Clinical Pharmacology Review

NDA:	22-222
Brand Name:	Ultrase
Generic Name:	Pancrelipase
Dosage form and Strength:	Delayed release capsules, 13,800 (MT12), 20,700 (MT18), and 23,000 Units (MT20)
Route of administration:	Oral
Indication:	Treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions
Sponsor:	Axcan Pharma
Type of submission:	Resubmission
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Submission date:	04/07/09, and 05/25/09
PDUFA Goal date:	10/07/09
Reviewer:	Lanyan (Lucy) Fang, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

NDA 22-222 for Ultrase MT12, MT18, MT20 delayed release capsules was reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III) in the first review cycle and the review was completed on 2/28/09.

During this review cycle, concerns were raised towards the *in vitro* food stability studies and the below information request was sent to the sponsor.

Information Request for Ultrase (NDA 22-222)

This is regarding the *in vitro* stability study. Based on the product description, the enteric-coating of minitablets in ULTRASE MT Capsules is designed to dissolve at PH $\geq$ 5.5 which allows delivery of the enzymes to the duodenum. However, it was shown in the *in vitro* stability study that the minitablets were stable in the pudding chocolate ($\approx$ PH 6.4) with mean remaining enzymatic activity of 101% and 95% after incubation with pudding for 30 and 60 minutes, respectively. This raises concern about the validity of the *in vitro* stability study. Please explain this observation and provide the data from the control

samples in the same study (i.e., minitablets subject to the same conditions but without being mixed with Pudding).

Response from Sponsor:

The enteric-coating polymer (HP55) is designed to dissolve at pH ≥ 5.5.

The experiment in pudding at a pH of approximately 6.4 was conducted with the understanding that this environment would potentially challenge the integrity of the film coating. However, when compared to dissolution testing and/or the physiological environment in which the mini-tablets dissolve, the following considerations must be taken into account:

- The dissolution test was conducted at room temperature. Based on the Arrhenius equation, which relates the temperature dependence on chemical reaction rates, a 2-3 fold decrease in reaction rates is predicted for every 100C decrease in temperature. This alone would slow down the ionization of the polymer and its solubilization when compared to the dissolution test temperature of 37°C;
- The pudding is a relatively viscous medium where molecular diffusion of the aqueous phase is reduced when compared to a buffered solution;
- Puddings are formulated with cellulosic polymers that capture a significant amount of water reducing the amount of free unbound water available for the enteric polymer ionization and dissolution; and
- Although each mini-tablet was in contact with food, there was no mixing during the test. In the absence of mixing, an acidic stagnant diffusion layer would exist around each mini tablet reducing the dissolution rate of the enteric polymer.

The points listed above explain the integrity of the mini-tablet enteric coating for up to 60 minutes in the pudding experiment. The film coating capacity to protect the enzymes from the acid media of the dissolution test was demonstrated by the 2-stage dissolution results (second stage at pH 6.0) presented in the report.

Before the product was mixed with the pudding, the lot used for this experiment had a functional enteric coating, i.e. satisfactory acid resistance and dissolution in the buffer phase, as demonstrated by the release Certificate of Analysis that reports a (b) (4) of dissolution following the 2-stage dissolution test (second stage at pH 6.0).

Finally, the validity of the lipase assay used in the dissolution test was confirmed by the calibration curve R2 greater than (b) (4) and by running a second sample of standard preparation weighed separately that was within (b) (4) when back calculated on the calibration curve as indicated in method (b) (4)

Reviewer's comment:

The sponsor confirmed that the minitablets were indeed mixed with the food matrix before the incubation although there was no mixing during the incubation. Overall, the sponsor's response is considered acceptable. However, in order to maximize the stability

of pancreatic enzymes, we recommend specific language in the label for mixing with food.

1) The Ultrase minitablets can only be mixed with acidic food (PH<5.5);
2) Mixing temperature should be room temperature;
3) The mixing process should be short (seconds) and the medicine should be taken right after the mixing.

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/s/

LANYAN FANG
09/08/2009

SUE CHIH H LEE
09/08/2009
The NDA is acceptable from a clinical pharmacology perspective provided that a mutual agreement on labeling language can be reached between the sponsor and Agency.