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:	March 9, 2010
PDUFA Date:	May 5, 2010
Date of Review:	April 30, 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

A Safety Update was submitted by the Sponsor on March 9, 2010. The Safety Update covered the period from November 1, 2009, to January 31, 2010, for post-marketing information, and from November 1, 2009, to January 31, 2010, for clinical study information. Pertinent findings from the Safety Update 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 UMT20CF08-01 is a multicenter, open-label, Phase IIIb trial designed to establish the efficacy and safety of ULTRASE® MT12 (enteric coated with HP-55, the formulation currently on the market) in the control to steatorrhea in cystic fibrosis children with pancreatic insufficiency. A total of 54 patients between 2 to 6 years of age enrolled in the study, of which, 5 of them failed the screening procedures and 4 were withdrawn before completing the study. In total, 45 patients completed the subject. The initial protocol was submitted to IND 41,387 on November 11, 2008 (Serial 086). Subsequently, the protocol was amended to include clarifications on the high fat diet, to better define the "optimized dose" of lipase to be used, to provide an objective criteria that will be used to determine this 'optimized dose' in order to not exceed the current Cystic Fibrosis Foundation guideline for maximum dosing to minimize the risk of fibrosing colonopathy (2500 Units of lipase/kg of body weight/meal or snack), and to include minor editorial changes (Protocol Amendment – Serial 087 dated February 28, 2009).

The enrolment of patients started on April 29, 2009, and was completed on September 25, 2009. The last subject completed the study on November 4, 2009. The database was closed on January 12, 2010. The clinical study report is under preparation.

ADVERSE EVENTS

Completed Clinical Study Update

Between November 1, 2009, and January 31, 2010, Axcan Pharma Inc. and its subsidiaries received 16 initial and one follow-up adverse event reports; additionally, a total of 27 adverse events were also reported. From these reports, 10 involved ULTRASE®, 5 involved VIOKASE®, one involved PANZYTRAT® and one involved pancreatic enzymes unspecified. No serious adverse event was received during the reporting period.

The table below 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, 2009, to January 31, 2010.

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, 2009, to January 31, 2010.

SOC / Preferred Term	ULTRASE®	VIOKASE®	PANZYTRAT®	Pancreatic enzymes unspecified	Total
Gastrointestinal disorders					
Abdominal discomfort	0	1	0	0	1
Abdominal distension	1	1	0	0	2
Abdominal pain	0	1	0	0	1
Abdominal pain upper	2	0	0	0	2
Abnormal faeces	1	0	0	0	1
Change in bowel habit	1	0	0	0	1
Constipation	1	0	0	1	2
Diarrhoea	3	1	1	0	5
Dyspepsia	1	0	0	0	1
Flatulence	1	0	0	0	1
Nausea	0	2	0	0	2
General disorders and administration site conditions					
Condition aggravated	1	1	0	0	2
Drug effect decreased	0	1	0	0	1
Medication residue	0	1	0	0	1
Withdrawal syndrome	1	0	0	0	1
Injury, poisoning and procedural complications					
Expired drug administered	0	1	0	0	1
Musculoskeletal and connective tissue disorders					
Arthralgia	1	0	0	0	1
Skin and subcutaneous tissue disorders					
Rash	1	0	0	0	1
Total	**15**	**10**	**1**	**1**	**27**

Coded with MedDRA dictionary

(Table above is taken from Page 6 of the Safety Update for NDA 22-222 dated March 9, 2010.)

For ULTRASE, the most frequently reported adverse event was diarrhea (3). The next most frequently reported adverse event was upper abdominal pain (2). The remaining adverse events were single occurrences. Please refer to the above table.

The above adverse events may have been related to ULTRASE, to a class effect, or 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) (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.) The limited adverse event data

presented above are consistent with the known adverse event profile of pancreatic enzyme products (PEPs).

CUMULATIVE SALES AND EXPOSURE

An estimate of the patient exposure to ULTRASE® MT Capsules was calculated for the period of November 1, 2009, to January 31, 2010 from the number of product units distributed in the United States.

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 supple-mentation 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 supple-mentation 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. The table below lists unit sales information for ULTRASE MT Capsules in the United States as well as the calculation of patient-exposure-years from November 1, 2009, to January 31, 2010.

Table 3. Unit Sales of ULTRASE® MT Capsules (November 1, 2009, to January 31, 2010) 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	188,712	137,338	467,218	434,007
Number of years of treatment	517	376	1,280	1,189
Total number of patient-treatment-years	3,362			

(Table above is taken from Page 8 of the NDA 22-222 Safety Update dated March 9, 2010.)

The estimate of the patient exposure during the 3-month reported period is 3,362 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, 2009, to January 31, 2010, as noted in the Safety Update Report dated March 9, 2010.

SUMMARY/CONCLUSION

The limited safety information submitted in the Safety Update Report covering the period from November 1, 2009, to January 31, 2010, appears to be consistent with the known adverse event profile of PEPs. The total U.S. sales of ULTRASE capsules during the reporting period were (b) (4) capsules. Patient exposure to ULTRASE was estimated to be 3,362 "patient treatment years".

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
04/30/2010

ANIL K RAJPAL
04/30/2010
I concur with Dr. Niak.