Medical Officer's Review of Safety Update Report

NDA #:	22-222
Applicant:	Axcan Pharma US, Inc.
Product:	ULTRASE® MT / ULTRASE
Therapeutic Class:	Pancreatic Enzyme Product (PEP)
Indication:	Treatment of exocrine pancreatic insufficiency (EPI)
Date Submitted/Received:	November 5, 2009
PDUFA Date:	May 5, 2010
Date of Review:	March 16, 2010
Clinical Reviewer:	Ali Niak, M.D., Medical Officer, DGP
Through:	Anil Rajpal, M.D., Acting Team Leader, DGP

BACKGROUND

ULTRASE® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been available on the United States (US) market since November 1991. Axcan Pharma Inc. has been marketing ULTRASE® MT Capsules since August 1999 in the US. In addition, ULTRASE® is currently marketed in Canada, Argentina, Brazil and Chile.

SAFETY UPDATES

Two safety updates were submitted by the Applicant (August 4, 2009, and November 4, 2009).

The first Safety Update covered the period from November 1, 2008, to May 31, 2009, for post-marketing information, and from October 1, 2008 to May 31, 2009, for clinical study information.

The second Safety Update covered the period from June 1, 2009, through November 3, 2009 for post-marketing information, and from June 1, 2009, to November 3, 2009, for clinical study information.

Pertinent findings from both Safety Updates are presented below.

Completed Clinical Study Update

Study UMT20CF07-01 is a multicenter, open-label, Phase 3 trial designed to establish the efficacy and safety of ULTRASE® MT20 (enteric coated with HP-55, the formulation currently on the market) in cystic fibrosis children aged 7-11 years old, with presence of pancreatic insufficiency. A total of 8 patients were initially planned to be enrolled with the expectation that approximately 5 patients would complete the study. The initial protocol was submitted to IND 41,387 on May 7, 2007 (Serial 070). Subsequently, the protocol was amended to include clarifications and minor editorial changes (Protocol Amendment – Serial 075, dated June 22, 2007). No further changes were made to the amended protocol dated June 22, 2007.

This study was initiated on July 28, 2007, in the US. At study completion in March 2008, 9 patients were screened; 7 patients were included in the Intent-To-Treat (ITT) population, and 3 were included in the Per Protocol (PP) Population. The PP Population included patients for whom both inpatient periods (washout and treatment phases) were completed, all bowel movements were collected and no major protocol violations occurred. The database was locked on May 30, 2008, and the data was analyzed by (b) (4) The results obtained from the statistical analysis became available on June 20, 2008. The clinical study report for this study was completed and approved on March 2, 2009.

The demographics and status of patients at the end of study are provided in Table 1 below.

Table 1. Demographics and status of patients enrolled in study UMT20CF07-01.

Subject No.	Gender	Ethnicity	Age (years)	BMI	PATIENT STATUS
0201	Male	Caucasian	11.5	17.2	Study completed
0202	Male	Caucasian	11.5	18.5	Study completed
0301	Male	Caucasian	11.5	15.9	Study completed
0302	Male	Caucasian	10.9	14.4	Study completed
0303	Male	Caucasian	11.4	15.8	Discontinued
0401	Male	Caucasian	7.6	15.1	Discontinued
0402	Male	Caucasian	10.0	17.6	Study completed
0403	Male	African	11.1	18.6	Study completed
0404	Male	Caucasian	7.6	14.6	Study completed

(Table above is taken from Page 5 of the NDA 22-222 Safety Update dated December 9, 2008.)

No patient died or experienced serious adverse events during this clinical study. Two patients (#0303 and #0401) did not complete the study because of adverse events.

Patient #0303 developed sinusitis and was treated with antibiotics and patient #0401 developed a Streptococcal throat infection and was treated accordingly with antibiotics as well. The above two events do not appear to have been related to ULTRASE®.

Ongoing Clinical Study Update

Study UMT12CF08-01 is a multicenter, Phase IIIb open label study designed to establish the efficacy and safety of ULTRASE® MT12 in the control of steatorrhea in cystic fibrosis (CF) children with pancreatic insufficiency aged 2-6 years old. Approximately 50 patients will be enrolled in the study to obtain 40 completed patients. Initial drafts of the protocol were submitted to IND 41,387 on April 29, 2008 and November 11, 2008. Based on Agency feedback, the protocol was amended to include clarifications on the high fat diet, to better define "optimized dose" of lipase to be used, and to provide the objective criteria that would be used to determine this "optimized dose." This was done in order to not exceed the current Cystic Fibrosis Foundation guideline for maximum dosing to minimize the risk of fibrosing colonopathy. The protocol was formally submitted to IND 41,387 on March 24, 2009.

The enrolment of patients was started in April 2009 and was completed on September 25, 2009. Fifty-three patients were enrolled and as of October 30, 2009, 40 of these patients were completed.

ADVERSE EVENTS

Completed Clinical Study Update

Between 01-Nov-2008 and 31-May-2009, Axcan Pharma Inc. and its subsidiaries received 25 initial adverse event reports including a total of 46 adverse events. From these initial reports, 11 involved ULTRASE®, 12 involved VIOKASE® and 2 involved PANZYTRAT®. One initial adverse event report received during the reporting period was assessed as serious and involved VIOKASE®.

One 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 had been taking VIOKASE® for many years without any problem and experienced the above mentioned adverse events after taking one pill found in a VIOKASE® bottle with a different appearance which was later identified as 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.

The adverse events of all 3 products from November 1, 2008, to May 31, 2009, are summarized in Table 2.

Table 2. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from November 1, 2008, to May 31, 2009.

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Cardiac disorders				
Cardio-respiratory arrest	0	1	0	1
Gastrointestinal disorders				
Abdominal pain	0	2	0	2
Abdominal pain upper	1	1	1	3
Abnormal faeces	0	1	0	1
Diarrhoea	1	3	1	5
Dyspepsia	0	1	0	1
Faecal volume increased	1	0	0	1
Frequent bowel movements	1	0	0	1
Gastritis	0	1	0	1
Glossodynia	0	1	0	1
Groin pain	0	1	0	1
Lip swelling	0	1	0	1
Nausea	0	1	1	2
Oral discomfort	0	1	0	1
Steatorrhoea	1	0	0	1
Swollen tongue	0	1	0	1
Tongue ulceration	0	1	0	1
Vomiting	0	0	1	1
General disorders and administration site conditions				
Asthenia	0	1	0	1
Drug effect decreased	1	0	0	1
Drug ineffective	4	0	0	4
Feeling abnormal	0	1	0	1
Product commingling	0	1	0	1
Therapeutic response decreased	0	1	0	1

Coded with MedDRA dictionary

(Table above is taken from Page 8 of the Safety Update for NDA 22-222 dated August 4, 2009.)

Table 2 (Continued)

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Injury, poisoning and procedural complications				
Incorrect dose administered	0	1	0	1
Investigations				
Blood glucose increased	1	0	0	1
Blood sodium decreased	0	1	0	1
Blood sugar level fluctuation	0	1	0	1
Drug screen positive	0	1	0	1
Weight decreased	1	0	0	1
Metabolism and nutrition disorders				
Diabetes mellitus	1	0	0	1
Nervous system disorders				
Loss of consciousness	0	1	0	1
Respiratory, thoracic and mediastinal disorders				
Throat irritation	0	1	0	1
Skin and subcutaneous tissue disorders				
Rash macular	0	1	0	1
Urticaria	0	1	0	1

Coded with MedDRA dictionary

(The table above is taken from Page 9 of the NDA 22-222 Safety Update dated August 4, 2009.)

Table 2 presents the adverse events of all three products recorded in the database classified by body system (MedDRA standard organ system classification scheme (SOC)) during the period from November 1, 2008, to May 31, 2009.

For ULTRASE, the most frequently reported adverse event was drug ineffectiveness (4). The remaining adverse events were single occurrences. Please refer to Table 2.

Ongoing Clinical Study Update

Between June 1, 2009, and November 3, 2009, Axcan Pharma Inc. and its subsidiaries received 26 initial adverse event reports including a total of 45 adverse events. From these initial reports, 21 involved ULTRASE®, 4 involved VIOKASE®, and 1 involved PANZYTRAT®. Of the 26 initial adverse event reports received during the reporting period, 1 involving ULTRASE MT20 was assessed as serious and is described below.

One case of ischemic colitis (manifested as thickening and ulcers in descending colon) was reported in 71 year-old female patient who was prescribed ULTRASE MT20 (pancrelipase) for an unknown indication. The case was medically confirmed. The causal relationship between the medicinal product and the reported event is not assessable, due to the lack of information regarding the indication of use, medical history and concurrent conditions, concomitant medication and therapy dates. However, the reporting physician considered the event to be possibly related to ULTRASE MT20.

Table 3 presents the adverse events of all three products recorded in the database classified by body system (MedDRA standard organ system classification scheme (SOC)) during the period from June 1, 2009, to November 3, 2009.

Table 3. Adverse Events (Preferred Term) Recorded for Pancreatic Enzyme Preparations in the Axcan Pharma Safety Database Classified by System Organ Class from June 1, 2009 to November 3, 2009.

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Gastrointestinal disorders				
Abdominal discomfort	1	0	0	1
Abdominal distension	2	0	0	2
Abdominal pain	1	0	0	1
Abnormal faeces	2	0	0	2
Bowel movement irregularity	1	0	0	1
Colitis ischaemic	1	0	0	1
Diarrhoea	5	0	0	5
Dyspepsia	1	0	0	1
Flatulence	1	0	0	1
Frequent bowel movement	4	0	0	4
Gastrointestinal disorder	1	0	0	1
Gastrointestinal pain	1	1	0	2
Glossodynia	1	0	0	1
Malabsorption	2	0	0	2
Oral discomfort	1	0	0	1
Paraesthesia oral	1	0	0	1
Steatorrhoea	2	0	0	2
Vomiting	1	0	0	1
General disorders and administration site conditions				
Chest pain	1	0	0	1
Drug ineffective	2	1	0	3
Feeling abnormal	1	0	0	1
Malaise	0	1	0	1

(Table above is taken from Page 6 of the NDA 22-222 Safety Update dated November 4, 2009.)

Table 3 (continued)

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Total
Investigations				
Blood glucose fluctuation	1	0	0	1
Blood glucose increased	1	0	0	1
Blood pressure increased	0	1	0	1
Haemoglobin urine present	0	0	1	1
Metabolism and nutrition disorders				
Increased appetite	1	0	0	1
Musculoskeletal and connective tissue disorders				
Back pain	1	0	0	1
Joint swelling	0	1	0	1
Skin and subcutaneous tissue disorders				
Night sweats	0	1	0	1
Pruritus generalised	1	0	0	1
Total	38	6	1	45

Coded with MedDRA dictionary

(Table above is taken from Page 7 of the NDA 22-222 Safety Update dated November 4, 2009.)

For ULTRASE, the most frequently reported adverse events were diarrhea (5), frequent bowel movement (4), abdominal distention (2), abnormal feces (2), malabsorption (2), steatorrhea (2), and drug ineffectiveness (2). The remaining adverse events were single occurrences. Please refer to Table 3.

The above adverse events may have been related to ULTRASE, to a class effect, to the underlying condition of exocrine pancreatic insufficiency. Contamination of the drug substance with *Bacillus cereus* and/or enterotoxin cannot be ruled out as a possible etiology for the adverse events reported; contamination of the drug substance was raised as a concern on inspection of the drug substance manufacturing facility ((b) (4); DMF (b) (4). (See also Consult Review from Division of Anti-infective and Ophthalmology Products [DAIOP] by Benjamin Lorenz dated June 5, 2009 and Health Hazard Evaluation by Anil Rajpal dated February 23, 2010.)

CUMULATIVE SALES AND EXPOSURE

An estimate of the patient exposure to ULTRASE Capsules was calculated for the periods of October 1, 2008, to May 31, 2009, and June 1, 2009, to November 3, 2009, from the number of product units distributed worldwide.

Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1. The majority of patients taking ULTRASE Capsules for the correction of steatorrhea are cystic fibrosis patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years. 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally are between the 20th and 40th percentile for weight.

2. Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts (Set 1) for males and females between the ages of 2-20 years.

   (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201).

   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. Therefore, an average dose of 1,500 USP lipase units/kg/meal from ULTRASE Capsule supplementation was assumed for calculation purposes.

3. It was assumed that patients would be consuming a total of 4 meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for ULTRASE MT12, ULTRASE MT18, and ULTRASE MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. Table 4 lists unit sales information for ULTRASE MT Capsules worldwide as well as the calculation of patient-exposure-years from October 1, 2008, to May 31, 2009. Table 5 lists unit sales information for ULTRASE MT Capsules worldwide as well as the calculation of patient-exposure-years from June 1, 2009, to November 3, 2009.

Table 4. Unit Sales of ULTRASE® MT Capsules (October 1, 2008, to May 31, 2009) and Patient Exposure

	MT12 Btl 100 ct	MT18 Btl 100 ct	MT20 Btl 100 ct	MT20 Btl 500 ct
Total number of bottles	(b) (4)			
Total number of capsules				
Number of days of treatment	290,068	357,688	916,606	943,768
Number of years of treatment	795	980	2,511	2,586
Total number of patient treatment years	6,872			

(Table above is taken from Page 11 of the NDA 22-222 Safety Update dated August 4, 2009.)

The estimate of the patient exposure during the 9-month reported period is 6,872 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day.

Table 5. Unit Sales of ULTRASE® MT Capsules (June 1, 2009, to November 3, 2009) and Patient Exposure

	MT12 Btl 100 ct	MT18 Btl 100 ct	MT20 Btl 100 ct	MT20 Btl 500 ct
Total number of bottles	(b) (4)			
Total number of capsules				
Number of days of treatment	274,665	196,726	601,387	569,894
Number of years of treatment	753	539	1,648	1,561
Total number of patient treatment years	4,501			

(Table above is taken from Page 8 of the NDA 22-222 Safety Update dated November 4, 2009.)

The estimate of the patient exposure during the 5-month period is 4,501 patient-treatment-years assuming an average daily dose of 1,500 USP lipase units/kg/meal and a total of 3 meals and 2 snacks per day.

LITERATURE UPDATE

No new relevant safety information pertaining to ULTRASE or other formulations of pancreatic enzyme preparations was noted in a search of medical literature for the periods from November 1, 2008, to May 31, 2009, as noted in the Safety Update Report dated August 4, 2009.

In the Safety Update Report dated November 4, 2009, seven articles were cited and discussed. These are summarized below:

- In a study on patients with diarrhea-predominant irritable bowel syndrome (D-IBS), Leeds et al.[1] detected pancreatic exocrine insufficiency in 6.1% of patients who fulfilled the Rome II criteria for D-IBS. The author suggested that pancreatic enzyme therapy might reduce diarrhea and abdominal pain in these patients, and that exocrine pancreatic insufficiency should be considered in patients with D-IBS. This reviewer believes that further studies are required to support or refute these novel observations.

[1] Leeds JS, Hopper AD, Sidhu R, Simmonette A, Azadbakht N, Hoggard N, Morley S and Sanders DS. Some Patients with Irritable Bowel Syndrome may have Exocrine Pancreatic Insufficiency. Clinical Gastroenterol and Hepatol. (2009). doi: 10.1016/j.cgh.2009.09.032.

- Wooldridge et al.[2] described the results of two studies of Zenpep for the treatment of cystic fibrosis (CF) patients with exocrine pancreatic insufficiency (EPI). It should be noted that Zenpep was recently approved (August 27, 2009) under NDA 22-210.
- In a meta-analysis by Waljee et al.[3], the efficacy and safety of pancreatic enzyme supplementation in chronic pancreatitis patients with steatorrhea is discussed. The author concludes that published trials show that: (1) enzyme supplementation improves CFA compared to placebo (although fat malabsorption is still present after enzyme supplementation); (2) stool frequency and consistency improve with supplementation (although no data on weight gain/loss are provided and minimal data on adverse events are available); and (3) Direct comparisons about the efficacy of different agents cannot be performed and insufficient data are available to determine optimal pancreatic enzyme supplementation (because important differences in patient population, pancreatic enzyme dosage and quantification of steatorrhea were present across trials and no head-to-head trials of different enzyme supplements have been performed).
- Trapnell et al.[4] described the results of a study of Creon for the treatment of CF patients with EPI. It should be noted that Creon was recently approved (April 30, 2009) under NDA 20-725.
- Munck et al.[5] described results of a cross-over study conducted in France of two formulations of "Creon"; it should be noted that the formulation and dosage strengths of "Creon" described in the article may not be the same as the currently approved Creon available in the US. One formulation was "Creon for children" (a preparation provided as a bulk of minimicrospheres in a glass container, with a small spoon containing 5000 lipase units per scoop); the other formulation was a capsule of "Creon 10,000." The author concluded that the proportion of patients with adverse experiences was comparable between groups. Three patients in the "Creon for Children" group experienced related treatment emergent adverse events (abdominal pain, constipation, vomiting) and one patient in the "Creon 10,000" group (severe diaper dermatitis). Two serious adverse events (SAEs) were observed; both considered unrelated to study medication: a bronchial obstruction and acute otitis during "Creon 10,000" treatment, and *Pseudomonas aeruginosa* colonization while receiving "Creon for Children". A toddler was prematurely withdrawn after six days of "Creon for Children;" he experienced moderate abdominal pain and diarrhea

[2] Wooldridge JL, Heubi JE, Amaro-Galvez R, Boas SR, Blake KV, Nasr SZ, Chatfield B, McColley SA, Woo MS, Hardy KA, Kravitz RM, Straforini C, Anelli M and Lee C. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency, J Cyst Fibros (2009). doi:10.1016/j.jcf.2009.07.006

[3] Waljee AK, Dimagno MJ, Wu BU, Schoenfeld PS and Conwell DL. Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. Aliment Pharmacol Ther (2009) 29 (3): 235–246.

[4] Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K and Caras S. Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis, J Cyst Fibros (2009), doi:10.1016/j.jcf.2009.08.008.

[5] Munck A., Duhamel J.F., Lamireau T., Le Luyer B., Le Tallec C, Bellon G, Roussey M, Foucaud P, Giniès JL, Houzel A, Marguet C, Guillot M, David V, Kapel N, Dyard F and Henniges F. Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cyst Fibros (2009) 8(1) : 14–18.

(possibly related to study medication) and vomiting (unlikely related to study medication).

- Colombo et al.[6] describes a study of twelve CF patients younger than 24 months with EPI (CFA less than 70%) treated with a formulation of "Creon for children" for 8 weeks. The author concluded that the treatment was well tolerated and significantly decreased fat malabsorption. None of the treatment emergent adverse events (TEAEs) were serious, led to death, or required discontinuation of the treatment or study. Adverse events reported for more than 2 patients were fever (4 patients, 33%) and cough (3 patients, 25%). The only treatment-related TEAE was constipation, reported for 2 patients (16.7%).
- In a meta-analysis, Taylor et al.[7] concluded that pancreatic enzyme supplements appear to improve fat malabsorption; no specific branded product or specific delivery system is superior for treatment of fat malabsorption in patients with EPI.

This reviewer concludes that there were no new significant safety findings pertaining to ULTRASE or other formulations of pancreatic enzyme preparations based on the above literature review.

SUMMARY/CONCLUSION

The limited safety information submitted in the Safety Update Report covering the periods from October 1, 2008, to May 31, 2009, and from June 1, 2009, to November 3, 2009, appears to be consistent with the known adverse event profile of PEPs. The total U.S. sales of ULTRASE capsules during the two reporting periods (October 1, 2008, to May 31, 2009, and June 1, 2009, to November 3, 2009) were (b) (4) capsules, respectively. Patient exposure to ULTRASE was estimated to be between 6,872 (October 1, 2008, to May 31, 2009) and 4,501 (June 1, 2009, to November 3, 2009) "patient treatment years".

[6] Colombo C, Fredella C, Russo MC, Faelli N, Motta V, Valmarana L, Longo L and D'Orazio C. Efficacy and Tolerability of Creon for Children in Infants and Toddlers With Pancreatic Exocrine Insufficiency Caused by Cystic Fibrosis. An Open-Label, Single-Arm, Multicenter Study. Pancreas (August 2009) 38(6): 693-699.

[7] Taylor JR, Gardner TB, Waljee AK, Dimagno MJ and Schoenfeld PS. Systematic review: efficacy and safety of pancreatic enzyme supplements for exocrine pancreatic insufficiency. Aliment Pharmacol Ther. (2009) doi: 10.1111/j.1365-2036.2009.04157.x

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

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/s/

ALI NIAK
03/18/2010

ANIL K RAJPAL
03/18/2010
I concur with Dr. Niak.