

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-725**

**OTHER REVIEW(S)**

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

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**Date:** April 16, 2009

**To:** Cristi Stark - Acting Chief, Project Management Staff  
Division of Gastroenterology Products (DGP)

**From:** Kathleen Klemm – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Through:** Lisa Hubbard – Acting Group Leader  
Mark Askine – Associate Director  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** NDA 20-725  
DDMAC comments on the draft Dear Pharmacist Letter for Creon  
(pancrelipase) Capsule, Delayed Release for Oral Use

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DDMAC has reviewed the proposed Dear Pharmacist Letter for Creon (pancrelipase) Capsule, Delayed Release for Oral Use (Creon). Our comments are provided using the draft Dear Pharmacist letter submitted via email on April 15, 2009.

Reference is made to our April 10, 2009, review of the Dear Healthcare Professional Letter. Reference is also made to the meeting between DGP and DDMAC on April 13, 2009, during which time our comments were discussed.

We have no further comments on the proposed Dear Pharmacist Letter.

Thank you for the opportunity to comment on the proposed Dear Pharmacist letter. If you have any questions, please contact me at 301.796.3946 or [Kathleen.Klemm@fda.hhs.gov](mailto:Kathleen.Klemm@fda.hhs.gov).

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/s/

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Kathleen Klemm  
4/16/2009 09:17:25 AM  
DDMAC PROFESSIONAL REVIEWER

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

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**Date:** April 10, 2009

**To:** Cristi Stark, M.S., Acting Chief, Project Management Staff  
Division of Gastroenterology Products (DGP)

**From:** Kathleen Klemm, Pharm.D. – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Through:** Sangeeta Vaswani, Pharm.D. – Acting Group Leader  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** NDA 20-725  
DDMAC comments on the draft Dear Healthcare Provider Letter for Creon (pancrelipase) Capsule, Delayed Release for Oral Use

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DDMAC has reviewed the proposed Dear Healthcare Provider (DHCP) Letter for Creon (pancrelipase) Capsule, Delayed Release for Oral Use (Creon) and offers the following comments.

Our comments are provided using the draft DHCP letter attached to the consult request submitted on April 7, 2009, and revised by DGP.

Unless otherwise noted, we agree with the changes made by DGP.

Thank you for the opportunity to comment on this proposed DHCP letter. If you have any questions, please contact me at 301.796.3946 or [Kathleen.Klemm@fda.hhs.gov](mailto:Kathleen.Klemm@fda.hhs.gov).

- The proposed DHCP letter states, “Solvay Pharmaceuticals, Inc. (b) (4) FDA approval of . . .” (emphasis added). DDMAC suggests replacing (b) (4) with “would like to inform you of”, as the text, (b) (4)” is (b) (4)
- The proposed DHCP letter makes numerous references to the “New” formulation of Creon and the “new” strengths, “new” prescribing information” and a “new” dosing schedule and Medication Guide. DDMAC suggests relaying to the sponsor that the term “New” should only be used for six months from the time the product is initially marketed. After six months, this term should be deleted.
- The proposed DHCP letter includes text regarding the zero-overfill pancrelipase formulation, the removal of mineral oil and the recommendation to assess patients’ vitamin levels and adjust vitamin doses as needed. DDMAC notes that this information is not included in the product labeling (PI), and wants to ensure that this text is accurate. Is this information important enough to be also included in the PI? Is its inclusion essential for the purpose of this letter?
- The proposed DHCP letter states the following:

FDA-approved CREON® is a **zero-overfill pancrelipase formulation** and the first pancreatic enzyme product (PEP) to meet the FDA’s new guidelines for the manufacturing and marketing of these products (bolded emphasis in original; underlined emphasis added).

Is the underlined text accurate, and is it necessary to include this text in this letter? DDMAC is concerned that this text sounds very promotional in tone.

- The proposed DHCP letter states the following:

(b) (4)

DDMAC suggests revising and adding additional context to this text, to ensure consistency with the PI. We suggest the following revisions:

**For patients** unable to swallow intact capsules, CREON capsules may be opened, and the contents mixed in **a small amount of acidic soft food with a pH of 4 or less, such as** applesauce, **at room temperature**, and administered **immediately** without crushing or chewing, **and** followed by **water or juice** to ensure complete ingestion. **Care should be taken to ensure that no drug is retained in the mouth** (emphasis added).

- The proposed DHCP letter states, “FDA-approved CREON is available by prescription only.” This text appears under the heading, “Summary of

Prescribing Changes for CREON®.” Is the prescription-only status of this product a change? If not, DDMAC suggests relocating this text away from this heading.

- The proposed DHCP letter states, “**New dosing schedule:** See section 2 of the attached prescribing information for details” (emphasis in original). Should any additional specific dosage information be discussed in this section of the DHCP letter?
- The proposed DHCP letter states, (b) (4)  
(b) (4) (bolded emphasis in original; underlined emphasis added). The underlined text is vague and minimizes the risks associated with Creon. We suggest deleting this text and replacing it with, “for Creon”, to convey that the Medication Guide offers important safety information specifically for Creon.
- The proposed DHCP letter states, (b) (4)  
(b) (4) (emphasis added). The bolded text is vague and could be used to promote the drug in a misleading manner. We suggest providing specific language regarding the clinical trial, as stated in the PI, to remove this misleading impression (e.g., study design, number of patients, dosing, endpoints, specific results).
- The proposed DHCP letter includes the heading “Dosing” which is followed by information regarding the new strengths of Creon. Should this heading be revised to “Dosage Forms and Strengths”?
- The proposed DHCP letter states, (b) (4)  
(b) (4) DDMAC suggests revising this text as follows: “Therapy should be initiated at the lowest recommended dose and gradually increased according to the Cystic Fibrosis Foundation Guidelines.”
- The proposed DHCP letter states, (b) (4)  
(b) (4) (emphasis added). DDMAC suggests revising the bolded text to, “The purpose of the Medication Guide is . . .”
- The proposed DHCP letter states, (b) (4)  
(b) (4) (emphasis added). For clarity, DDMAC suggests revising the bolded text to, “for **healthcare providers** talking to patients” (emphasis added).
- The proposed DHCP letter states (b) (4)  
(b) (4) (emphasis added). DDMAC suggests deletion of the text, (b) (4), (b) (4),

(b) (4).

Additionally, DDMAC suggests adding context to the text, “with different pancreatic enzyme products” to convey that this class includes Creon. For example, this sentence could be revised to: “Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products, **such as CREON**” (emphasis added).

- The proposed DHCP letter omits important risk information from the PI. Specifically, the Warnings and Precautions section of the PI states the following (in pertinent part):

Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth following administration. CREON should not be crushed or chewed or mixed in foods having a pH greater than 4. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity.

Potential for Risk of Hyperuricemia

Caution should be exercised when prescribing CREON to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

Allergic Reactions

Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued CREON treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

- Furthermore, we note that the PI includes treatment-emergent adverse events that occurred in greater than or equal to 6% of patients treated with Creon, including dizziness (6%) and cough (6%).
- The proposed DHCP letter states the following:

(b) (4)

Consistent with the PI, DDMAC recommends revising the heading to: “Potential Viral Exposure from the Product Source.” Additionally, DDMAC recommends deleting the bolded text because it minimizes the risks associated with Creon.

- The proposed DHCP letter includes the heading, [REDACTED] (b) (4) [REDACTED] (emphasis added). The bolded text is promotional; therefore, DDMAC suggests deletion.

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/s/

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Kathleen Klemm  
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DDMAC PROFESSIONAL REVIEWER



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Rockville, MD 20852  
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## Memorandum

### PROJECT MANAGER'S REVIEW

**Application Number:** NDA 20-725

**Name of Drug:** Creon® (Pancrelipase Delayed Release Capsules)

**Sponsor:** Solvay Pharmaceuticals

**Material Reviewed:** Creon® (Pancrelipase Delayed Release Capsules) Carton and Container Labels

**OBP Receipt Date:** November 12, 2008

**Amendment Reviewed:**

#### Background:

Creon® (Pancrelipase Delayed Release Capsules) is a New Drug Application (NDA) indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. Creon is a pancreatic enzyme product (PEP) consisting of porcine-derived lipases, proteases, and amylase.

#### Labels Reviewed:

Creon® (Pancrelipase Delayed Release Capsules) Container Label

- 6,000 Lipase Units -12 ct, 100ct, 250ct, and Wee Care 250 ct Trade Bottle labels
- 6,000 Lipase Units -12 ct, 100ct, 250ct, and Wee Care 250 ct Foil pouches
- 12,000 Lipase Units -12 ct, 100ct, 250ct, and WeeCare 250 ct Trade Bottle labels
- 12,000 Lipase Units -12 ct, 100ct, 250ct, and WeeCare 250 ct Foil pouches
- 24,000 Lipase Units -12 ct, 100ct, and 250ct Trade Bottle labels
- 24,000 Lipase Units -12 ct, 100ct, and 250ct Foil pouches

Creon® (Pancrelipase Delayed Release Capsules) Carton Label

- 6,000 Lipase Units -12 ct, 100ct, 250ct, and WeeCare 250 ct Trade Carton labels
- 12,000 Lipase Units -12 ct, 100ct, 250ct, and WeeCare 250 ct Trade Carton labels
- 24,000 Lipase Units -12 ct, 100ct, and 250ct Trade Carton labels

## Review

### I. Container

#### A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor- “Marketed By: Solvay Pharmaceuticals, Inc.” The label does not conform to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 0032-XXXX-X. The NDC number conforms to 21 CFR 207.35 as a 4-1 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the center of the label “See package insert for dosage and administration” appears on all labels. This conforms to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The name that appears on the label is not the proprietary name, Creon<sup>®</sup>. The proprietary name with associated strengths- Creon<sup>®</sup> 6000, Creon<sup>®</sup> 12,000, Creon<sup>®</sup> 24,000 appears on the label. The established name, Pancrelipase appears as Pancrelipase Delayed Release Capsules. This does not conform to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase Delayed Release Capsules is used in type at least half as large as the most prominent presentation of the proprietary name, Creon<sup>®</sup>. This conforms to the regulation. The graphic enclosing the ingredients appears as “Each capsule contains...”. This does not conform to the regulation.
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only” and “Protect from Moisture”). This conforms to the regulation.
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the center portion of the label. This conforms to the regulation.

8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the right of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Free Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
10. 21 CFR 201.51 Declaration of net quantity of contents – The label does prominently state the net quantity of contents in terms of numerical count in units directly under the proprietary and established name. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- The label states “See package insert for dosage and administration.” This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for “Rx Only”, “ PROTECT FROM MOISTURE”, identifying lot number, storage conditions, “Keep Bottle tightly closed after opening,” and reference to the package insert. This conforms to the regulation.
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This does not conform to regulation.

**B. Foil Pouch**

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor- “Marketed By: Solvay Pharmaceuticals, Inc.” The label requirement does not conform to the regulation
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 0032-XXXX-X. The NDC number conforms to 21 CFR 207.35 as a 4-1 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-On the center of the label “See package insert for dosage and administration” is printed. This conforms to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The name that appears on the label is not the proprietary name, Creon®. The proprietary name with associated strengths- Creon® 6000, Creon® 12,000, Creon® 24,000 appears on the label. The established name, Pancrelipase appears as Pancrelipase Delayed Release Capsules. This does not conform to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase Delayed Release Capsules is used in type at least half as large as the most prominent presentation of the proprietary name, Creon. This conforms to the regulation.
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”) and (“KEEP BOTTLE INSIDE FOIL POUCH UNTIL READY TO DISPENSE”) (PROTECT FROM MOISTURE). This conforms to the regulation.
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration Date appears perpendicular to the Proprietary name along the side of the wrapper. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements – No bar code appears. This does not conform to the regulation.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Free Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
10. 21 CFR 201.51 Declaration of net quantity of contents – The label does prominently state the net quantity of contents in terms of numerical count in units directly under the proprietary and established name. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- The label states “See package insert for dosage and administration.” This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for “Rx Only”, “PROTECT FROM MOISTURE”, an identifying lot number, storage conditions, “Keep Bottle tightly closed after opening,” and reference to the package insert. The

label does not bear a statement to direct the pharmacist of the type of container to be used to maintain product identity, strength, quality and purity once the product is removed from the foil pouch and original container. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This does not conform to regulation.

## **II. Carton**

- A. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- "Marketed By: Solvay Pharmaceuticals, Inc." The label requirement does not conform to the regulation
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers -The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 0032-XXXX-X. The NDC number conforms to 21 CFR 207.35 as a 4-1 Product-Package Code configuration. This conforms to the regulation.
- C. 21 CFR 201.5 Drugs; adequate directions for use - On the side top panel of the carton the statement "See package insert for dosage and administration" appears. This conforms to the regulation.
- D. 21 CFR 201.6 Drugs; misleading statements - The name that appears on the label is not the proprietary name, Creon®. The proprietary name with associated strengths- Creon® 6000, Creon® 12,000, Creon® 24,000 appears on the label. The established name, Pancrelipase appears as Pancrelipase Delayed Release Capsules. This does not conform to the regulation.
- E. 21 CFR 201.10 Drugs; statement of ingredients - The established

name, Pancrelipase Delayed Release Capsules is used in type at least half as large as the most prominent presentation of the proprietary name, Creon. This conforms to the regulation. The graphic enclosing the ingredients appears as "Each capsule contains...". This does not conform to the regulation.

- F. 21 CFR 201.15 Drugs; prominence of required label statements -All required statements ("Rx Only" and "PROTECT FROM MOISTURE"). This conforms to the regulation.
- G. 21 CFR 201.17 Drugs; location of expiration date - The expiration date does not appear on the carton. This does not conform to the regulation.
- H. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
- I. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Free Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
- J. 21 CFR 201.51 Declaration of net quantity of contents - The label does prominently state the net quantity of contents in terms of numerical count in units directly under the proprietary and established name. This conforms to the regulation.
- K. 21 CFR 201.55 Statement of dosage - The carton states "See package insert for dosage and administration." This conforms to the regulation.
- L. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for "Rx Only," storage conditions, "Keep Bottle tightly closed after opening," and reference to the package insert. However, the label does not have a does not have an identifying lot number. This does not conform to the regulation.
- M. 21 CFR 208.24 Distribution and dispensing of a Medication guide-If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This does not conform to regulation.

### III. Conclusions

- A. The proposed carton and vial labeling are acceptable only upon the following changes:
1. “Marketed by” is printed on all carton and container labels. This does not conform to 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor. The PI states **Manufactured by:** Solvay Pharmaceuticals GmbH  
Hannover, Germany  
**Marketed By:** Solvay Pharmaceuticals, Inc.  
Marietta, GA 30062
  2. The name that appears on all of the labels is not the proprietary name, Creon<sup>®</sup>. The proprietary name with associated strengths- Creon<sup>®</sup> 6000, Creon<sup>®</sup> 12,000, Creon<sup>®</sup> 24,000 appears on the label. The established name, Pancrelipase appears as Pancrelipase Delayed Release Capsules. This does not conform to CFR 201.6. Please revise the proprietary name to Creon<sup>®</sup> and the established name to Pancrelipase.
  3. The graphic enclosing the ingredients appears on the carton label, “Each capsule contains ...”, “Keep Bottle inside foil ....”, and “Marketed by...” does not conform to CFR 201.10. Please remove the graphic enclosures from the carton and container labels and consider enlarging the statement “Each capsule contains....”.
  4. “Warnings: See package Insert” and the statement “Store CREON...” appears crowded and is misleading on all labels. This does not conform to CFR 201.15. Please add spacing sufficient to separate storage conditions from the warnings statement or remove “Warnings: See package insert” from the container and carton labels.
  5. The expiration and lot information do not appear on the carton labels. Please add the expiration date and lot information to carton labels per CFR 201.17.
  6. A Bar code does not appear on the foil pouch for any strength. Please add a bar code to the foil pouches per CFR 201.25.
  7. The label does not bear a statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality and purity once it is removed from the foil pouch and original container. This does not conform to CFR 201.100. Please provide a statement to the

authorized dispenser describing an appropriate dispensing container.

8. Revise the term “Free Proteases” to “Protease” to conform to the USP Monograph for Pancrelipase Delayed-Release Capsules on all labeling.
9. Please add a statement instructing the authorized dispenser to provide a medication guide to each patient to whom the drug is dispensed per 21 CFR 208.24 on all carton and container labeling.

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Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBS

Comment/Concurrence:

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Emanuela Lacana, Ph.D.  
Product Reviewer  
Division of Therapeutic Proteins  
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/s/

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: March 27, 2009

To: Carol Drew  
Regulatory Counsel  
Office of Regulatory Policy

Through: Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis

Todd Bridges, R.Ph., Team Leader  
Division of Medication Error Prevention and Analysis

From: Deevonne Hamilton-Stokes, R.N., B.S.N., Safety Evaluator  
Medication Error Prevention and Analysis

Subject: Citizen Petition 2009P-0059-0001  
Petitioner: Eurand Pharmaceuticals  
Consult on Request to Require Solvay to Use a Trade Name Other Than Creon for Its New Pancrelipase Delayed-Release Capsules and To Use Distinct and Different Packaging and Trade Dress

Drug Name(s): Creon (Pancrelipase Delayed-Release Capsules, USP)

Application Type/Number: NDA # 20-725

NDA Applicant: Solvay Pharmaceuticals

OSE RCM #: 2009-330

## CONTENTS

1	BACKGROUND.....	3
1.1	Introduction.....	3
1.2	Regulatory Background -- Pancreatic Enzyme Products .....	3
1.3	Product Information -- CMP and TbMP.....	4
1.4	DMEPA Review History .....	4
2	DISCUSSION .....	6
3	CONCLUSIONS.....	8

## ATTACHMENTS

1. Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (April 2006)

2. OSE review # 03-0170 (October 10, 2003)

3. OSE review # 2006-1123 (April 9, 2007)

## **1 BACKGROUND**

### **1.1 Introduction**

This review is written in response to a request from the Office of Regulatory Policy (ORP) for the Division of Medication Error Prevention and Analysis (DMEPA) to analyze and assess concerns about the use of the proposed name, Creon, for the Solvay Pharmaceuticals (Solvay) to-be-marketed product (TbMP) for pending NDA 20-725 submitted under 505(b)(2). Solvay currently markets an unapproved pancreatic enzyme product (referred to here-in as the currently marketed product (CMP) in multiple strengths, under the proprietary names Creon® 5, Creon® 10, and Creon® 20.

ORP requested this information in response to a citizen petition submitted on February 6, 2009, by Eurand Pharmaceuticals (the petitioner). The petition requests that FDA (1) require Solvay to market and sell the TbMP using a proprietary name other than Creon, (2) require distinct and different packaging and trade dress to distinguish the TbMP from the CMP, and (3) prohibit Solvay from suggesting in its sales and marketing efforts that data and findings generated in studies of the CMP are directly applicable to the TbMP. This review addresses the first two requests.

### **1.2 REGULATORY BACKGROUND -- PANCREATIC ENZYME PRODUCTS**

Pancreatic Enzyme Products (PEPs) were first marketed prior to the Food Drug and Cosmetic Act of 1938 and continue to be available in the U.S. as nutritional supplements and throughout the world as over-the-counter (OTC) and prescription therapies. In the 1990's concerns about potency and safety, including fibrosing colonopathy, led to a series of regulatory decisions establishing that PEPs were not generally recognized as safe and effective. It was determined that PEPs would be considered misbranded due to variations in potency. The Agency declared its intent to consider all PEPs as new drugs requiring an approved new drug application (NDA) for continued marketing while exercising enforcement discretion regarding unapproved PEPs to ensure continued availability of exocrine pancreatic insufficiency products.<sup>1</sup>

In April 2006, the Agency issued a final guidance to assist manufacturers of these products in preparing and submitting NDAs, entitled Guidance to Industry: *Exocrine Pancreatic Insufficiency Drug Products – Submitting NDA*<sup>2</sup> (Attachment 1).

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<sup>1</sup> See 60 FR 20162 (April 25, 1995), publication of a Final Rule calling for all PEPs to be marketed drug product under approved NDAs by April 2008; and 72 FR 60860 (October 26, 2007), Notice extended this period of enforcement discretion until April 28, 2010 under prescribed conditions.

<sup>2</sup> The Guidance identifies various NDA application topics (chemistry, manufacturing, and controls) which are unique to PEPs and for which NDAs should provide information, among them, Overages: “Since high doses of pancreatic enzymes have been associated with safety problems (see 69 FR 23411), the finished product should be formulated to 100 percent of the label-claimed lipase enzyme activity. With suitable justification (e.g., manufacturing losses), however, overages may be acceptable. Amylase and protease activity in the formulation should remain within justified limits.” (Guidance at page 5). The TbMP has been reformulated to conform to the new zero-overfill manufacturing guidelines.

### **1.3 PRODUCT INFORMATION – CMP AND TBMP**

The two Creon product formulations (CMP and TbMP) are both pancreatic enzyme products prescribed to improve digestion of food, especially fat. The CMP and TbMP share the same active pharmaceutical ingredient (API), pancrelipase -- that comprises three types of enzymes -- (lipase, protease, and amylase). The two product formulations are indicated for the same unrestricted patient populations (adult and pediatric patients), for the same intended conditions of use (for mal-digestion due to exocrine pancreatic insufficiency, often associated with cystic fibrosis or other conditions), and rely on the same dosing titration recommendations (aside from the new dosing schedule reflective of the new dosage strengths in the reformulated product). A brief description of similarities and differences of these products follows.

#### *The CMP*

Solvay introduced the CMP, the Creon Microspheres product(s), to the U.S. market in 1987 using the proprietary names Creon® 5, Creon® 10, and Creon® 20, respectively. All dosage strengths contain pancrelipase (comprised of lipase, protease, and amylase enzymes from porcine pancreatic origin) and are dosed based on lipase units. For example, Creon® 5 Minimicrospheres® pancrelipase delayed release capsules contain pancrelipase (lipase 5,000 USP units, protease 18,750 USP units and amylase 16,600 USP units per capsule). The inactive ingredients include dibutyl phthalate, dimethicone hydroxypropylmethylcellulose phthalate, light mineral oil and polyethylene glycol.

#### *The TbMP*

The TbMP also contains delayed-release, porcine-derived pancrelipase, dosed based on the lipase units, and is to be available as capsules with the following strengths (lipase USP units/protease USP units/amylase USP units):

Creon® 6,000 USP units/19,000 USP units/30,000 USP units  
Creon® 12,000 USP units/38,000 USP units/60,000 USP units  
Creon® 24,000 USP units/76,000 USP units/120,000 USP units

The actual lipase activity is nearly the same for the CMP and the TbMP, and the difference in the labeled lipase units in the TbMP label relative to the CMP reflects the labeling changes that were made to meet FDA's requirement to label the actual amount of lipase in a capsule at production, including overage. (The CMP contains the same amount of lipase (6,000 units) but was labeled as 5,000). The TbMP label more accurately reflects the lipase content of the product, which could minimize the risk of overdosing, and hence, the risk of fibrosing colonopathy.

The dosage of all Creon products should be individualized and based on the degree of steatorrhea present, and the fat content of the diet. Clinical experience should dictate initial starting dose, recommendations vary by age group, and patients may also be dosed on their actual body weight. Therapy should be initiated at the lowest recommended dose and gradually increased.

### **1.4 DMEPA REVIEW HISTORY**

In 1987, Solvay introduced the unapproved CMP, Creon® to the U.S. market using the proprietary name Creon® with numerical suffixes correlating to the lipase components of the different dosage strength products (Creon® 5, Creon® 10, and Creon® 20). In 1993, Solvay

revised the CMP formulation from the microsphere to the minimicrosphere, and submitted an NDA for the revised formulation in August 1997. In September 1997, Solvay was placed under the Application Integrity Policy (AIP) and the Creon NDA review was suspended. In April 2003, the Agency revoked the AIP status and review of the NDA was resumed.

As part of the 2003 review cycle for pending NDA 20-725, DMEPA<sup>3</sup> evaluated the proposed proprietary names, Creon Minimicrospheres® 5, Creon Minimicrospheres® 10, and Creon Minimicrospheres® 20 for potential confusion that could lead to medication errors caused by sound-alike or look-alike names<sup>4</sup>. DMEPA determined that the names were unacceptable, as summarized below (see OSE review # 03-0170, dated October 10, 2003, Attachment 2).<sup>5</sup>

First, DMEPA recommended against inclusion of the dosage form modifier “minimicrospheres” as part of the proprietary name because such inclusion precludes a company from using the same proprietary name for future dosage forms of the product without making the proprietary name (i.e., by including minimicrospheres) misleading. Second, DMEPA recommended against use of the numerical suffixes “5”, “10”, and “20” in conjunction with the proprietary name, Creon. The recommendation against including the numerical suffixes was based on postmarketing cases of confusion with other like-products using similar numerical suffixes. The numerical suffixes were misinterpreted as “the number of capsules” to be taken or to be dispensed, rather than the product strength based on units of lipase. To avert potential errors associated with the Creon product lines, DMEPA recommended that the numerical suffixes following the name be revised to read “5,000”, “10,000”, and “20,000” respectively. This number reflected what was understood to be the actual number of lipase units contained for each strength of drug product, and because of the relatively large size of the numbers would be less likely to be misinterpreted as the number of capsules to administer per dose.

On November 17, 2006,<sup>6</sup> Solvay proposed the proprietary names Creon® 6, Creon® 12, and Creon® 24 to reflect a new Creon capsule formulation that would be available in three strengths, 6,000, 12,000 and 24,000 USP units of lipase. The proposed numerical suffixes were revised to reflect the actual USP units for the lipase component. According to the Division of Gastroenterology Products (DGP), the Creon CMP also contained 6000 USP units but this information was not correctly reflected on the container labels and labeling.

DMEPA’s April 9, 2007, review of the proposed names Creon® 6, Creon® 12, and Creon® 24 determined that the names were unacceptable because of the inclusion of the numeric suffixes (see OSE review # 2006-1123, dated April 9, 2007, Attachment 3). DMEPA rejected the proposed names Creon® 6, Creon® 12, and Creon® 24 and recommended that Solvay revise the

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<sup>3</sup> DMEPA was formerly known as the Division of Medication Errors and Technical Support (DMETS).

<sup>4</sup> 21 CFR 201.10(c)(5) states that the labeling of a drug may be misleading by reason of “[d]esignation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.”

<sup>5</sup> On October 9, 2003, a Not Approvable Letter was issued for NDA 20-725.

<sup>6</sup> The November 17, 2006, submission was in sent response to the April 2004, Guidance for Industry, to reformulate the Creon capsule, and included a complete response to the October 9, 2003 Not Approvable Letter.

name for each dosage strength to read Creon® 6,000, Creon® 12,000, and Creon® 24,000 respectively, for the same reasons outlined above.<sup>7</sup>

As requested, Solvay subsequently revised the proprietary names to Creon® 6,000, Creon® 12,000, and Creon® 24,000. DMEPA was then requested to re-review the proposed proprietary names and the labels and labeling for the product(s). Upon review of the labels and labeling, DMEPA noted that all three API enzymes (lipase, protease and amylase) were listed on the principal display panel of the labels, indicating that they were all part of the API, pancrelipase. Because the proposed TbMP name only referenced the lipase enzyme strength of the API, DMEPA became concerned that the proposed name would be misleading (see 21 CFR 201.6(b)).<sup>8</sup> DMEPA discussed this concern with the review team on February 2, 2009. It was determined that all three enzymes comprising the API pancrelipase (lipase, protease and amylase) were considered part of the API, and therefore the proposed proprietary name would need to be revised to eliminate the singular reference to the strength of lipase alone, and should simply state “Creon.”

## 2 DISCUSSION

The petitioner’s objection to the use of the proposed proprietary name Creon is largely based on the differences in formulation of the CMP compared to the TbMP and that because of these putatively significant product formulation differences, the CMP and TbMP should carry different proprietary names, and distinct and different packaging and trade dress. However, for the reasons discussed below, DMEPA disagrees that the Creon product reformulation from the CMP to the TbMP warrants the actions requested by the petitioner.

The petitioner states:

- marketing and selling phthalate-free and phthalate-containing products under the same proprietary name could potentially endanger the safety and health of patients who have phthalate sensitivities or are otherwise attempting to minimize their phthalate intake.
- confusion about the presence or absence of mineral oil in a drug product could result in serious medication errors in patients with exocrine pancreatic insufficiency.
- because of the variability of raw pancreatic extract products, marketing and selling such products with differing active ingredient sources under the same proprietary name and similar trade dress without demonstrating comparability of the active ingredients could be confusing and potentially endanger the safety and health of patients.

According to DGP, the inactive ingredients phthalate and mineral oil are considered excipients. DGP considers the removal of phthalate to improve the safety of the TbMP and that its removal and that of mineral oil do not necessitate reclassification of the API of the product. Therefore, the API, and the three types of enzymes (lipase, amylase, and protease) comprising pancrelipase, remains the same in both formulated products. DMEPA agrees that revisions in excipients or

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<sup>7</sup> On August 16, 2007, Solvay received an Approvable Letter for NDA 20-725 because the clinical effectiveness and short-term safety of Creon has not been established.

<sup>8</sup> According to 21 CFR 201.6(b): “The labeling of a drug which contains two or more ingredients may be misleading by reason, among other reasons, of the designation of such drug in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.”

inactive ingredients do not typically necessitate a change in the proprietary name of products.<sup>9</sup> Therefore, because these differences do not represent changes in the API, these changes do not necessitate a change in the proprietary name, and DMEPA considers the proposed proprietary name “Creon” to be acceptable for the TbMP.

Although the CMP and TbMP are not considered comparable because they are obtained from different sources and therefore not interchangeable, the API name of both the CMP and TbMP is pancrelipase, which is comprised of amylase, lipase, and protease, specified in the United States Pharmacopeia (USP) monograph. While the API raw material for the two substances is obtained from different sources, according to DGP, with improved chemistry, manufacturing, and control standards, the TbMP should have a higher consistency in product quality and stability. DMEPA defers to DGP on this point. Therefore, the differences in animal source and extraction processing of the API do not represent significant differences and do not necessitate a change in the proprietary name.

It is important to note that Solvay has made additional revisions to the Creon labels/labeling (including carton and container labeling) to bring the TbMP into compliance with current review standards. As such, the TbMP labels and labeling have been revised to accurately reflect the USP units for all three enzymes of the active ingredient, and to correctly reflect the amount of USP units contained in each capsule. The USP units of the TbMP are the same as what is contained in the CMP. With greater drug stability, the labeled dose of the TbMP will more accurately reflect the lipase content of the product. Because all three active ingredient enzymes must be reflected on the labels and labeling, the TbMP will be marketed with the stand-alone proprietary name “Creon” without modifiers referring to only one of the enzymes (lipase) as is the case with the proprietary name on the three strengths of the CMP, Creon® 5, Creon® 10 and Creon® 20.

While DMEPA considers the above-circumstances adequate to base our conclusion that reformulation from the CMP to TbMP does not warrant a proprietary name different from Creon, other circumstances mitigate the potential for product confusion.

The labeling and the Risk Evaluation and Mitigation Strategy (REMS) for the TbMP, which includes a Medication Guide, will inform patients regarding the different stability, dosing instructions, and different labeled dosage strengths.

The Creon TbMP packaging is already contemplated to be different from the CMP because the TbMP container labels and carton labeling include (1) the disclosure “Dispense enclosed Medication Guide to each patient”, (2) all three enzymes of the active ingredient are identified on the labels and labeling, and (3) a simplified Creon proprietary name that deletes any numerical suffixes. Collectively, these visual elements already provide a different appearance between the CMP and the TbMP packaging. Additionally, DMEPA has requested that a container label disclosure be added to indicate “new formulation” for a 6-month period. These differences will also help to minimize confusion that could arise during the time-limited product transition period and preclude the need to require completely new and different packaging and trade dress to distinguish the TbMP from the CMP.

DMEPA understands that there will be a transition plan that will occur over a short amount of time. Consequently, the TbMP and the CMP will not coexist in the market for a considerable amount of time (< 2 months). As part of its transition plan, Solvay will disseminate a Dear

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<sup>9</sup> If changing or removing an excipient or inactive ingredient between two otherwise similar drug products creates a safety concern where both formulated products remained on the market could be easily distinguished (e.g., sulfite-containing versus sulfite-free), then a proprietary name change would be more likely warranted.

Health Care Provider Letter and Dear Pharmacist Letter when the TbMP product is launched. These educational letters (as well as sales representative training and field activity) will inform professional on why and how CMP must be replaced by the TbMP. The letters will identify the FDA-approved Creon as containing pancrelipase and identifying the three types of enzymes, but different from the unapproved product because the drug has been reformulated to conform to the zero-overfill manufacturing guidelines. While these letters do not discuss removal of the two excipients, the letters will explain the different dosing instructions and different labeled dosage strengths, fully describe the transition dosing for patients already taking the unapproved Creon product (which is simply a one capsule of the TbMP for the one capsule of the CMP), and the need for a new prescription for the TbMP in patients currently taking the CMP. Because the products are not interchangeable, the pharmacist will not be able to merely refill the patient's CMP prescription with the TbMP. This information to clinicians should help to reduce the risk of product confusion during the transition period.

### **3 CONCLUSIONS**

The Creon CMP and TbMP product differences involving excipients will not adversely affect the dosing, safety, or efficacy of the product(s). The name of the API (pancrelipase, comprised of lipase, amylase, and protease) in both products is the same. Clinically, and for purposes of proprietary name review, the Creon CMP and the TbMP are considered to be the same drug product.

Based on the information and above analysis, DMEPA supports the denial of Eurand Pharmaceutical's petition to require Solvay to use a proprietary name other than "Creon" to market and sell their TbMP. While we do not support requiring a new proprietary name for the improved TbMP, or completely altering the TbMP packaging and trade dress, we support various Agency recommendations for revising the new Creon labels and labeling to distinguish the TbMP from the CMP based on new dosage strengths, as well as for Solvay developing letters to inform health care providers about the reformulated product during the transition period.

If you have further questions or need clarification, please contact Phuong (Nina) Ton OSE Project Manager, at 301-796-1648.



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: February 23, 2009

To: Donna Griebel, M.D., Director  
**Division of Gastroenterology Products**

From: Jodi Duckhorn, MA, Team Leader  
**Patient Labeling and Education Team  
Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Creon (pancrelipase delayed release cap) 600, 12000, 24000

Application Type/Number: NDA 20-725

Applicant/sponsor: Solvay Pharmaceuticals

OSE RCM #: 2008-1686

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review of the Medication Guide (MG), we have:

- simplified wording and clarified concepts where possible,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

It is important to note that we did not review the MG for content consistency with the Professional Information (PI). It was agreed with DGP that due to time constraints, this review was strictly limited to patient-friendly language, formatting, and maintaining the standard of a MG (per 21 CFR 208.20).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

Please let us know if you have any questions.

12 pp Withheld in Full Immed. After This Page as (b)(4) Draft Labeling.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Mary Dempsey  
2/23/2009 01:23:28 PM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
2/24/2009 08:54:55 AM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: February 19, 2009

To: Donna Griebel, M.D., Director  
Division of Gastroenterology Products

Through: Todd Bridges, RPh, Team Leader  
Denise Toyer, Pharm D, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Creon (Pancrelipase Delayed-release Capsules, USP)

Application Type/Number: NDA# 20-725

Applicant: Solvay Pharmaceuticals

OSE RCM #: 2008-1683

# CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND.....	3
1.1 Introduction.....	3
1.2 Regulatory History.....	3
1.3 Product Information .....	4
2 METHODS AND MATERIALS .....	5
2.1 FDA’s Adverse Event Reporting System (AERS) Database Search .....	5
2.2 Labels and Labeling Risk Assessment.....	5
3 RESULTS.....	6
3.1 AERS Database Search.....	6
3.2 Presentation of Lipase Strength Adjacent to the Proprietary Name.....	7
3.3 Product Strength Differentiation .....	7
3.4 Lack of Product Strengths on Container Labels .....	7
3.5 Foil Overwrap Labeling .....	7
3.6 Lack of a Medication Guide Statement.....	7
3.7 Insert Labeling .....	7
4 DISCUSSION .....	7
4.1 Presentation of Lipase Strength Adjacent to the Proprietary Name.....	7
4.2 Differentiation of the Product strengths .....	7
4.3 Lack of Product Strengths on Container Labels .....	8
4.4 Foil Overwrap Labeling .....	8
4.5 Lack of a Medication Guide Statement.....	8
4.6 Lack of “Do Not Crush or Chew Statement” .....	8
4.7 Presentation of Product Strength in Insert Labeling .....	9
5 CONCLUSIONS AND RECOMMENDATIONS .....	9
5.1 Comments to the Division.....	9
5.2 Comments to the Applicant.....	9
6 REFERENCES .....	11
APPENDICES .....	12

## **EXECUTIVE SUMMARY**

The results of the Label and Labeling Risk Assessment indicate that the information on the labels and labeling introduces vulnerability that could lead to medication errors. Specifically, we are concerned with the inclusion of the lipase strength being displayed with the proprietary name, the lack of differentiation of product strengths, the small size of the container labels, and the lack of a caution statement on the container label and carton labeling and within the dosage and administration section of the insert labeling.

The Division of Medication Error Prevention and Analysis (DMEPA) believes the risk we have identified can be addressed and mitigated prior to drug approval and provide recommendations in Section 5 that aims at reducing the risk of medication errors.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to a request from the Division of Gastroenterology Products to evaluate the product's labels and labeling for their potential to contribute to medication errors. Revised container labels, carton and insert labeling were evaluated to identify areas that could lead to medication errors.

### **1.2 REGULATORY HISTORY**

Creon is one of the many pancreatic enzyme drug products already marketed without an approved NDA. The Applicant introduced Creon Microspheres products to the U.S. market in 1987 (Creon® 5, 10, 20). The Applicant revised the product formulation from the microsphere to the minimicrosphere and submitted an NDA for this formulation in August 1997. The Applicant was placed under the Application Integrity Policy (AIP) in September 1997 and the review of the Creon NDA was suspended. The Agency revoked the AIP status in April 2003 and the review of the NDA was restarted. However, in October 2003, this NDA received a Not Approvable.

DMEPA reviewed the name Creon Minimicrospheres® 5, 10, and 20 in OSE review # 03-0170 dated October 10, 2003 and found the name unacceptable because we did not recommend the modifier "minimicrospheres" in conjunction with the proprietary name, Creon. Additionally, we also commented that in order to avert potential errors associated with the Creon product line, we recommended the Applicant revise the proprietary name so that the numerical modifiers, "5", "10", and "20", read "5,000", "10,000", and "20,000". The latter clearly represents the lipase component and are not numbers that would likely be misinterpreted as the number of capsules per dose.

In response to the "Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products- Submitting NDAs" dated April 2006, the Applicant has now reformulated Creon capsules. The new Creon capsule formulation will be available in three strengths: 6,000, 12,000 and 24,000 USP units of lipase.

DMEPA reviewed the name Creon® 6, 12, and 24 in OSE review # 2006-1123, dated April 9, 2007, and found the name unacceptable because the numerical suffixes (6, 12, 24) could be misinterpreted as the number of capsules to be taken, instead of the intended Applicant meaning to signify the lipase component of Creon. We recommended the Applicant revise the name to Creon 6,000, Creon 12,000 and Creon 24,000.

DMEPA also reviewed labels and labeling in OSE review # 2007-850 (dated April 16, 2007), # 2007-1220 (dated June 25, 2007), and # 2007-1531 (dated July 20, 2007).

The Applicant received an Approvable letter for this Application dated 16 August 2007 because the clinical effectiveness and short-term safety of Creon has not been established.

The Applicant revised the names to Creon 6,000, Creon 12,000 and Creon 24,000 to clearly reflect the lipase components per DMEPA's request in OSE review# 2006-1123.

After an internal meeting with the Division, it was determined that all three ingredients (lipase, protease and amylase) were active ingredients. The strength of just one ingredient (the lipase) cannot be represented without the strengths of the other ingredients. Thus, based on this information the proprietary name that we found acceptable was Creon. However, a Citizen Petition was submitted which states the proposed product and the currently marketed product are significantly different drug products and should have different proprietary names. Thus, until we fully evaluate the Citizen Petition, we will not make a final determination regarding the proposed trade name, Creon.

### **1.3 PRODUCT INFORMATION**

Creon capsules are orally administered and contain delayed-release, porcine-derived pancrelipase. Creon capsules are indicated for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency. Creon capsules are a pancreatic enzyme product prescribed to improve digestion of food, especially fat. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of Creon should be individualized and based on the degree of steatorrhea present, and the fat content of the diet. Patients may also be dosed on their actual body weight. Dosing recommendations are as follows:

#### **Children 4 Years and Older and Adults:**

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal or less than 4,000 lipase units/g fat ingested per day.

#### **Children Older than 12 Months and Younger than 4 Years:**

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal or less than 4,000 lipase units/g fat ingested per day.

#### **Infants (up to 12 months):**

Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

(b) (4)

Creon is available as capsules with the following enzymes:

	Creon® 6,000 Contains	Creon® 12,000 Contains	Creon® 24,000 Contains
Lipase, USP units	6,000	12,000	24,000
Free Proteases, USP units	19,000	38,000	76,000
Amylase, USP units	30,000	60,000	120,000

## 2 METHODS AND MATERIALS

### 2.1 FDA'S ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Since Creon is a currently marketed product, the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports related to Creon. DMEPA previously performed an AERS search for Creon in OSE review # 2006-1123, dated April 9, 2007. For this review, DMEPA performed an updated AERS search on December 4, 2008 for medication errors submitted for Creon since the aforementioned review. The MedDRA High Level Group Term "Medication Error" and Preferred Term "Pharmaceutical Product Complaint" along with the active ingredient (Pancrelipase), proprietary name (Creon), and verbatim terms "Creo%" and "Pancrel%" were used to perform the search.

The cases were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the case to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. Those cases that did not describe a medication error with Creon were excluded from further analysis. The cases that described a medication error possibly relevant to this review of this product were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

### 2.2 LABELS AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because our staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error prevention staff uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on 19 June 2008 the following revised labels and labeling for Division of Medication Error Prevention and Analysis review (see Appendices A-F for images):

- Foil Pouch Labeling (100 count and 250 count): 6,000 USP units, 12,000 USP units, and 24,000 USP units
- Container Label (100 count and 250 count): 6,000 USP units, 12,000 USP units, and 24,000 USP units
- Carton Labeling (100 count and 250 count): 6,000 USP units, 12,000 USP units, and 24,000 USP units
- Professional Sample Foil Pouch Labeling (12 count): 6,000 USP units, 12,000 USP units, and 24,000 USP units
- Professional Sample Container Label (12 count): 6,000 USP units, 12,000 USP units, and 24,000 USP units
- Professional Sample Carton Labeling (12 count): 6,000 USP units, 12,000 USP units, and 24,000 USP units
- Insert Labeling (no image)

### **3 RESULTS**

#### **3.1 AERS DATABASE SEARCH**

Our search yielded one new case. This case involved the wrong technique of administration. The reporter stated a 3 year old boy chewed Creon capsules instead of swallowing them, which

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<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

resulted in ulcers on the tongue, inside the mouth and lips. The outcome was unknown and no causality was stated.

### **3.2 PRESENTATION OF LIPASE STRENGTH ADJACENT TO THE PROPRIETARY NAME**

Numerical modifiers signifying the lipase strength of Creon (6000, 12000, 24000) are presented in conjunction with the proprietary name.

### **3.3 PRODUCT STRENGTH DIFFERENTIATION**

The product strengths lack prominence and are not well differentiated from one another.

### **3.4 LACK OF PRODUCT STRENGTHS ON CONTAINER LABELS**

The strengths are not always present on the principle display panel of the small container labels.

### **3.5 FOIL OVERWRAP LABELING**

We noted that the bottles are packaged in a foil pouch with the instructions to “keep bottle inside foil pouch until ready to dispense”.

### **3.6 LACK OF A MEDICATION GUIDE STATEMENT**

The labels and labeling do not have a Medication Guide statement.

### **3.7 INSERT LABELING**

In the Dosage and Administration section, there is not a statement indicating that the capsule and capsule contents should not be chewed or crushed and should be swallowed whole.

The product strength is present with only the lipase amount and does not include the amount of protease and amylase throughout the insert labeling.

## **4 DISCUSSION**

### **4.1 PRESENTATION OF LIPASE STRENGTH ADJACENT TO THE PROPRIETARY NAME**

Following a meeting with the Division, it was determined that lipase, protease and amylase were all active ingredients. Given this fact, one strength (lipase component) should not be represented without the strengths of the remaining components (protease and amylase). Therefore presenting only the lipase components in conjunction with the tradename Creon is misleading because it highlights only one active ingredient and not the collective ingredients.

### **4.2 DIFFERENTIATION OF THE PRODUCT STRENGTHS**

The labels and labeling for the three product strengths appear small and look identical. Although a colored vertical stripe appears on the right side of the labels and labeling, this alone will not distinguish the product strengths from one another. The “each capsule contains...” boxes represent the collective product strength on the principle display panel. Thus the size and prominence of the boxes (strengths) will need to be increased and distinguished from one another with different colors or some other means. Based on postmarketing experience, labels and labeling that are not adequately differentiated increase the risk of confusion and also

contribute to product selection errors that can lead to an over or under dose because the wrong strength is dispensed and administered.

#### **4.3 LACK OF PRODUCT STRENGTHS ON CONTAINER LABELS**

The container labels for the sample 12 count and trade size 100 count bottles are very small. We question why the Applicant has used such a small label for the sample 12 count bottle and the 100 count bottle. This small size does not allow for the product strengths to be listed in their entirety on the principle display panel of the container labels. The strengths appear on the side panel or under a “lift here” sticker. This is not sufficient because the information is hidden and not prominently displayed. The products cannot be adequately differentiated if the strengths do not appear on the principle display panel.

#### **4.4 FOIL OVERWRAP LABELING**

We noted that the bottles are packaged in a foil pouch with the instructions to “keep bottle inside foil pouch until ready to dispense”. We questioned how long an opened pouch would be stable for on a pharmacy shelf, since the dosing for Creon is individualized and patients may be prescribed a quantity other than what is supplied in the bottle (e.g. patient may be prescribed and dispensed 200 capsules, with 40 capsules remaining in the Creon bottle in a pouch that is opened, which may be used to fill another patient’s prescription). This concern regarding the stability of an opened pouch was conveyed to the Applicant by the Division. In response the Applicant submitted data to the Division showing that Creon is stable with or without the foil pouch for 16 months. Therefore, we concur with the Division that Creon will have an expiration date of 16 months listed on the labels and labeling.

#### **4.5 LACK OF A MEDICATION GUIDE STATEMENT**

Creon was determined to need a Medication Guide in order to ensure that patients are adequately informed about the risk of fibrosing colonopathy and the theoretical risk of viral infections from the porcine-derived products. However, the labels and labeling lack a statement informing healthcare practitioners to dispense the Medication Guide with Creon. Ensuring that the Medication Guide statement is prominently displayed will help to alert healthcare practitioners to provide this essential information along with Creon.

#### **4.6 LACK OF “DO NOT CRUSH OR CHEW STATEMENT”**

The container labels, carton labeling and Dosage and Administration section of the insert labeling does not include a statement indicating that the capsule and capsule contents should not be chewed or crushed. This information should be prominently displayed on the labels and labeling in order to prevent patients from advertently chewing the capsules or the capsule contents. This information should also be included in the Dosage and Administration section as this is the location where practitioners will typically be referring to regarding the correct administration of Creon.

#### **4.7 PRESENTATION OF PRODUCT STRENGTH IN INSERT LABELING**

The strengths are not presented in their entirety throughout the package insert. Following a meeting with the Division, it was determined that lipase, protease and amylase were all active ingredients. Given this fact, one strength (lipase) should not be represented without the strengths of the remaining components (protease and amylase).

### **5 CONCLUSIONS AND RECOMMENDATIONS**

The Label and Labeling Risk Assessment findings indicate the inclusion of the lipase strength being displayed with the proprietary name, the lack of differentiation of product strengths, the small size of the container labels, the lack of a Medication Guide statement and the lack of a caution statement regarding capsule administration on the container label and carton labeling and in the Dosage and Administration section introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risk we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

#### **5.1 COMMENTS TO THE DIVISION**

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Nina Ton, OSE project manager, at 301-796-1648.

#### **5.2 COMMENTS TO THE APPLICANT**

##### **5.2.1 All Labels and Labeling**

- A. We have determined that lipase, protease and amylase are all active ingredients. Given this fact, the strength of the lipase component should not be represented without the strengths of the remaining protease and amylase components because it is misleading and highlights only one active ingredient and not the collective ingredients. Therefore, delete the lipase strengths that appear beside the proprietary name.
- B. The “each capsule contains...” boxes represent the product strength on the principle display panel (see below). Thus the size and prominence of the boxes (strengths) will need to be increased and clearly differentiated from one another. Differentiation may be accomplished through the use of colors, shading, highlighting or some other means. Although presently there is a colored vertical stripe appearing on the right side of the labels and labeling, this alone will not distinguish the product strengths from one another. Based on postmarketing experience, labels and labeling that are not adequately differentiated increase the risk of confusion and also contribute to product selection errors that can lead to an over or under dose because the wrong strength is dispensed and administered.

(b) (4)

- C. Increase the size of the container labels (professional sample 12 count and trade 100 count) in order to allow the presentation of the strengths in their entirety to appear on the principle display panels. The small label size does not allow for the product strengths to be listed in their entirety on the principle display panel of the container labels (see example below). Although the strengths appear on the side panel or under a “lift here” sticker, this is not sufficient and does not prominently convey the product strengths. The products cannot be adequately differentiated if the strengths do not appear on the principle display panel.

(b) (4)

- D. Include the bolded statement: “Creon capsules and capsule contents should not be crushed or chewed. Capsules should be swallowed whole.” on the principle display panel of the container labels and carton labeling.
- E. Include one of the following statements: “Dispense the enclosed Medication Guide to each patient” or “Dispense the accompanying Medication Guide to each patient” on the principle display panel of the container labels and carton labeling. Use the first sentence (“enclosed”) if the Medication Guide will be inside the carton/container and the entire carton/container is considered a unit-of-use bottle that is dispensed to a single patient. Use the second sentence (“accompanying”) if the Medication Guide is glued to the container/carton, as a tear-off sheet, etc). Ensuring that the Medication Guide statement is prominently displayed will help to alert healthcare practitioners to provide this essential patient information along with Creon.

### 5.2.2 *Insert Labeling*

- A. In order to prevent patients from inadvertently chewing Creon capsules or the capsule contents, include the bolded statement “Creon capsules and capsule contents should not be crushed or chewed. Capsules should be swallowed whole.” to follow the sentence ‘Creon capsules should always be taken.....sufficient fluid.’ in the Dosage and Administration section.
- B. Revise the strengths throughout the insert labeling to clearly represent all of the strengths of the three active ingredients. Since the lipase, protease and amylase are all active ingredients, one strength (lipase) should not be represented without the strengths of the remaining components (protease and amylase). Additionally, throughout the insert labeling revise the table titles which refer to the strength of Creon from “Strength of Creon Capsules by Lipase Units” to read: “Strength of Creon Capsules”.

## **6 REFERENCES**

- 1. OSE Review #2006-1123, Proprietary Name Review for Creon; April 9, 2007;**
- 2. OSE Review # 2007-850; Label and Labeling Review for Creon; April 16, 2007;**
- 3. OSE Review # 2007-1531; Label and Labeling Review for Creon; July 20, 2007;**
- 4. Adverse Events Reporting System (AERS)**

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

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Deveonne Hamilton-Stokes  
2/19/2009 04:57:22 PM  
DRUG SAFETY OFFICE REVIEWER

Todd Bridges  
2/19/2009 05:14:17 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
2/20/2009 11:38:37 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
2/23/2009 08:02:56 AM  
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

**DATE:** December 3, 2008

**TO:** Cristi Stark, Regulatory Project Manager  
Ethan Hausman, Medical Officer  
Division of Gastroenterology Products

**FROM:** Khairy Malek, Medical Officer  
Good Clinical Practice Branch 1  
Division of Scientific Investigations

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch 1  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**NDA:** # 20-725

**APPLICANT:** Solvay Pharmaceuticals

**DRUG:** Creon (pancrelipase) Delayed-Release Capsules

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard

**INDICATIONS:** 1. Exocrine Pancreatic Insufficiency

**CONSULTATION REQUEST DATE:** 8/13/2008

**DIVISION ACTION GOAL DATE:** 12/12/2008

**PDUFA DATE:** 12/20/2008

## I. BACKGROUND:

Pancreatic exocrine insufficiency (PEI) is a syndrome characterized by poor absorption of fats, proteins and to a lesser extent, carbohydrates. This manifests primarily in patients with cystic fibrosis and/or chronic pancreatitis. PEI causes inhibition of digestion of starch, fat and protein which results in steatorrhea, abdominal pain and weight loss.

The new NDA is for a pancrelipase delayed-release drug in a capsule form. The particles are released in the stomach but do not dissolve due to the pH-resistant enteric coating which dissolves in the duodenum. The study selected for inspection was protocol S245.3.126 entitled, "A double-blind, randomized, multi-center, placebo-controlled, cross-over study to assess the efficacy and safety of pancrelipase delayed-release 24,000 unit capsule in subjects with pancreatic insufficiency due to cystic fibrosis." The study was designed to be held in an observation facility to ensure maximum compliance with regard to dietary and stool collection requirements. The sites inspected were selected due to having a relatively large number of subjects. In addition, site #23 was selected because the review division had concerns about "unspecified data quality issues."

## II. RESULTS (by Site):

Name of CI Location	Protocol #: and # of Subjects:	Inspection Dates	Final Classification
Bruce Trapnell, M.D. Site 25 U. of Cincinnati, Div. of Pulmonary Biology- 3333 Burnett Avenue Cincinnati, OH 45229	Protocol S245.3.126 6 Subjects	10/31- 11/6/2008	NAI
Barry Steinmetz, M.D. Site 23 Long Beach Medical Center 1760 Termini Ave., Suite 300 Long Beach, CA 90804	Protocol S245.3.126 6 Subjects	10/14- 10/27/2008	Pending (Preliminary classification: VAI)
Richard Arhens, M.D. Site 10 University of Iowa Hospitals and Clinics 200 Hawkins Dr., Iowa City IA 52242-1083	Protocol S245.3.126 7 Subjects	12/2- 12/5/2008	Pending (Preliminary classification: NAI)

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Bruce Trapnell, M.D.- Site #25  
University of Cincinnati, Division of Pulmonary Biology-3333 Burnett Ave.  
Cincinnati, OH 45229
  - a. What was inspected: A total of 6 subjects were enrolled in the study and all completed with no early terminations
  - b. General observations/commentary: The inspection revealed no violations of the federal regulations.
  - c. Assessment of data integrity: The data from this site are reliable and can be used in support of the NDA.

2. Barry Steinmetz, M.D.-Site # 23  
Long Beach Medical Center, 1760 Termini Ave., Suite 300, Long Beach, CA 90804

Observations noted for this site are based on preliminary evaluation of the establishment inspection report (EIR), which is currently under review. An inspection summary addendum will be generated if conclusions change upon completion of our review.

- a. What was inspected: At this site, 6 subjects were screened, but only 2 subjects were randomized and completed the study.
- b. General observations/commentary: There were a number of violations observed at this site. The significant inspectional findings are as follows:
  - The subjects' diaries did not include accurate documentation of the medications given to the subjects, the fat intake per day, the protein intake per day, and the total calorie intake per day. Review of the diaries reveals multiple corrections performed after the study was completed with no documentation of the reasons for the changes.
  - The medications were not dispensed accurately and at the proper time
  - The diet requirements were not followed as per protocol.
  - Certain adverse events were not reviewed by the clinical investigator (CI) in a timely fashion.
  - The CI did not use the current protocol but instead used the original protocol. He

stated that he was not aware of the existence of the correct protocol amendment that he should have used until after the study was completed because the amendment was misdirected to the wrong office.

- Drug accountability records for both subjects were not accurate. For example, records for subject NAC note that 200 pills were dispensed, 160 pills were used, and 79 pills returned. This resulted in a discrepancy of 39 pills such that we are unable to determine the total amount of drug used by this subject. A similar discrepancy was noted for subject RCC, resulting in a discrepancy of 4 pills.
- c. Assessment of data integrity: Data from this site do not appear acceptable in support of the respective indication, as review of the site revealed protocol deviations that impact the primary efficacy endpoint. Specifically, review of the medication counts revealed discrepancies for both subjects such that it is not clear that the subjects were compliant with the protocol requirement. Additionally, the subjects' diets did not meet the protocol requirements for fat content and was over the specified amount.
3. Richard Arhens, M.D.- Site # 10  
University of Iowa Hospitals and Clinics, 200 Hawkins Dr., Iowa City, IA 52242

Observations noted for this site are based on the Form FDA 483 and communications with the field investigator; the EIR has not yet been received. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. What was inspected: The field investigator reviewed the records of all the subjects in the study.
- b. General observations/commentary: The field investigator did not find any violations of federal regulations.
- c. Assessment of data integrity: The data from this site can be used in support of the NDA.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from the sites of Dr. Trapnell and Dr. Arhens are considered reliable and can be used in support of the NDA. Data from the site of Dr. Steinmetz are not considered reliable for the reasons discussed above, and we recommend that the data generated at this site not be used in support of the pending application.

Khairy Malek, M.D.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

#### CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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Constance Lewin  
12/3/2008 05:40:14 PM  
MEDICAL OFFICER  
Entered into DFS on behalf of Dr. Khairy Malek.

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** November 24, 2008

**To:** Cristi Stark, DGP, ODEIII

**From:** Shefali Doshi, Consumer Safety Officer, DDMAC  
Kathleen Klemm, Regulatory Review Officer, DDMAC

**Subject:** NDA 20-725  
DDMAC labeling comments for CREON (pancrelipase) CAPSULES

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DDMAC has reviewed the proposed PI and PPI for CREON (dated 11/20/08 in the EDR) and the proposed carton and container labels (dated 08/19/08 in the EDR) and offers the following comments:

### PI

1. General comment – DDMAC notes that there are inconsistencies between the information presented in the PI and the information presented in the Highlights section. DDMAC recommends that the final version of the label be revised to present consistent information throughout all sections of the PI.

2. Lines 30-31 of the proposed PI state, ‘ (b) (4)



3. Lines 47-50 of the proposed PI state the following:

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents added to a small amount of low acidic soft food with a pH of 4 or less, such as applesauce, at room temperature. The Creon-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion.

Line 80 of the proposed PI presents additional information, stating that, “CREON should not be crushed or chewed, or mixed in foods having a pH greater than 4.” Could you clarify for DDMAC the meaning of low acidic soft food with a pH of 4 or less? The use of the terms “low acidic” in conjunction with “pH 4 or less” is confusing. Also, is the type of juice that a patient drinks of issue, given that orange juice is acidic?

4. Line 66 of the proposed PI states, ‘ (b) (4)  

5. Lines 67-68 of the proposed PI state the following:  
 (b) (4)  
 (b) (4)
6. General comment – DDMAC notes that warnings 5.2 – 5.4 all begin with the term “Potential”. We feel the use of this term is misleading because it minimizes the important risk information that follows. We recommend that this term be deleted.
7. DDMAC notes that lines 90-100 include a comment that this section will be revised after the AC. Therefore, DDMAC will not provide comment on this section at this time.
8. General comment – DDMAC notes that throughout the Adverse Reactions Section, the term “enumerates” is used. We find the use of this term overly fanciful and recommend it be revised. Specifically, line 113 could be revised to read, “Table 2 lists treatment-emergent adverse events . . .” or “Table 2 presents data on ...”
9. Line 121 of the proposed PI presents “Table 2: Treatment-Emergent Adverse Events in Cystic Fibrosis Patients.” DDMAC recommends that the adverse events that occurred at a higher frequency in the placebo group compared to the Creon group be deleted.

10. Lines 121-122 of the proposed PI state, (b) (4)

[Redacted]

11. Line 126 of the proposed PI states, (b) (4)

[Redacted]

12. Lines 139-140 of the proposed PI state, (b) (4)

[Redacted]

13. Similar statements are made on lines 140-141, line 151 and lines 155-156, (b) (4)

[Redacted]

14. Lines 149-151 of the proposed PI state, (b) (4)

[Redacted]

15. Lines 157-159 of the proposed PI state the following:

[Redacted] (b) (4)

[Redacted] (b) (4)

16. Lines 161-163 of the proposed PI state the following:

[Redacted] (b) (4)

[Redacted] (b) (4)

17. DDMAC notes that section 6.3 – Postmarketing Experience (lines 164-166) will be updated and therefore has no comments on this section at this time.

18. DDMAC also notes that section 8.1 – Use in Pregnancy (lines 172-183) will be updated and therefore has no comments on this section at this time.

19. Lines 189-196 (Section 8.3 – Pediatric Use) present seemingly contradictory information from what is discussed in the Dosage and Administration section. [Redacted] (b) (4)

[Redacted]

20. Lines 234-235 of the proposed PI state, [Redacted] (b) (4)

[Redacted]

21. Lines 270-286 of the proposed PI present references, and we also note that endnotes are presented throughout the PI. We recommend that all endnotes for references to published literature be deleted. These articles may include information which is not consistent with the approved labeling, and the sponsor may use this information to misleadingly promote their drug.

### **Carton and Container Labels**

DDMAC notes the comments submitted by Yana Mille and has no additional comments at this time.

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### **PPI**

#### **1. Omission and Minimization of Risk**

##### **DDMAC comment:**

*The proposed PPI minimizes the risk of CREON because it omits the Warning and Precaution regarding fibrosing colonopathy. We recommend that this risk be included, using consumer-friendly language, and with an emphasis commensurate with the risk.*

#### **2. What is CREON Capsules?**

- 

(b) (4)

##### **DDMAC comment:**

*According to the Indications and Usage section of the PI, “CREON<sup>®</sup> (Pancrelipase Delayed-Release Capsules) is indicated*

(b) (4)

*(underline emphasis added).*

*We recommend that the indication in the PPI be consistent with the indication in the PI (i.e., convey “...caused by cystic fibrosis or other conditions”).*

3. **What should I tell my healthcare provider before starting CREON capsules?**

**DDMAC comment:**

*We note that the Highlights section and the Warnings and Precautions section of the PI also state that caution should be exercised also in patients with renal impairment, hyperuricemia, and neutropenia. We recommend that these conditions also be listed, in consumer-friendly language.*

*We also recommend conveying that patients should notify their physician if they are pregnant or thinking of becoming pregnant during treatment with CREON, as conveyed in the Use in Specific Populations section of the PI.*

4. **How should I take CREON Capsules?**

-  (b) (4)

**DDMAC comments:**

*We feel that this section **oversimplifies** the complex dosage and administration instructions for CREON. We do not feel that the statement,*

 (b) (4)  
*We recommend that this section of the PPI be revised.*

*We noticed that the instructions conveyed in this section of the PPI comes from the Administration section of the PI (section 2.2); however, we are unsure what patients these instructions are applicable to. Also, it is unclear in this section of the PPI as to when CREON should be taken (during meals, during snacks). We note that in the Dosage section of the PI for infants up to 12 months of age, instructions are given regarding the amount of CREON to be given per formula amount/ breast-feeding. For*

children less than four years of age, instructions are given in the Dosage section of the PI regarding the amount of CREON to be given per meal. For those greater than four years of age, the amount of CREON to be given during each meal or snack is conveyed in the Dosage section of the PI.

Would it be helpful to use the term “spheres” in parentheses when first discussing the contents of the capsules (“Do not crush or chew the capsules or their content”) because the term “spheres” is used in steps C and D?

We recommend including, in consumer-friendly language, the reason why CREON Capsules should not be crushed or chewed, placed on foods with a particular pH, and why it should be followed with water or juice (if emptying the contents of the capsule onto food), as conveyed in the Dosage and Administration, Warnings and Precautions section, and Patient Counseling Information sections of the PI (i.e., these actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity).

We note that the PPI (and Patient Counseling Information section of the PI) provides examples of soft foods to sprinkle the spheres onto with the statement, “If you have difficulty swallowing the capsules, carefully open the capsules and sprinkle the contents on a small amount of room temperature applesauce, pudding, mashed or pureed bananas or carrots as described below” (underline emphasis added). However, we noticed that the Dosage and Administration section of the PI has deleted pudding, mashed or pureed bananas or carrots.

Given the importance of the pH range of the soft food that the spheres should be added to, we feel that patients should be provided with examples of such foods, if possible. Is there a particular reason why pudding, mashed or pureed bananas or carrots was deleted from the Dosage and Administration section of the PI? Should it be deleted from the PPI and Patient Counseling Information section of the PI?

**5. What are the possible side effects of CREON capsules?**

**DDMAC comment:**

We note that the most common side effects are listed in the PPI; however, we recommend that these most common side effects be consistent with those that will be listed in the Highlights section of the PI.

Thank you for the opportunity to comment on this proposed label.

If you have any questions on the comments for the PI, please contact Katie Klemm at 301.796.3946 or [Kathleen.Klemm@fda.hhs.gov](mailto:Kathleen.Klemm@fda.hhs.gov).

If you have any questions on the comments for the PPI, please contact Shefali Doshi at 301.796.1780 or [Shefali.Doshi@fda.hhs.gov](mailto:Shefali.Doshi@fda.hhs.gov).

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/s/

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Shefali Doshi  
11/24/2008 02:43:56 PM  
DDMAC REVIEWER

<b>MEMORANDUM</b>	<b>Division of Medication Errors and Technical Support</b> <b>Office of Surveillance and Epidemiology</b> <b>(HFD-420; White Oak Bldg. 22, Mail Stop 4447)</b> <b>Center for Drug Evaluation and Research</b>
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**TO:** Joyce Korvick, MD  
Acting Director, Division of Gastroenterology Products, HFD-180

**THROUGH:** Todd D. Bridges, RPh, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**FROM:** Deveonne Hamilton-Stokes, RN, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**DATE:** July 16, 2007

**SUBJECT:** **DMETS Label and Labeling Review**  
Drug: Creon ® 6,000  
Creon ® 12,000  
Creon ® 24,000  
(Pancrealipase Delayed-release Capsules, USP)  
6,000 USP units, 12,000 USP units and 24,000 USP units  
NDA #: 20-725  
Sponsor: Solvay Pharmaceuticals

**PROJECT #:** 2007-1531

This memorandum is in response to a June 29, 2007, request from the Division of Gastroenterology Products for review of the revised container labels and carton labeling for Creon. The label and labeling revisions were made in response to DMETS' OSE Review # 2007-850, dated April 16, 2007.

DMETS acknowledges that the sponsor has addressed most of our recommendations. However, upon review of the sponsor's response and revised labels and labeling for Creon, we have identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety. Additionally, the sponsor states the plan for transition of the Creon products was submitted on April 11, 2007. However, we cannot locate this information in the response provided by the sponsor on this date. Please make this information available to DMETS for review and comment.

**A. CONTAINER LABEL**

1. The sponsor utilizes the same blue font color for the "Creon" portion of the proprietary name and for all three product strengths (see below). Although the sponsor uses differing color strips (blue, green, brown) to differentiate the strengths, DMETS feels this does not provide an adequate difference to minimize the types of selection errors we have encountered with medication errors. We recommend that each numerical portion of the proprietary name (i.e., 6,000, 12,000, 24,000) have a different and distinguishable color from the "Creon" portion of the proprietary name. Additionally, ensure that the color of the vertical strip is the same color as the numerical portion of the proprietary name of the corresponding product strength to increase differentiation.

2.

(b) (4)

3. Increase the size of the numerical portion of the proprietary name, so that it is the same size as "Creon", as this will be used to distinguish these products from one another.
4. Delete or relocate the graphic image above the proprietary name. In its current location it distracts from important information such as the proprietary name and the strength.
5. Ensure the statement "usual dose" is used in conjunction with the statement "See package insert" on the professional sample containers and on the 100 count Creon 6,000, if space permits.
6. Revise the lift here statement to read: "Lift here for Active ingredients", if space permits.

#### C. FOIL POUCH LABELING

1. See Container Comments A1 through A4.
2. We note each pouch contains the same violet color strip. This may also contribute to visual similarity of each pouch leading to selection errors. In revising the color differentiation scheme for the product outlined in comment A1, consider the removal of the violet strip that appears on all strengths or revise it to match the color chosen in the new scheme so that there are no color overlaps on any pouch.

#### D. CARTON LABELING

See Container A1 through A4.

We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have any questions concerning this memorandum, please contact Tanya Clayton, OSE Project Manager, at 301-796-0871.

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/s/

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Deveonne Hamilton-Stokes  
7/20/2007 05:30:08 PM  
DRUG SAFETY OFFICE REVIEWER

Todd Bridges  
7/22/2007 05:23:10 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
7/23/2007 05:08:35 PM  
DRUG SAFETY OFFICE REVIEWER

# MEMORANDUM

**Division of Medication Errors and Technical Support  
Office of Surveillance and Epidemiology  
HFD-420; WO22, Mail Stop 4447  
Center for Drug Evaluation and Research**

**To:** Joyce Korvick, MD  
Acting Director, Division of Gastroenterology Products  
HFD-180

**Through:** Todd Bridges, RPh, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Carol A. Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Deveonne Hamilton-Stokes, BSN, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**Date:** June 5, 2007

**Subject: Proposed Capsule Imprints**  
Drug: Creon 6,000  
Creon 12,000  
Creon 24,000  
(Pancrelipase Delayed-release Capsules, USP)  
6,000 USP units, 12,000 USP units and 24,000 USP units  
NDA#: 20-725  
Sponsor: Solvay Pharmaceuticals

**Review #:** 2007-1220

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This memorandum is written in response to the May 30, 2007, request from the Division of Gastroenterology Products (HFD-180), for assessment of the proposed capsule imprints for Creon 6,000, Creon 12,000, and Creon 24,000. The sponsor has proposed capsule imprints of “CREON 6”, “CREON 12”, and “CREON 24” for the Creon 6,000, Creon 12,000, and Creon 24,000 products, respectively.

DMETS notes that the currently marketed Creon capsules are imprinted with “SOLVAY” and the four digit middle portion of their respective NDC number; the last two digits of which seem to be product specific to the strength (e.g., “1205” for Creon 5, “1210” for Creon 10, and “1220” for Creon 20).

Instead of the proposed imprints of just a portion of the strength, DMETS recommends the use of imprints which are a continuation of the line of imprints utilized for currently marketed Creon products that utilize the company name and NDC #. The drug name is also acceptable in lieu of the company name (e.g., “CREON” and “1206” for Creon 6000, “CREON” and “1212” for Creon 12,000, and “CREON” and “1224” for Creon 24,000). This consistency should help to minimize confusion and potential error among healthcare professionals and patients especially during the time period when all six strengths are marketed. This consistency will help minimize confusion because it is an identification scheme that practitioners are aware of.

We would be willing to meet with the division for further discussion, if needed. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. If you have any questions concerning this memorandum, please contact Tanya Clayton, OSE Project Manager, at 301-796-0871.

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/s/

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Deveonne Hamilton-Stokes  
6/25/2007 03:59:15 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
6/27/2007 02:13:05 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
6/27/2007 02:31:14 PM  
DRUG SAFETY OFFICE REVIEWER

<b>MEMORANDUM</b>	<b>Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology (HFD-420; White Oak Bldg. 22, Mail Stop 4447) Center for Drug Evaluation and Research</b>
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**TO:** Brian Harvey, M.D, Ph.D.  
Director, Division of Gastroenterology Products, HFD-180

**THROUGH:** Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**FROM:** Deveonne Hamilton-Stokes, RN, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**DATE:** January 25, 2007

**SUBJECT:** **DMETS Label and Labeling Review**  
Drug: Creon ® 6  
Creon ® 12  
Creon ® 24  
(Pancrealipase Delayed-release Capsules, USP)  
6,000 USP units, 12,000 USP units and 24,000 USP units  
NDA #: 20-725  
Sponsor: Solvay Pharmaceuticals

**PROJECT #:** 2007-850

This memorandum is in response to a April 9, 2007, request from your Division for review of the professional sample container labels and carton labeling for Creon (NDA 20-725) submitted on April 3, 2007. DMETS reviewed the trade label and labeling in OSE review 2006-1123 dated December 29, 2006. DMETS also made recommendations in that review with regards to the proprietary name.

In the review of the labels and labeling, DMETS has identified the following areas of improvement, which may minimize potential user error.

**A. GENERAL COMMENTS**

1. Revise the name as recommended in DMETS previous review 2006-1123 on all labels and labeling to clearly reflect the lipase component i.e. Creon 6,000, Creon 12,000 and Creon 24,000.
2. The font color used for the text on the Creon 6 ( (b) (4) ) and Creon 12 ( (b) (4) ) is too light and is difficult to read on the contrasting white background. Revise the colors in order to increase readability and provide sufficient color contrast.
3. Since the bottles are unit-of-use, please ensure they have child-resistant caps (CRC) to be in compliance with the Poison Prevention Act.

**B. FOIL POUCH LABELING PROFESSIONAL SAMPLE**

1. The established name appears less than ½ the size of the proprietary name. Increase the prominence of the established name so that it is at least ½ the size of the proprietary name per

21 CFR 201.10(g)(2).

2. Relocate the statement "KEEP BOTTLE INSIDE FOIL POUCH UNTIL READY TO TAKE." to above the dosage and administration statement to ensure that this important information is not missed.
3. Decrease the UNIT-OF-USE and Rx only statement, as they are as prominent as the trade name and more prominent than the established name and strength.
4. Ensure the lettering of the foil pouch is readable as we are unable to ascertain, since the draft labeling we reviewed is in black and white.

#### C. CONTAINER LABELING PROFESSIONAL SAMPLE

1. See General Comments A1 and A2.
2. As currently presented the established name is listed as pancrealipase delayed release capsules. However, information pertaining to the actual amount of lipase, protease and amylase is not presented. Add the strength statement: Each capsule contains enteric coated spheres of: Lipase 6,000 USP Units, Free Protease 19,000 USP Units and Amylase 30,000 USP units. This will provide healthcare providers with the actual amount of these individual components.

#### D. CARTON LABELING PROFESSIONAL SAMPLE

See General Comments A1 and A2

We would be willing to meet with the Division for further discussion, if needed. If you have any questions concerning this memorandum, please contact Tanya Clayton, Project Manager, at 301-796-0871.

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/s/

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Deveonne Hamilton-Stokes  
4/16/2007 03:44:28 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
4/17/2007 11:55:02 AM  
DRUG SAFETY OFFICE REVIEWER  
Also signing for Carroll Holquist, DMETS Director