was counseled on the proper administration of his medication and was discontinued from further study participation. The investigator considered this event mild in intensity, not related to study drug, and resolved.

Patient No. 0114 was a 48 year old female who had elevated blood pressure upon admission to the research facility. The hypertension persisted, and the patient was referred to her physician for evaluation and was discontinued from the study. The investigator considered the event as moderate in intensity, not drug related, and resolved.

Patient No. 0116 was a 68 year old female who complained of angina pectoris, nausea and vomiting upon admission to the research facility. The patient was referred to the emergency room but she did not present there; a subsequent visit with her cardiologist resulted in her being scheduled for open heart surgery. The study investigator considered the events to be moderate (nausea, vomiting) to severe (angina pectoris) in intensity, not related to study drug, and on-going.

These cases of study withdrawal due to AEs are summarized below in Table 29 (electronically scanned and copied from Applicant).

Table 29: Adverse Events Leading to Study Withdrawal in the Viokace Clinical Program

Study	Patient number	AE Preferred Term	Other Comments
STEA-VK00-US01	22	Hepato-renal syndrome Bacterial peritonitis Ascites	SAE
VIO16IP07-01	0105	Atrial fibrillation	AE occurred prior to initiation of VIOKASE®16 treatment
	0114	Hypertension	AE occurred prior to initiation of VIOKASE®16 treatment
	0116	Angina pectoris Nausea Vomiting	AE occurred prior to initiation of VIOKASE®16 treatment

Source: 5.3.5.2 STEA-VK00-US01 Table 23 p. 62, 63-64; 5.3.1.1 VIO16IP07-01 P.55-56

7.3.4 Significant Adverse Events

All significant adverse events are described above in Sections 7.3.1, 7.3.2, and 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

The most serious safety concern with PEP administration is fibrosing colonopathy (submucosal fibrosis). See section 7.2.6 above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Viokace development program consisted of three clinical studies each with a different study design so AEs were analyzed separately per individual study.

Study VIO16EPI07-01
Of the 50 patients included in the safety population randomized, a total of 9 patients experienced treatment-emergent adverse events. Seven patients in the Viokace treatment group experienced 16 AEs, and two patients in the placebo group experienced four AEs. Table 30 below provides an overview of treatment-emergent adverse events which occurred in the safety population.

Table 30: Treatment-Emergent Adverse Events Overview (Safety Population)

Parameter	Viokace 16 (N=30)	Placebo (N=20)
Total Number of TEAEs	16	4
Total Number of Serious TEAEs	1	0
Patients with TEAEs	7 (23%)	2 (10%)
Patients with Serious TEAEs	1 (3%)	0
Patients with Possibly, Probably or Definitely Related TEAEs	3 (10%)	0
Patients Discontinued due to TEAEs	0	0

Source: Applicant's Summary of Clinical Safety: page 17; Table 2.7.4.2.1-1

In the Viokace group, the most frequently represented organ system was Gastrointestinal Disorders. There were 5 patients in the Viokace group that had gastrointestinal AEs, including anal pruritus (2 patients), abdominal pain, ascites, and flatulence. In addition, two patients had biliary tract stones. There were no gastrointestinal AEs reported in the placebo group. All of the other adverse events occurred in only one patient. See Table 31 below for the complete list of Treatment-Emergent Adverse Events by this Reviewer's analysis.

Table 31: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

MedDRA Primary System Organ Class/ Preferred Term	Viokace (N=30)	Placebo (N=20)
Total Number of TEAEs	16	4
Total Number of Patients with any TEAEs	7 (23.3%)	2 (10.0%)
Blood And Lymphatic System Disorders		
Anemia	1 (3.3%)	0
Gastrointestinal Disorders		
Anal pruritus	2 (6.7%)	0
Abdominal pain	1 (3.3%)	0
Ascites	1 (3.3%)	0
Flatulence	1 (3.3%)	0
General Disorders and Administration Site Conditions		
Edema peripheral	1 (3.3%)	0
Hepatobiliary Disorders		
Biliary tract stones	2 (6.7%)	0
Hydrocholecystis	1 (3.3%)	0
Infections and Infestations		
Viral infection	1 (3.3%)	0
Nervous System Disorders		
Headache	1 (3.3%)	0
Renal and Urinary Disorders		
Renal cyst	1 (3.3%)	0
Skin and Subcutaneous Tissue Disorders		
Rash	1 (3.3%)	0
Musculoskeletal and Connective Tissue Disorders		
Myalgia	0	1 (5.0%)
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1 (3.3%)	1 (5.0%)

Source: Adapted from Applicant's Summary of Clinical Safety: page 17; Table 2.7.4.7-1

In general, there were few AEs reported during the treatment period of Study VIO16EPI 07-01, with most only occurring in one patient. This was in contrast to other pivotal studies of PEPs which were performed with a majority of cystic fibrosis patients. Since most patients with cystic fibrosis are affected with the disease from birth, and thus have other organ systems chronically affected (e.g. respiratory system), more AEs would be expected in a patient population which included them. Since, by entry criteria, the patient population for this EPI study did not include any CF patients, it is not unexpected that fewer AEs occurred.

Careful review of the adverse event datasets by this Reviewer did not reveal any obvious or noteworthy safety signals. However, with such a small number of TEAEs occurring, it is difficult to draw any clinical conclusions.

Study STEA-VK00-US01

In the Phase 2b study, there were a total of 20 non-serious TEAEs reported by ten patients in the two Viokace treatment groups. The only TEAE that occurred in more than one patient was constipation, which was experienced by two patients (11.8%), one in each of the Viokace treatment groups. There was no obvious effect of dose of Viokace on the pattern of AEs that were observed. The most frequently represented System Organ Class (SOC) was Gastrointestinal Disorders: there were 5 patients (29.4%) across the two Viokace treatment groups with AEs in this SOC. A summary of all AEs reported during Study STEA-VK00-US01 is presented below in Table 32 (electronically scanned and reproduced from Applicant).

Table 32: Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Statistic	Treatment Group		Total
		VIOKASE® 16 8-tab (N=9)	VIOKASE® 16 16-tab (N=8)	(N=17)
Number of Non-Serious TEAEs	N	12	8	20
Number of Patients With at Least One Non-Serious TEAE	n (%)	6 (66.7)	4 (50.0)	10 (58.8)
Blood and Lymphatic System Disorders	n (%)	0	1 (12.5)	1 (5.9)
Lymphadenopathy	n (%)	0	1 (12.5)	1 (5.9)
Gastrointestinal Disorders	n (%)	3 (33.3)	2 (25.0)	5 (29.4)
Constipation	n (%)	1 (11.1)	1 (12.5)	2 (11.8)
Abdominal Pain Upper	n (%)	0	1 (12.5)	1 (5.9)
Dyspepsia	n (%)	0	1 (12.5)	1 (5.9)
Gingival Ulceration	n (%)	1 (11.1)	0	1 (5.9)
Nausea	n (%)	1 (11.1)	0	1 (5.9)
Infections and Infestations	n (%)	1 (11.1)	0	1 (5.9)
Candidiasis	n (%)	1 (11.1)	0	1 (5.9)
Investigations	n (%)	1 (11.1)	0	1 (5.9)
Blood in Stool	n (%)	1 (11.1)	0	1 (5.9)
Musculoskeletal and Connective Tissue Disorders	n (%)	1 (11.1)	1 (12.5)	2 (11.8)
Arthralgia	n (%)	1 (11.1)	0	1 (5.9)
Back Pain	n (%)	1 (11.1)	0	1 (5.9)
Flank Pain	n (%)	0	1 (12.5)	1 (5.9)
Nervous System Disorders	n (%)	1 (11.1)	0	1 (5.9)
Headache	n (%)	1 (11.1)	0	1 (5.9)
Reproductive and Breast Disorders	n (%)	0	1 (12.5)	1 (5.9)
Vaginal Mycosis	n (%)	0	1 (12.5)	1 (5.9)
Vascular Disorders	n (%)	1 (11.1)	0	1 (5.9)
Hypotension	n (%)	1 (11.1)	0	1 (5.9)

Source: STEA-VK00-US01 Study Report: page 52; Table 13.2

Study VIO16IP07-01

In the bioactivity single dose study, VIO16IP07-01, there were a total of nine subjects who experienced at least one AE. The only AEs reported by more than one subject were dizziness and pharyngolaryngeal pain, which were reported by two subjects each. None of the AEs were considered to be drug related. A summary of all AEs reported during Study VIO16IP07-01 is presented below in Table 33 (electronically scanned and copied from Applicant).

Table 33: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	(N=20) n (%)
Number of Subjects with Any Event	9 (45)
Cardiac Disorders	2 (10)
Angina pectoris	1 (5)
Atrial fibrillation	1 (5)
Gastrointestinal Disorders	2 (10)
Abdominal pain upper	1 (5)
Nausea	1 (5)
Vomiting	1 (5)
Infections and Infestations	1 (5)
Infection	1 (5)
Musculoskeletal and Connective Tissue Disorders	1 (5)
Back pain	1 (5)
Nervous System Disorders	3 (15)
Akathisia	1 (5)
Dizziness	2 (10)
Paraesthesia	1 (5)
Psychiatric Disorders	1 (5)
Anxiety	1 (5)
Disorientation	1 (5)
Respiratory, Thoracic and Mediastinal Disorders	2 (10)
Pharyngolaryngeal pain	2 (10)
Vascular Disorders	1 (5)
Hypertension	1 (5)

Source: Applicant's Summary of Clinical Safety: page 24; Table 2.7.4.2.1.1-5

The majority of the AEs reported were considered by the Investigator to be mild in intensity. Three subjects experienced AEs that were moderate or severe in intensity. Two of these subjects (Patient No. 0116 with severe angina pectoris and moderate nausea and vomiting, and Patient No. 0114 with moderate hypertension) withdrew from the study prior to receiving Viokace or the liquid meal (Ensure Plus®). The third subject experienced an infection approximately one week after completing the study that was considered by the Investigator to be serious, moderate in intensity, and unrelated to study drug administration.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were conducted in all three studies in the Viokace development program. The mean change from baseline for the assessed hematology and chemistry parameters across the bioactivity, Phase 2b, and Phase 3 studies provided no indication of a deleterious effect with either Viokace or placebo treatment. The only parameter that indicated a possible trend was blood urea nitrogen (BUN) which exhibited an increase from baseline of approximately 33% for Viokace compared to a drop of approximately 15% for placebo. This effect could be due to an increase in nutrient absorption with Viokace treatment, combined with the high fat diet required by study procedures. Although BUN levels increased in some patients, the increase was not a clinically meaningful increase.

There were several parameters that were above normal or at the high end of the reference range at baseline, including alkaline phosphatase and glucose levels. These elevated levels were seen in both Viokace and placebo groups. With alkaline phosphatase, there was a slight decrease in these values with treatment. Glucose levels tended to increase with treatment in both groups, which could have been due to the dietary changes required for the study. The mean changes provide no indication of an effect with either Viokace or placebo treatment.

Due to the chronic nature of the underlying disease in the patient population of all studies, minor variability in lab values is not unexpected.

7.4.3 Vital Signs

Vital signs and physical examination information were collected in all three studies. The only trend observed was while on treatment with Viokace, there were slight increases in means for body weight and BMI, and slight decreases in means for heart rate and blood pressure. However, the changes were smaller than the corresponding standard deviations and were not considered to be of clinical significance, especially given the short duration of the studies.

7.4.4 Electrocardiograms (ECGs)

Viokace is not systemically absorbed and electrocardiogram evaluation was not part of the Viokace clinical development program.

7.4.5 Special Safety Studies

There were no special safety studies performed in the Viokace clinical development program.

7.4.6 Immunogenicity

Viokace and other porcine-derived PEPs are not systemically absorbed, and immunogenicity testing was not performed as part of the Viokace clinical development program.

7.5 Other Safety Explorations

No other safety explorations were performed. No non-clinical studies of the active pharmaceutical ingredients were conducted in support of this NDA.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Viokace and other porcine-derived PEPs are not systemically absorbed and human carcinogenicity studies were not part of the PEP clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

No studies with Viokace were conducted in pregnant women. It is likely that Viokace will be used by pregnant women and women of reproductive potential. PEPs have likely been used over their history by pregnant women, but are not absorbed and no effects of active ingredients on pregnant women or their offspring are known. The labeling of this product should address safety in pregnancy.

7.6.3 Pediatrics and Effect on Growth

The Viokace development program consisted of three clinical studies, each with an exclusively adult patient population with EPI secondary to CP. No clinical studies were done in pediatric patients, and in addition, no studies in patients with CF.

In contrast to the substantial body of literature to support dosing, safety and efficacy of the *enteric-coated PEP products* in pediatric patients with *EPI due to CF*, data from the literature are inadequate to support safety, efficacy or dosing for PEP products in pediatric patients for the treatment of EPI due to CP or EPI due to conditions other than CF. Because pediatric patients should be growing and are therefore likely to be at greater risk for poor weight gain and/or malnutrition than adults, to claim a pediatric indication for the treatment of EPI due to CP, demonstration of adequate growth and nutrition in pediatric patients is required.

The pivotal safety and efficacy studies of Viokace were performed in adult patients receiving concomitant PPI therapy; efficacy was not demonstrated in an earlier trial in adult patients receiving Viokace alone. Therefore, concomitant treatment with acid suppressive therapy appears to be necessary for this product to be effective. The safety and efficacy of chronic PPI use in children has not been established. Thus, safety and efficacy of Viokace use in children has not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

PEPs are not systemically absorbed and there is no potential for abuse, withdrawal, or rebound.

An important safety issue regarding PEP use and the potential for overdose is fibrosing colonopathy (FC). The etiology of FC has not been definitively established, but is thought to be associated with high dose lipase exposure, although some reports indicate the risk of FC is associated with the excipients.[8,9] In order to optimize therapy while minimizing the risk of FC, the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA recommends starting lipase doses according to age as described below.

The CFF recommends the following dose schedule for full meals:

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.[10]
- Children <4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Doses in excess of 2,500 USP lipase units/kg/meal should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to significantly improve a documented low coefficient of fat absorption.
- The recommended per meal dose should be halved when ingesting snacks.
- Doses in excess of 6,000 USP lipase units/kg/meal have been associated with fibrosing colonopathy.

Recommendations for snacks are half the dose taken at meals. Daily doses are not to exceed 10,000 U lipase/kg/day (3 meals, 2 snacks).

Although the CFF recommendations above list dosing for pediatric patients with CF, the safety and efficacy of Viokace use in children has not been established. Pediatric dosing guidelines should not be included in product labeling for Viokace.

7.7 Additional Submissions

A 120-Day Safety Update Report was submitted by the Applicant on March 5, 2010. Pertinent findings from the report are presented below:

The Applicant reported that all Viokace studies were completed with the safety information included in the original NDA submission on October 31, 2009.

[8] Borowitz, DS; Grand, RJ; Durie, PR; Consensus Committee (sup A). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatrics.127(5), Nov 1995, pp 681-684. (PMID: 7472816)
[9] Borowitz, DS; Grand, RJ; Durie, PR; Consensus Committee (sup A). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. J Pediatrics.127(5), Nov 1995, pp 681-684. (PMID: 7472816)
[10] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46. (PMID: 16782527)

Previous formulations of Viokace had been marketed in the US (under the trade name "Viokase". Adverse events obtained by the post-marketing surveillance of "Viokase" were mostly classified as gastrointestinal disorders with a few single AEs in other categories. Review of the post-marketing data did not provide any new relevant safety information.

- An estimate of the patient exposure to Viokace was calculated for the period of September 1, 2009 to January 31, 2010 from the number of product units distributed in the US. Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:
- The majority of patients taking Viokace for the treatment of exocrine pancreatic insufficiency are adult patients.
- The average weight of males and females adults is 60 kg.
- A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzymes supplementation has been recommended by the FDA in conjunction with the CFF in the Guidance for Industry "Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs", therefore, an average dose of 1,500 USP lipase units/kg/meal from Viokace supplementation was assumed for calculation purposes.
- Patients would be consuming a total of four meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the average dose administered is 360,000 USP lipase units/day. Table 34 below (electronically scanned and copied from Applicant) displays the US Unit Sales of Viokace and the patient exposure from September 1, 2009 to January 31, 2010.

Table 34: US Unit Sales and Patient Exposure from Sept. 1, 2009 - Jan. 31, 2010

	VIOKASE® 8	VIOKASE® 16
Number of tablets		(b) (4)
Number of lipase units		
Number of days of treatment	262,560	60,596
Number of years of treatment	719	166
Total number of patient treatment years	885	

Source: Applicant's Safety Update: page 7; Table 2

Thus, there were no new or additional safety findings reported in the 120-day Safety Update.

8 Postmarketing Experience

"Viokase" has been available on the U.S. market as a prescription drug since 1949. "Viokase" is also available on the Canadian market as a prescription drug. Few adverse events have been reported during that time, either in the literature or directly to the manufacturer or Applicant.

Please see Section 7.7 above for more information on the postmarketing experience of Viokace.

9 Appendices

9.1 Literature Review/References

Please see individual references noted throughout this review.

9.2 Labeling Recommendations

This NDA is recommended to receive a Complete Response action secondary to CMC issues; however, the labeling was negotiated with the Applicant during this review cycle. Please see the attached label for the most current version.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

9.4 Additional Tables

9.4.1 Table 1: Study VIO16EPI07-01: Proportion of Formed/Normal Stools (Intent-To-Treat Population)

Parameter Phase / Analysis Type	Statistic	Treatment Group Viokase®16 (N=30)	 Placebo (N=20)
Proportion of Formed/Normal Stools (%)			
Wash-Out Phase	n	30	20
	Mean	33.12	34.27
	SD	37.740	38.511
	Median	21.11	23.61
	Min., Max.	0.0, 100.0	0.0, 100.0
Treatment Phase / Observed Case	n	30	20
	Mean	45.86	37.23
	SD	33.269	37.906
	Median	50.00	25.40
	Min., Max.	0.0, 100.0	0.0, 100.0
	LSMean (SE)	45.6 (4.6)	34.3 (5.8)
	p-value [a]	0.1203	
Change from Wash-Out Phase to Treatment Phase / Observed Case	n	30	20
	Mean	12.74	2.96
	SD	32.036	27.757
	Median	9.17	0.00
	Min., Max.	-50.0, 81.8	-33.3, 100.0
Percent Change from Wash-Out Phase to Treatment Phase / Observed Case	n	17	13
	Mean	8.53	-9.91
	SD	65.602	68.792
	Median	-7.69	-12.50
	Min., Max.	-100.0, 157.1	-100.0, 175.0

[a] P-value from an ANCOVA model including treatment group and pooled site as fixed effects and Wash-Out Phase proportion of formed/normal stools as a covariate.
Notes:
1. LSMean= Least Squares Mean; SE= Standard Error.
2. Proportion of formed/normal stools is defined as: (Total number of formed/normal stools during the completed days of the inpatient period/Total number of stools during the completed days of the inpatient period) x 100%.
3. Since there are no missing Treatment Phase values, only the 'Observed Case' analysis type is diplayed.

Source: VIO16EPI107-01 Study Report (Page 84, Section 14, Table 14.2.4.1)

Best Available Copy

9.5 Additional Information

9.5.1 Patient 4617 Narrative

The above patient's medical history included chronic hepatopathia since 2009, CP since 2008, icterus mechanicus since 2008, diabetes mellitus since 2007, arterial hypertension (grade III) since 2005 and ischemic heart disease (NYHA type II) since 2005. Patient also suffered from obesity since an unknown date and had a tumor of Vater's papilla with choledocho-duodeno-anastomosis performed on an unknown date. Patient's surgical history included an aorto-coronary bypass in 2005, a cholecysto-duodeno-anastomosis in 2008 and a gastro-entero-anastomosis in 2008.From 25 April 2009 to 01 May 2009, the patient was on high-fat diet as required by the protocol (100g fat/day). On 24 May 2009, the patient started treatment with the study drug and restarted the high-fat diet. On (b) (6), the patient went to hospital for the inpatient period of the Treatment Phase. On 27 May 2009, the patient's state worsened (he

became yellow). On 28 May 2009, the inpatient Treatment Phase was completed and the high-fat diet required by the protocol stopped. The patient's hospitalization was then prolonged by the gastroenterologist because of icterus and vomiting. During hospitalization, diagnosis of gallstones, hydropic gallbladder and inflammatory pseudotumoral changes of the head of pancreas (with compression on the choledoc and pancreatic ducts), ascites and cystis renis, were made. Conservative symptomatic treatment led to clinical improvement.

On (b) (6) the patient was discharged with atrial natriuretic peptide as well as recommendations for diabetic diet and fat restriction. The patient was re-admitted to hospital on (b) (6) for suspicion of choledocolithiasis and pancreatic tumor. An ultrasound revealed lithiasis in the bile duct and tumoral process involving the head of the pancreas. Surgical treatment was required; a laparotomy showed a large inoperable malignant tumorous process on the head of the pancreas and ascites. Because the tumor was inoperable, only a palliative cholecystectomy was performed. The patient was discharged from hospital on (b) (6) upon his own request and died at home on (b) (6). The Investigator considered that the inoperable malignant tumor of the head of pancreas was a progression of the pre-existing CP. The patient's attending physician considered that the cause of death was overall weakness/fatigue and coma that were related to the tumor of the head of pancreas (disease progression). Axcan considered that the high fat diet (study procedure) may have played a role in the occurrence of cholelithiasis, choledocholithiasis and hydrops of gallbladder by stimulating the gallbladder leading to the migration of the preexisting calculi. All other reported events were considered to be part of chronic illness and/or represent outcomes of disease progression occurring in a patient with heavy medical and surgical history.

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

/s/

MARJORIE F DANNIS
11/10/2010

ANIL K RAJPAL
11/10/2010
I concur with Dr. Dannis.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 22542 Applicant: Axcam Pharma,US Stamp Date: Oct. 30, 2009

Drug Name: (pancrelipase, USP)- formerly known as Viokase **NDA/BLA Type: NDA**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?				No global TOC, but format allows substantive review to begin
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?				RPM to discuss with Sponsor
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	2.7.4
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			See Pancreatic Enzyme Products

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: S245.3.124 Indication: treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery				Guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Will need further discussion of draft labeling
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			See Pancreatic Enzyme Products Guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Further discussion needed here
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

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/

MARJORIE F DANNIS
12/23/2009

ANIL K RAJPAL
12/23/2009