DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH Deputy Director for Safety DGIEP/ODE III CDER/FDA
Subject	Signatory Summary Review
NDA/Supplement #	NDA 020725/S011
Applicant Name	Abbott Pharmaceuticals, Inc.
Date of Submission	12/10/2010
PDUFA Goal Date	6/10/2010
Proprietary Name / Established (USAN) Name	Creon (pancrelipase)
Dosage Forms / Strength	Delayed-Release Capsules, (3,000 lipase/9,500 protease/15,000 amylase)
Proposed Indication(s)	Pancreatic insufficiency due to cystic fibrosis and other conditions
Action/Recommended Action:	*Approval*

DIVISION RECOMMENDATION:
I concur with the CDTL and the review team regarding their evaluation of this new dosage strength. We recommend the approval of Creon (pancrelipase) Delayed-Release Capsules, 3,000 lipase/9,500 protease/15,000 amylase USP units with agreed upon labeling changes.

I. Regulatory History:

This "Prior Approval" supplemental new drug application provides for an additional lower dosage strength of Creon. There is no change in the approved indication: "treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions".

The sponsor submitted this supplement on December 10, 2010. During the review cycle a major amendment was received on 3/7/2011, which resulted in an extension of the review clock as stated in our letter dated 4/8/2011. The PDUFA goal date for this supplement is 6/10/2010.

This supplement was submitted in response to PREA Requirement: PMR #751-1:

> "Deferred requirement for development of an age appropriate formulation for Creon (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding".

The issues of most importance to this review are the capsule and container closure changes, process validation and microbiological content. These are reviewed in detail in the Chemistry Reviews. The most significant challenge in manufacture of this smaller dosing form was to provide conditions which would maintain the activity of the enzymes and prevent degradation under storage and use conditions. According to the chemistry and manufacturing review the sponsor has provided evidence that they have done so with the manufacture of this new dosage form.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. DMEPA:

The DMEPA review team pointed to an issue regarding wording in the package insert between the recommended dose and the proposed 3,000 lipase unit product. They felt there was potential for confusion and medication error in dosing. This was discussed at a review team meeting on 5/31/2011 and labeling modifications were agreed upon by the review team.

The major points and recommendations are captured in the DMEPA review and agreed upon.

• "The 3,000 unit dose went before the Pediatric Review Committee (PeRC) which confirmed it fulfilled the PREA requirement"
• "ONDQA stated that doses lower than 3,000 units (e.g., 2,000 units) were not achievable (b) (4)
• "The clinical review team stated that there is no clinical difference between 1, 1,000 unit increments of lipase (e.g., a dose of 2,000 units of lipase versus 3,000 units of lipase)"

The recommended labeling changes were sent to Abbott who agreed with the changes. See labeling section below.

B. DRISK:

The DRISK review team suggested minor editorial changes to the Medication Guide.

C. Chemistry and Manufacturing:

As noted in the review, the capsule shell is different in this dosage compared to those already approved and marketed in size and composition. The 3,000 lipase unit capsule is made of hydroxypropylmethylcellulose (HPMC) and not the (b) (4) gelatin capsule shells used in the already approved formulations. The sponsor

utilizes the same enteric coated beads in this dosage form as in the already approved formulations.

Because the new dosage form is intended to deliver the enteric coated beads directly to the patient by opening the capsule placing them directly on the tongue or on food, the sponsor used a (b) (4) capsule for ease of handling. This capsule is not completely full. Stability of the enzymes was tested under accelerated conditions to evaluate the stability of the enteric-coated beads in both the HPMC and (b) (4) gelatin capsules. The newer HPMC capsules "conferred a higher resistance to moisture and preserved the lipase activity and dissolution, which are critical quality attributes".

In order to further ensure protection form moisture and preserve the activity of the enzymes, Abbott proposed to use a new container-closure system. This container has a cap which contains a desiccant insert. In use stability studies were necessary to determine if the desiccant system would ensure activity. This was discussed with the sponsor on June 6th. They provided results from such a study. The CDTL review of these results stated the following:

"The study was conducted on containers stored at 25°C and 60% RH. Bottles were open daily, multiple times and capsules withdrawn at specified days. Although the sponsor estimated that the product would be fully consumed by patients within two weeks (70 capsules total, five capsules a days would account for a two weeks supply), the in-use stability study was conducted for 4 weeks. The sponsor conducted extensive analysis of the product using the release testing protocol for drug product. The assay results are all within specification and do not show any significant negative trend, (b) (4) at week two and is (b) (4) by week four (from (b) (4) % at week 0 to (b) (4) at week (b) (4) at week four, with 5% acceptance limit). Taking into consideration that all other results do not show significant trends and that the product will very likely be consumed within two weeks, the in-use stability study demonstrated an acceptable stability profile for the product, stored in the original container, under conditions of use.

The process validation protocol was submitted and the following comments were summarized by the CDTL in this regard:

"The initial submission did not contain any information on validation of process used to fill capsule at 3,000 U USP. In a teleconference with the sponsor, the Division of Therapeutic Proteins agreed that submission of a validation protocol would be sufficient. The sponsor provided a process validation protocol that describes the in-process testing, control parameters and action limits/acceptance criteria for the tests. The sponsor will conduct enhanced testing during the validation to ensure that the process is adequately controlled. The combination of proposed in-process and release tests, coupled with the enhanced testing during validation, is sufficient to ensure that the 3000 U USP lipase strength capsule meet the expected quality standard."

The quality microbiology reviewer recommended approval. Below find the reviewer's summary of an issue and its resolution through discussion and agreement with the sponsor as:

"In regard to issue number 2, the sponsor submitted a proposal where microbial testing was incorporated as in-process control at multiple process steps and provided alert and action limits. The proposed plan was adequate. (b) (4) On June 2, 2011 FDA communicated to Abbott that batches of materials with microbial testing at the action limit should be rejected, and that alert limit investigations should include an evaluation of the manufacturing process operations. Abbott agreed with the conclusion and submitted a revised plan, reviewed and approved by OPS Micro. The review issues were satisfactorily resolved."

Quality biopharmaceutical reviewer concluded that "the Comparative dissolution data and bio-waiver request were submitted in response to an agency information request sent in the context of S008. The comparative dissolution data supported the bio-waiver request, and the Biopharmaceutics group recommends granting the bio-waiver".

"I concur with the conclusions reached by the chemistry reviewers. There are no outstanding issues."

D. Pre-Clinical Phamacology/Toxicology: Not applicable
E. Biopharmaceutics: Not applicable
F. Clinical/Statistical: Not applicable
F. PREA Requirement: PMR #751-1

Deferred requirement for development of an age appropriate formulation for Creon (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by December 31, 2010.

At the PERC committee meeting held on 3/2/2011, it was determined that this PMR was considered FUFILLED. (b) (4) The 3,000 unit capsule would fulfill the need for a dose which falls in the mid range of the 2,000 and 4,000 unit approximate doses recommended by the CF guidelines.

III. Labeling Recommendations:

The following were recommendations sent to Abbott in response to concerns that DMEPA raised during labeling review. The sponsor agreed to these.

A. Highlights of Prescribing Dosage Section - Infants (up to 12 months)

Revise first bullet to read as follows: 'Infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding'.

B. Full Prescribing Information (Administration Section 2.1)
Change dose listed for infants up to 12 months of age from (b) (4) to '3,000 lipase units per 120 mL of formula or prior to breast-feeding'.

C. Full Prescribing Information (Dosage Section 2.2)

1. Paragraph 1 should be revised as follows: 'Creon should be administered in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences (also known as Conferences) provided in the following paragraphs, except for infants. Although the Conferences recommend doses of 2,000 to 4,000 lipase units in infants up to 12 months, Creon is available in only a 3,000 lipase unit capsule. Therefore, the recommended dose of Creon in infants up to 12 months is 3,000 lipase units'.

2. Dosage - Infants (up to 12 months): Revise the usual dosage to read as follows: 'Creon is only available in the strength of 3,000 USP units of lipase thus infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Do not mix Creon capsule contents directly into formula or breast milk prior to administration [*see Administration (2.1)]*'.

Additional comments were sent regarding carton and container labeling see below.
1. To conform to 21 CFR 201.100(b)(7), add a statement on the carton and directed to the pharmacist specifying that the 3000 USP units is a unit of use. The product must be dispensed in the original container to preserve product identity, strength, quality and purity based on stability data. Recommend the following statement, "Pharmacist: Dispense in original container with enclosed Medication Guide to each patient." The statement should be prominent.

Please separate the 'original container' statement from the 'Medication Guide' statement as follows:

Pharmacist: Dispense in original container

Dispense enclosed Medication Guide to each patient

2. To conform to 21 CFR 201.57(c)(17)(iv), add a statement to the "HOW SUPPLIED/STORAGE", subsection "Storage and Handling" to declare that the 3000 USP units capsule configuration must be stored and dispensed in the original container.

These were agreed upon by Abbott

IV. Post-Market Requirements/Commitments: no new ones proposed
As noted above this supplement fulfills PMR #751-1

Note that this product has had the Medication Guide Only REMS eliminated and that the Medication Guide will be required but regulated under 21 CFR 208. This was accomplished through an additional supplement 014, which requested the elimination of the Medication Guide submitted on April 29, 2011, and approved on 5/9/2011. Thus, changes to the Medication Guide with the approval of this supplement 011 will no longer be made under FDAAA.

Material Reviewed/Consulted OND Review Package, including:	
DTP Reviews	Kimberly Rains Mary K W Lee Jessica Cole
CDTL Review	Emanuela Lacana
ONDQA Biopharmaceutics Review	Tien-Mien Chen
OSE/DMEPA	Denise V Baugh
OSE/DRISK	Steve Morin

DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DTP= Division of Therapeutic Proteins
DMEPA= Division of Medication Error Prevention and Analysis

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/s/

JOYCE A KORVICK
06/10/2011