Antiviral Drugs Advisory Committee Meeting

NDA 20-725
Pancrelipase Delayed Release Capsules (Creon)

Ethan D. Hausman, MD
Medical Officer, FDA/CDER

2-December-2008

Clinical Background

- Creon is a:
  - Porcine (pig) derived
  - Pancreatic enzyme replacement product (PEP)
  - Intended to treat pancreatic exocrine insufficiency (PEI)

- Contains: Lipase, Amylase, Protease

Clinical Background

- PEI causes fat/protein/carbohydrate malabsorption with gastrointestinal symptoms and stunted growth in children

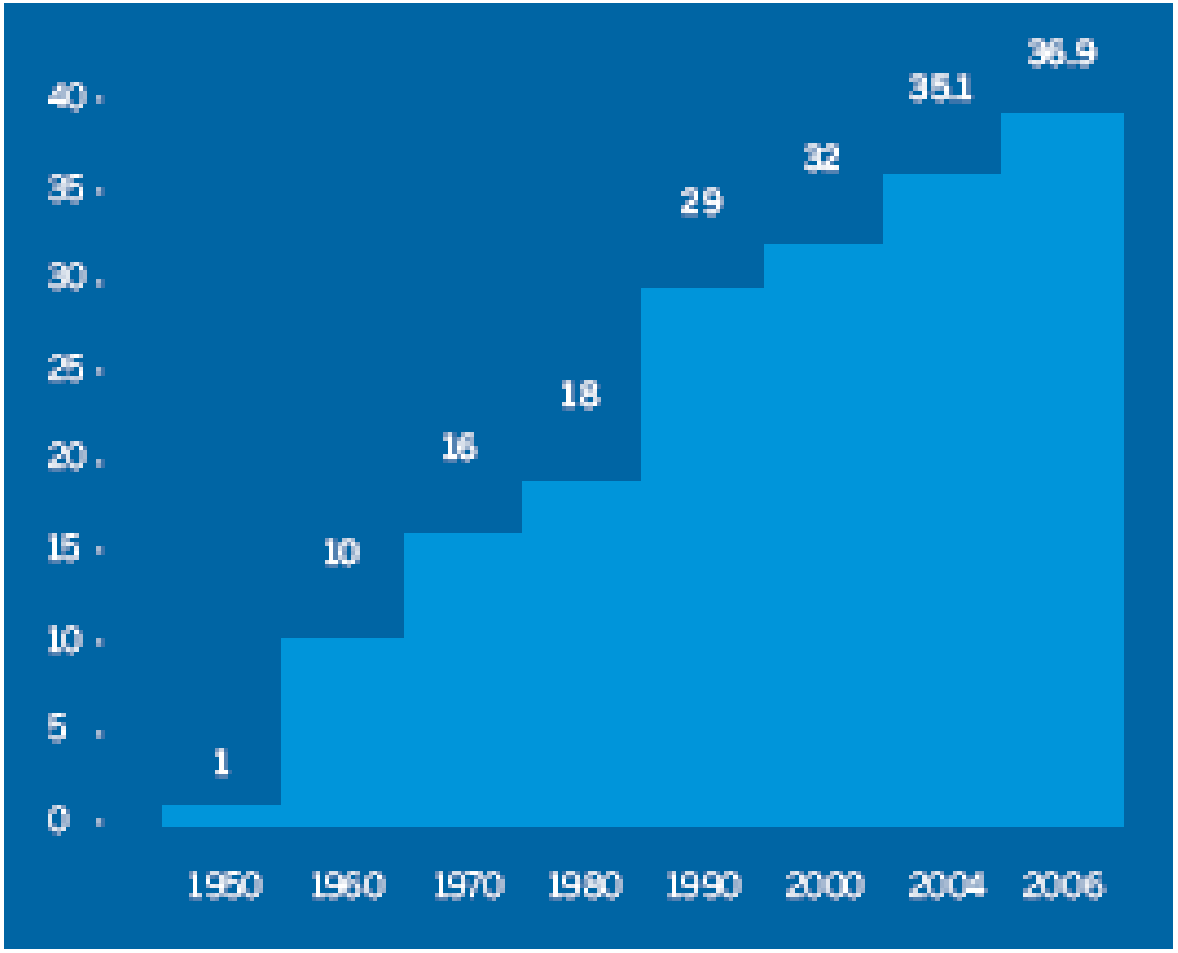
- Conditions characterized by PEI:
  - Cystic Fibrosis (CF); US incidence 1/2,500 live births.[1*]
  - Chronic Pancreatitis (CP); US incidence 1/2,500 adults.[2]

- Treatment effect assessed by change in clinical symptoms (bloating, flatus, large fat laden stools) and coefficient of fat absorption (CFA).[3,4]

- Improved CFA → improved nutrition → improved growth and pulmonary function → improved long-term outcomes.[5]

* References on slide 30

Median Survival (years) of CF Patients[6]



Regulatory History of PEPs

PEPs have been available in the US since before the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938. Currently available PEPs are marketed as nutritional supplements rather than as new drugs

- **Drugs**: marketing requires approval under the new drug (NDA) process which requires sufficient evidence to establish
  - safety and efficacy of the drug for the labeled indication
  - consistent purity and potency of the drug
  - consistent adherence to good manufacturing
  - accurate labeling
- **Nutritional supplements**: generally regulated as foods. The law does not generally require FDA review or approval prior to marketing. Manufacturers are responsible for
  - determining safety
  - establishing that any representations or claims are substantiated by adequate evidence to show that the claims are not false or misleading.

Regulatory History of PEPs

- 1990s: FDA evaluated the safety and effectiveness of the PEPs in an effort to determine the appropriateness of allowing PEPs to be marketed as non-prescription/over-the-counter drugs.

- 1995: Based on a large body of clinical evidence including data received from the public, FDA determined there is sufficient clinical evidence to support improved clinical outcomes for patients with PEI treated with PEPs; such as patients with CF. [7]

Regulatory History of PEPs

- However, the following issues with then-marketed products could affect safety and efficacy
  - Potential transmission of porcine viruses
  - Variation in bioavailability among similar dosage forms between manufacturers
  - Variation in bioavailability within the same product from one manufacturer (e.g., lot-to-lot and within-lot variability)
- Additionally, patients with diseases requiring PEP therapy need medical monitoring, necessitating prescription only status (rather than over the counter availability).

Regulatory History of PEPs

- Therefore, FDA determined that PEPs did not meet the regulatory definition of safe and effective drugs.

- FDA determined that NDAs are required to bring PEPs to market through adequate drug development processes.

- FDA published a Guidance for industry regarding requirements for new drug applications for PEPs. In addition to addressing manufacturing issues such as lot-to-lot variability and viral issues, the Guidance specifically addressed clinical study requirements.

PEP Guidance Summary

- Because a wealth of clinical data existed to support improved clinical outcomes for PEPs, it was established that safety and effectiveness of a new PEP could be demonstrated by
  - One short-term adequate and well controlled trial in a well characterized PEI population, for example
    - A two-week cross-over study
    - In 10 to 25 patients with CF
- There was adequate clinical evidence to establish stool fat markers such as coefficient of fat absorption (aka: CFA) for determining efficacy.

PEP Guidance Summary

- Since children with PEI due to CF are a recognized need group, evidence of safety and efficacy in pediatric subgroups (for example newborns, infants, and adolescents) is required (evidence from ≥1 pediatric group may support extrapolation to others).

- Demonstrate efficacy at
  - ≤ 2,500 Lu/kg/meal **OR** ≤4,000 Lu/gram dietary fat/day

    - Based on Cystic Fibrosis Foundation Guidelines developed in concert with FDA
    - Risk of fibrosing colonopathy, a serious adverse event resulting in colonic stricture, increases with increasing lipase dose
    - Increases in CFA with lower lipases doses was established

- Perform full viral risk assessments, and show removal and/or inactivation of viral agents per ICH Q5A.

Regulatory History of Creon

- 1997: NDA 20-725 submitted
  - October 2003: Additional information required.
- 2006: Applicant submits additional information.
  - August 2007: Additional clinical information required including studies with product intended to be marketed at the time of approval.

Pivotal Study: Received June-2008

- Determination of safety and efficacy are based on clinical data from a single Pivotal Study.
- Study performed with the intended to be marketed product (Creon).
- No prior adequate and well-controlled studies were performed with the intended-to-be-marketed product.

Pivotal Study Design

- Multi-center, 3-week, randomized, double-blind, placebo-controlled, cross-over study in 32 patients with CF, 12 to 43 years old.
  - Group 1: Creon → Placebo
  - Group 2: Placebo → Creon

Patients were their own controls

Inclusion/Exclusion Criteria

- Inclusion:
  - 12 years old and older
  - CFA <70% or fecal elastase <50 ug/gram stool within 1 year of enrollment
  - Treatment with non-Creon PEP at stable dose for at least 3 months prior to enrollment

- Exclusion:
  - Weight loss greater than 5% within 3 months of enrollment
  - History of fibrosing colonopathy

Dose Based on Diet

- Dose: 4,000 Lu/g dietary fat/day
- Diet designed to meet caloric requirements based on age and activity
  - At least 40% of calories derived from fat
  - Minimum daily intake of 100 grams of fat
- Note: Upper limit of CF Foundation/FDA recommended dose.[3,4,5,6,7]

Study Schedule

Screening Period	**Cross-Over Period 1** **7 Days Inpatient**		**Wash-out (WO)**	**Cross-Over Period 2** **7 Days Inpatient**		**Follow-up**
Visit 1	Visit 2 (Day 1)	Visit 3 (Day 6 or 7)	3 to 14 days	Visit 4 (Day 1)	Visit 5 (Day 6 or 7)	One week after Visit 5
Screening Procedures; Continue Prior PEP	Day 1 of treatment Creon or Placebo	Complete 1st 72 hour CFA collection	Resume Prior PEP Regular Diet	Day 1 of treatment Placebo or Creon	Completed 2nd 72 hour CFA collection	Safety Follow-up
	← ← Study Diet →→ First stool dye given at end of Day 2.			← ← Study Diet →→ First stool dye given at end of Day 2.		

Source: After Applicant's Table 2; page 23 of the Clinical Study Report, NDA Volume 3 page 1,142.

Demographics

Trait	Statistic	Creon→ Placebo	Placebo →Creon	Total
Age (years)	N Mean (SD) Median Minimum /Maximum	16 22.8 (6.5) 22.5 12 / 38	16 22.2 (7.8) 21.5 22 / 43	32 22.5 (7.1) 22.0 12 / 43
Age Strata **12 to 18 y** **>18 y**	N (%)	5 (31) 11 (69)	6 (38) 10 (62)	11 (34) 21 (66)
Gender **Male** **Female**	N (%) N (%)	9 (56) 7 (44)	12 (75) 4 (25)	21 (66) 11 (34)
Race **Caucasian**	N (%)	16 (100)	16 (100)	32 (100)
[1] Placebo CFA ***≤40%*** ***>40%***	***N (%)***	***7 (44)*** [2] ***9 (56)***	***3 (19)*** ***13 (81)***	***10 (31)*** ***22 (69)***

[1]Assessment rather than demographic characteristic. Used in place of Non-Treatment Baseline

[2] One patient was withdrawn after the first cross-over period.

Source: After Sponsor's Study Report; Table 7, page 50

Efficacy Population

- Full Analysis Population (FAP): at least 1 randomized dose <u>and</u> CFA from both CO periods; N=31

- Modified FAP: excludes data from two patients with major protocol deviations for diet and dose and where data integrity was not assured; N=29

Efficacy Assessment

- Mean difference CFA
  - Creon minus placebo

$$\text{CFA} = \left(\frac{\text{Dietary Fat Ingested} - \text{Fat Excreted in Stool}}{\text{Dietary Fat Ingested}}\right) \times 100$$

CFA: Modified Full Analysis Population

Change in CFA (%) for Modified Full Analysis Population			
	Creon	**Placebo**	**Creon - Placebo**
n	29	29	
Adjusted* Mean (s.e.)	89 (2)	49 (2)	
Adjusted* Mean Treatment Difference vs. Placebo (95% C.I.)			41 (34, 47)
p-value for Adjusted Mean Treatment Difference			<0.001

Source: FDA Statistical Review; Rounded to whole integers

Adjusted mean estimates are based on an ANOVA model with treatment, sequence, and period as fixed effects and subject within sequence as a random effect .

Normal CFA in healthy patients for this age group ≥95%

Sensitivity Analyses

- Sensitivity analyses: no clinically meaningful differences in response by age (12 to <18 vs. ≥18 years) or gender. Effects by race could not be assessed.

- Mean increase in CFA with Creon treatment was greater in patients with Placebo CFA ≤ 40% [increase 60%] than in patients with a Placebo CFA > 40% [increase 30%].

Safety; Short-Term

- Duration of exposure:
  - 5.2 (SD 0.4) days
  - No clinically meaningful difference in exposure by gender, age, placebo period CFA.

Safety

- Deaths: None

- Withdrawals: One 18 year-old female (Creon → Placebo) withdrew after CO1 due to weight loss >5% (violation of inclusion criteria).

- Two serious adverse events (AEs) in a single patient. 12 year-old male (Placebo → Creon) with duodenitis and gastritis >2 weeks after last Creon dose. Recovered without sequelae. Relationship to Creon could not be established.

Common AEs

Adverse Reactions Occuring in ≥ 2 Patients; N(%)			
Medical Dictionary for Regulatory Activities (MedDRA)		**Creon**	**Placebo**
System, organ, class	**Preferred Term**	**N=32**	**N=31**
Gastrointestinal Disorders	Abdominal Pain	3 (9)	8 (26)
	Flatulence	3 (9)	8 (26)
	Abnormal Feces	1 (3)	6 (19)
	Vomiting	1 (3)	1 (3)
	Abdominal Pain, upper	0	3 (9)
General disorders and administration site conditions	Pyrexia	0	2 (7)
Investigations	Weight Decreased	1 (3)	2 (7)
Nervous system disorders	Dizziness	2 (6)	1 (3)
	Headache	2 (6)	8 (26)
Respiratory, thoracic and mediastinal disorders	Cough	2 (6)	0
	Nasal Congestion	2 (6)	1 (3)
Patients with Any Adverse Reactions		**16 (50)**	**22 (71)**

Fibrosing Colonopathy (FC)

- No cases of FC were reported.
- However, FC is a histopathologic condition.[8,9]
  - Surveillance procedures (colonoscopy +/- biopsy) were not incorporated into the Pivotal Study.
  - No cases expected due to short duration of exposure.[9]

Clinical Laboratory Studies

- No clinically meaningful difference in mean blood uric acid levels Creon vs. Placebo.

- 3 patients had decreased neutrophil counts during Creon treatment, 1 with absolute neutropenia [<1,500 cells/uL].

  – No notable concomitant adverse events. No association of PEP treatment with neutropenia in the literature.

Summary

- Efficacy of Creon capsules has been demonstrated in patients with CF ages ≥12 years.
  - Adjusted Mean Difference in CFA Creon minus Placebo
    - Modified FAP: 41% (95% C.I., 34%, 47%); $p < 0.001$
- Short-term safety of Creon capsules has been demonstrated in patients with CF ages ≥12 years.

References

1. Scriver CR., Beaudet AL, Sly WS, Valle D, et al. The Metabolic and Molecular Basis of Inherited Disease, 8th Ed., McGraw-Hill, NY USA. 2001; page 5121.

2. Go VLW, Everhart JE. Pancreatitis. In: Everhart JE, ed. Digestive Disorders in the United States: Epidemiology and Impact. US Department of Health and Human Services, National Institutes of Health. Washington, DC: US Government Printing Office, 1994:691-712.

3. Borowitz, D, Baker, RD, Stallings, et al., Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis, J Pediatric Gastroenterology and Nutrition. 35: 246-259. 2002.

4. Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127:681-684.

5. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, et. al., Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. J Am Diet Assoc. 2008; 108: 832-839

6. Cystic Fibrosis Foundation 2007 Annual Report, page 2, http://www.cff.org/UploadedFiles/aboutCFFoundation/AnnualReport/2007-Annual-Report.pdf

7. Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs, http://www.fda.gov/CDER/guidance/6275fnl.htm

8. FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ et al., High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM, 1997. 336(18); 1283-1289.

9. Waters BL. Cystic Fibrosis with Fibrosing Colonopathy in the Absence of Pancreatic Enzymes. Pediatric and Developmental Pathology. 1, 74–78, 1998.

Cystic Fibrosis Foundation Dose Guidelines

- Breastfed or formula fed infants: 2,000 to 4,000 lipase units per 120 ml formula or with each breast feeding event.
- Children ≤4 years old eating soft or solid foods: begin with 1,000 USP lipase units/kg/meal.
- Children >4 years old: begin with 500 lipase units/kg/meal.
- Maximum dose: Doses in excess of 2,500 lipase units/kg/meal (10,000 lipase units/kg/day) should be used with caution and only when accompanied by documented three-day fecal fat measurements in order to document significant improvement of a previously documented low coefficient of fat absorption.
- Doses in excess of 6,000 lipase units/kg/meal (24,000 lipase units/kg/day) have been associated with fibrosing colonopathy and should not be used.

Cystic Fibrosis Foundation Dose Guidelines

- The recommended per meal dose should be halved when ingesting snacks.
- Recommendation based on 3 meals and 2 to 3 snacks per day.
- For older patients where dose is administered as lipase units/kg/meal, doses should be decreased because these patients ingest less fat per kilogram of body weight.