Clinical Pharmacology Review

NDA:	20-725
Brand Name:	Creon
Generic Name:	Pancrelipase Enzyme
Dosage form and Strength:	Delayed release capsules, 6,000, 12,000, and 24,000 Units
Route of administration:	Oral
Indication:	Adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency
Sponsor:	Solvay Pharmaceuticals
Type of submission:	Responses to Approvable Letter
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCPB Division:	DCP III
Priority:	6 months
Submission date:	06/19/08, 09/17/08
PDUFA Goal date:	12/19/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Background:

Creon (pancrelipase) delayed release (DR) capsule and several other pancreatic enzyme products are currently on the market without FDA approval. Creon is a pancreatic enzyme supplement of porcine origin. NDA 20-725 for Creon DR capsules was initially submitted on 07/31/97 by Solvay, but the NDA was suspended and then revoked on 04/09/03 for review. Creon was deemed not approvable on 10/09/03 mainly due to CMC (chemistry, manufacturing, and controls) deficiencies.

Sponsor undertook reformulation of their Creon product. However, the clinical trials had been completed previously using the original formulation (same as that currently on the market). As agreed upon between the Agency and the sponsor, an *in vivo* intubation bioavailability study, comparative dissolution data, and comparative analytical characterization data were used to link the to-be-marketed (TBM) formulation to the formulation used in clinical trials.

Included in the 11/17/06 resubmission was an *in vivo* intubation bioavailability study (protocol No. S245.2.003) plus comparative dissolution and analytical characterization

data. An *in vitro* stability study on Creon content when mixed with acidic foods was also submitted. No new clinical trials were conducted for this resubmission.

The results of the *in vivo* intubation study were reviewed by the Office of Clinical Pharmacology (OCP). It was concluded by OCP that the comparability between TBM formulation and the clinically tested formulation has not been demonstrated. The DSI audit report (dated 06/08/07) for the study and analytical sites of the *in vivo* intubation study (No. S245.2.003) also raised several incompliance issues. The resubmission was deemed approvable in the 08/16/07 letter. The sponsor was informed that a new clinical trial using the TBM formulation of Creon would be needed and several CMC deficiencies needed to be addressed.

The results of *in vitro* stability study on Creon content when mixed with acidic foods were also found inadequate. The use of pellets (Creon capsule content) in a bag of polypropylene cloth does not reflect the realistic contact of individual pellets with food. Furthermore, only one bag per each of 6 food types was performed which did not provide statistically meaningful data (i.e., mean ± standard deviation, SD) per each food type. Thus, the original *in vitro* stability study is not robust enough to produce adequate results to support the claim of alternative mode of administration.

Upon request for a new *in vitro* stability study using the Agency's proposed study design, the new study results were submitted on 09/17/08 for a second cycle review.

Synopsis:

The new *in vitro* stability study using the Agency's proposed study design was submitted on 09/17/08 and therefore it is reviewed here. Please see Attachment 1 for the study procedures and results for details.

The Creon content was weighed carefully and transferred into a beaker containing the amount of food (approximately 10g) corresponding to a single application. After mixing thoroughly, the incubation was performed at 25°C for 30 or 60 minutes respectively in a thermostated water-bath. There were 6 food types tested. Per each food type and per each time point, 30 and 60 min, 5 beakers were obtained. The content of each beaker was rinsed and transferred with the aid of a sufficient amount of simulated gastric fluid onto a sieve (710 μm).

The residual pellets collected were performed according to dissolution test procedures. The lipase activity was determined according to USP method and the recovery was compared with the actual activity of Creon capsule. The actual activity of Creon capsule was determined independently from an aliquot obtained from mixing of 20 capsules. The actual lipase activity was (b) (4) USP-u/cps with an average fill weight of (b) (4) mg. The % recovery of lipase from the *in vitro* study is shown below.

Table 1. The Recovery of Lipase Activity from *In Vitro* Stability Study

Type of Food	pH value	Recovery (n=5) Mean ± SD	
		30 min	60 min
Apple Sauce (Beech Nut)	3.6	90.2 ± 2.3	89.2 ± 1.7
Apple Sauce (Gerber Products Company)	3.6	90.8 ± 1.7	88.2 ± 3.4
Chiquita Bananas (Beech-Nut)	4.2	85.3 ± 3.1	85.9 ± 1.4
Bananas (Gerber Products Company)	4.2	86.6 ± 2.3	86.3 ± 1.6
Tender Sweet Carrots (Beech-Nut)	4.9	84.7 ± 2.4	85.9 ± 1.9
Carrots (Gerber Products Company)	5.1	85.8 ± 0.7	82.1 ± 2.3

The sponsor reported that the above dissolution data all met the proposed dissolution specification, NLT (b) (4) (Q) in 30 min.

Reviewer's Comments:
It appears that the 60-min results were similar to those observed at 30 minutes for most of the foods tested, indicating that no more lipase was released and degraded from the enteric coated pellets after 30 min. The % recovery of lipase, however, decreased as pH of the food was greater than 4.0. The label should be modified accordingly to allow certain type of acidic food for mixing with Creon capsule contents. It should be emphasized that as stated in the proposed label, the Creon content after mixing with food should be swallowed immediately.

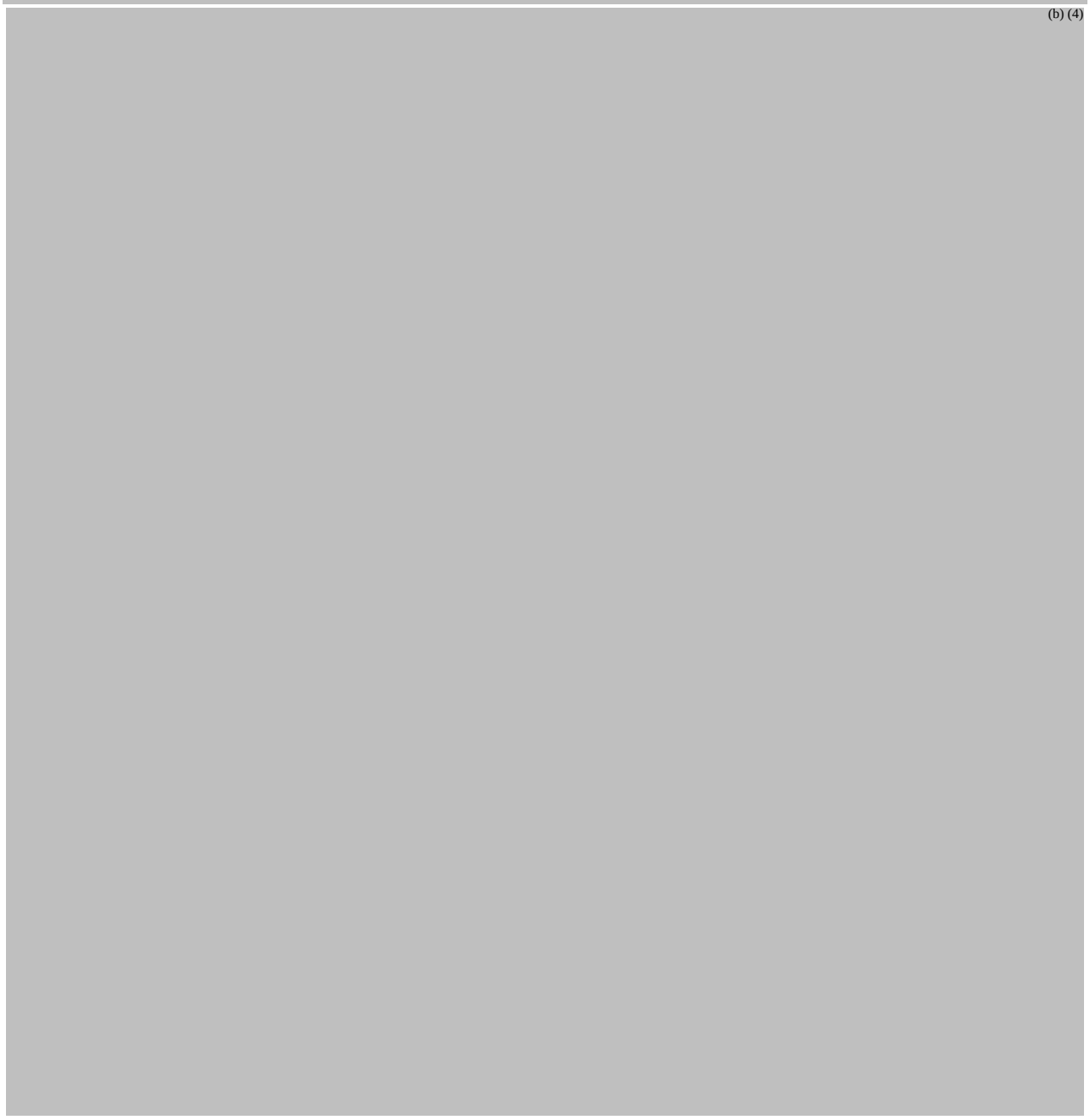
Recommendations:
The *in vitro* stability study on Creon content when mixed with food submitted on 09/17/08 has been reviewed by Office of Clinical Pharmacology (OCP). From OCP standpoint, the results of the *in vitro* stability study indicate that not all the foods tested may be used for mixing with Creon capsule contents and this will be reflected in the label. The following labeling comments need to be conveyed to the sponsor.

Labeling Comments: (Need to be sent to the sponsor)

The sponsor's proposed labeling (May 2008 version) needs revision as follows: (blue and underlined for addition and ~~red and strikethrough~~ for deletion by the Agency).

(b) (4)


(b) (4)


(b) (4)

(b) (4)

4. Subsection **12.3 Pharmacokinetics** should be changed to Subsection 12.2.

11/10/08
Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 11/10/08

NDA 20-725 for
Creon DR (Pancrelipase) Capsules

Attachment 1

Sponsor's Proposed Labeling
(May, 2008 Version)

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NDA 20-725 for
Creon (Pancrelipase) DR Capsules

Attachment 2

In Vitro Stability Study of Creon Content When Mixed with Food

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/s/

Tien-Mien Chen
11/10/2008 05:56:06 PM
BIOPHARMACEUTICS

Sue Chih Lee
11/10/2008 05:59:06 PM
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