



NDA 20-725

NDA APPROVAL

Solvay Pharmaceuticals
Attention: Donald A. Ruggirello
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Ruggirello:

Please refer to your new drug application (NDA) dated July 31, 1997, received August 1, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Creon (pancrelipase) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated September 17, 1999, January 25, 2001, March 15, 2001, August 1, 2001, February 1, 2002, March 22, 2002, December 16, 2002, January 15, 2003, June 20, 2003, June 27, 2003, July 1, 2003, July 9, 2003, August 4, 2003, August 7, 2003, August 8, 2003, August 25, 2003, August 28, 2003, September 11, 2003, September 18, 2003, October 3, 2003, October 17, 2003, October 21, 2003, November 5, 2003, July 22, 2004, September 7, 2004, October 21, 2004, March 8, 2005, October 25, 2005, November 17, 2006, January 24, 2007, February 5, 2007, February 6, 2007, February 14, 2007, February 27, 2007, March 2, 2007, March 6, 2007, March 12, 2007, March 15, 2007, March 19, 2007, March 21, 2007, March 23, 2007, April 2, 2007, April 3, 2007, April 11, 2007, April 12, 2007, April 13, 2007, April 17, 2007, April 18, 2007, April 19, 2007, April 20, 2007, May 11, 2007, May 14, 2007, May 23, 2007, June 26, 2007, July 12, 2007, July 31, 2007, August 10, 2007, August 20, 2007, November 8, 2007, December 14, 2007, February 4, 2008, February 22, 2008, June 19, 2008, August 12, 2008, August 22, 2008, August 25, 2008, September 5, 2008, September 8, 2008, September 16, 2008, September 18, 2008, September 22, 2008, November 3, 2008, November 6, 2008, November 18, 2008, November 20, 2008, November 24, 2008, December 5, 2008, December 18, 2008, February 6, 2009, February 16, 2009, February 24, 2009, March 2, 2009, March 3, 2009, March 4, 2009, March 6, 2009, March 9, 2009, March 12, 2009, March 13, 2009, April 14, 2009 and April 17, 2009.

The June 19, 2008 submission constituted a complete response to our August 16, 2007 action letter.

This new drug application provides for the use of Creon (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 20-725."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels, submitted on April 14, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 20-725.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

We are waiving the pediatric study requirement for ages 0 months to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually

diagnosed below 1 month of age, so there would not be enough eligible patients in this age range to study.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

For administrative purposes, all submissions related to this pediatric requirement must be clearly designated “**Required Pediatric Assessments**”.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies:

2. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Creon (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 20, 2010
Study Completion Date:	by January 1, 2021
Final Report Submission:	by June 20, 2021

3. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Creon (pancrelipase) Delayed-Release Capsules.

The timetable you submitted on April 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 20, 2010
Study Completion Date:	by January 1, 2021

Final Report Submission: by June 20, 2021

Submit the protocols to your IND 47,546, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirement:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitments in your submissions dated March 6, 2009 and April 17, 2009. These commitments are listed below.

4. Solvay commits to complete Study S245.3.124, a multi-center, randomized, double-blind, placebo-controlled trial of the safety and effectiveness of Creon (pancrelipase) Delayed-Release Capsules in patients 18 years and older with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. The study will have an open-label 6-month extension.

Final Report Submission: by September 20, 2009

5. Solvay commits to perform routine monitoring of the enveloped viral load entering the manufacturing process. The control strategy will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with action limits and specifications.

Final Protocol Submission: by October 20, 2009

Final Report Submission: by October 20, 2010

6. Solvay commits to continue developing sensitive qPCR assays that provide adequate assurance that process capability for the inactivation of non-enveloped viruses is not exceeded. The revised assay and assay validation data, together with new action limits, will be submitted to the Agency.

Final Report Submission: by October 20, 2009

7. Solvay commits to develop and implement specifications for infectious porcine circoviruses (PCV) 1 and 2 in the drug substance. The proposed methods, including relevant method validation, will be submitted to the Agency.

Final Report Submission: by October 20, 2010

8. Solvay commits to assess the risk to product quality associated with porcine hokovirus, and submit a control strategy for mitigating this risk to product quality.

Final Report Submission: by October 20, 2009

9. Solvay commits to revise the acceptance criteria for the viral infectivity tests for swine vesicular disease virus (SVDV), encephalomyocarditis virus (EMCV) and porcine rotavirus (Rota) to “none detected.”

Final Report Submission: by July 1, 2009

10. Solvay commits to provide detailed plans for its animal disease surveillance program and continued risk assessment evaluation for source animals. The proposed plans will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these plans will be implemented.

Final Report Submission: by October 20, 2009

11. Solvay commits to assess the risk to product quality due to the potential infection of swineherds with parasites.

Final Report Submission: by October 20, 2009

12. Solvay commits to provide a detailed description of its plans for preventing cross-contamination with material from other species, particularly with ruminant tissues.

Final Report Submission: by October 20, 2009

Submit clinical protocols to your IND 47,546 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled “**Postmarketing Commitment Protocol**”, “**Postmarketing Commitment Final Report**”, or “**Postmarketing Commitment Correspondence.**”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Creon (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweighs the risk of fibrosing colonopathy with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients. The REMS, once approved, will create enforceable obligations.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Creon (pancrelipase) Delayed-Release Capsules poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Creon (pancrelipase) Delayed-Release Capsules. FDA has determined that Creon (pancrelipase) Delayed-Release Capsules is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Creon (pancrelipase) Delayed-Release Capsules. In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Creon (pancrelipase) Delayed-Release Capsules.

Your proposed REMS, submitted on April 17, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the Timetable for Submission of Assessments of the REMS included in your April 17, 2009 submission.

Your REMS assessment plan should include an evaluation of:

- a. Patients' understanding of the serious risks of Creon (pancrelipase) Delayed-Release Capsules
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and

21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 20-725 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 20-725
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 20-725
(NEW INDICATION FOR USE)
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Cristi Stark, Regulatory Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:

Package Insert

REMS (including Medication Guide)

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

/s/

Julie Beitz

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