CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-725

PHARMACOLOGY REVIEW(S)
Reviewer: David B. Joseph, Ph.D.
Acting Pharmacology Team Leader, DGP

Sponsor and Address: Solvay Pharmaceuticals, Inc.
Marietta, Georgia

Drug: CREON®

Other Names: Pancrelipase Delayed-Release Capsules

Drug Class: digestive aid for treatment of exocrine pancreatic insufficiency/pancreatic enzyme preparation

Date of Submission: June 19, 2008

Date of CDER CDR Receipt: June 20, 2008

Date of Review: November 18, 2008

Submission Contents: No nonclinical information was submitted.

Introduction:

Creon® (Pancrelipase Delayed-Release Capsules) is a pancreatic enzyme product that was submitted for marketing approval under the amendment dated November 17, 2006 (Complete Response to Not Approvable Letter). Creon® is distinct from Creon® Minimicrospheres® (Pancrelipase Delayed-Release Capsules), a product that is marketed in the United States without a NDA or OTC monograph. Creon® Minimicrospheres® was deemed as not approvable after the initial review of NDA 20,725 (letter to Sponsor dated October 9, 2003). In the second review cycle, Creon® (the to-be-marketed product) was deemed as approvable (letter to Sponsor dated August 16, 2007). The approvable action was based on clinical and CMC deficiencies. All nonclinical studies were reviewed in the pharmacology/toxicology reviews from the first and second review cycles (Pharmacology/Toxicology reviews of NDA 20,725 dated September 4, 2003 and June 25, 2007). The present review is limited to the proposed labeling.

LABELING:

The nonclinical portions of the proposed labeling include the “INDICATIONS AND USAGE” section under the “HIGHLIGHTS OF PRESCRIBING INFORMATION”, “Pregnancy” subsection, “Mechanism of Action” subsection, and the “Carcinogenesis, Mutagenesis,
Impairment of Fertility” subsection. Each of these labeling sections/subsections is reviewed below.

**Sponsor’s Proposed Version:**

**“HIGHLIGHTS OF PRESCRIBING INFORMATION”**

**“INDICATIONS AND USAGE**

CREON Capsules is a pancrelipase indicated for the treatment of maldigestion in patients with exocrine pancreatic insufficiency.”

**Evaluation:** The term “pancrelipase” is used inappropriately as the established pharmacologic class for Creon®. However, “pancrelipase” is an appropriate non-proprietary name for the drug substance. Pancrelipase is described by the USP Dictionary (2008) as a concentrate of pancreatic enzymes standardized for lipase content. Creon® and other products containing pancrelipase have a long history of successful treatment of patients with EPI (exocrine pancreatic insufficiency). The ability of pancrelipase to improve digestive function has also been demonstrated in preclinical studies. The Sponsor previously submitted two studies using the minipig model of EPI. In one study, Creon® Minimicrospheres® (the currently marketed product) produced a dose-dependent improvement in the digestion of fat and dry matter in pancreatic duct-ligated minipigs. In the other study, Creon® Minimicrospheres® produced a dose-dependent increase in the digestion of fat, protein, and starch in the same model of EPI. The increase in daily fecal output was partially reversed by Creon® Minimicrospheres® (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). The term “digestant” accurately describes the pharmacologic effect of pancreatic enzyme preparations such as Creon®, and is therefore considered to be a scientifically valid pharmacologic class. However, the term “pancreatic enzyme preparation” is commonly used as a classification for products that contain pancreatic enzymes of porcine or bovine origin. Since “pancreatic enzyme preparation” is an accurate description of the chemical nature and origin of the drug, this term is also considered to be a scientifically valid pharmacologic class. Both “digestant” and “pancreatic enzyme preparation” are terms that provide useful information about Creon®, and are each considered as a clinically meaningful pharmacologic class. Therefore, it is recommended that the established pharmacologic class under the “INDICATIONS AND USAGE” section of the Highlights should be “pancreatic enzyme preparation digestant”.

**Recommended Version:**

**“HIGHLIGHTS OF PRESCRIBING INFORMATION”**

**“INDICATIONS AND USAGE**

CREON Capsules is a pancreatic enzyme preparation digestant indicated for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency.”
Sponsor’s Proposed Version:

“8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C

Evaluation: The use of the term (b) (4) is inappropriate.

Therefore, “pancrelipase” should be substituted for (b) (4).

Recommended Version:

“8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C

Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pancrelipase should be given to a pregnant woman only if clearly needed.”

Sponsor’s Proposed Version:

“12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)
Evaluation: The information stated in this subsection is accurate. However, changes in the language are recommended, as shown below.

Recommended Version:

“12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

The porcine pancreatic enzymes in CREON Capsules are enteric-coated to resist gastric destruction or inactivation. The enzymes catalyze the hydrolysis of fats to monoglycerol, glycerol, and fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars, thereby acting as a replacement for digestive enzymes physiologically secreted by the pancreas.”

Sponsor’s Proposed Version:

“13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed.”
SUMMARY AND EVALUATION:

Creon® (Pancrelipase Delayed-Release Capsules) is a pancreatic enzyme product that was submitted for marketing approval under the amendment dated November 17, 2006 (Complete Response to Not Approvable Letter). Creon® is distinct from Creon® Minimicrospheres® (Pancrelipase Delayed-Release Capsules), a product that was deemed as not approvable after the initial review of NDA 20,725 (letter to Sponsor dated October 9, 2003). Creon® Minimicrospheres® is marketed in the United States without a NDA or OTC monograph. The Sponsor intends to discontinue marketing of Creon® Minimicrospheres®, after obtaining approval for Creon® (the to-be-marketed product). Creon® was deemed as approvable in the second review cycle (letter to Sponsor dated August 16, 2007).

Because of the long history of clinical use of pancreatic enzyme products, toxicology studies of the drug substance are usually not needed, particularly for porcine-derived pancrelipase. The preclinical review of pancreatic enzyme products is generally directed to safety information about the excipients, given that patients with exocrine pancreatic insufficiency may require daily ingestion of a large quantity of product (i.e. capsules) to achieve adequate digestion. Preclinical information about the excipients in Creon® Minimicrospheres® was previously reviewed. No major safety issues were identified, and the product was recommended for approval (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). However, the Sponsor is now seeking approval of a new formulation, Creon®, which is distinguished from Creon® Minimicrospheres® by qualitative and quantitative differences in the excipient content, in addition to manufacturing changes for the drug substance. Therefore, the preclinical information in the original NDA submission cannot be used as the sole basis for supporting the approval of Creon®, from a preclinical viewpoint. Safety information about the Creon® excipients that are not present in Creon® Minimicrospheres® was reviewed. This information was deemed as adequate to support the safe use of Creon® in humans, even at the estimated maximum dose level (Pharmacology/Toxicology review of NDA 20,725 dated June 25, 2007). For the Creon® excipients that are also present in Creon® Minimicrospheres®, the previously reviewed safety information (i.e., animal toxicity studies, regulatory information, and safety evaluations from health authorities) provides a reasonable assurance of safety (Pharmacology/Toxicology review of NDA 20,725 dated June 25, 2007).

RECOMMENDATIONS:

From a preclinical viewpoint, the application is recommended for approval, with the provision that the labeling be changed as described in the “LABELING” section of this review.

David B. Joseph, Ph.D.                   Date
Acting Pharmacology Team Leader
Division of Gastroenterology Products
cc:
Orig NDA 20,725
DGP
DGP/CSO
DGP/Dr. Joseph

DJ/dbj: 11/18/08
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/s/

David Joseph
11/18/2008 10:50:13 AM
PHARMACOLOGIST
ADDENDUM TO PHARMACOLOGIST'S REVIEW OF
NDA 20,725 DATED JUNE 25, 2007

Reviewer: David B. Joseph, Ph.D.

Date: August 13, 2007

As stated on page 14 of the review dated June 25, 2007, the “Pregnancy” subsection was omitted from the proposed labeling. My comments on this labeling omission are shown below.

“However, the pharmacology/toxicology reviewer agrees that a “Pregnancy” subsection is not needed in the labeling, since the drug fulfills the regulatory requirements for the omission of this subsection. 21 CFR 201.57 (April 1, 2007) states that the “Pregnancy” subsection “may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus”. It is reasonable to assume that the digestive enzymes present in the drug substance are not absorbed in their original state, given that these are large proteins. However, it is likely that the enzymes are digested in the small intestine and absorbed as short-chain peptides and individual amino acids. A preclinical study demonstrated that pancreatic lipase, procolipase/colipase, and trypsin were not absorbed after oral administration of Creon® Minimicrospheres® (the presently marketed product) in pancreatic duct-ligated pigs or in pancreatectomized pigs (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). These results support the omission of the “Pregnancy” subsection.”

As per the recommendation of Dr. Abigail Jacobs (ODE Associate Director for Pharmacology and Toxicology, Office of New Drugs), I am now recommending that a “Pregnancy” subsection should be included in the labeling. Although it is unlikely that the digestive enzymes in pancrelipase are absorbed in their original state, the potential for indirect harm to the fetus should be considered, as indicated in the regulation cited above. In a Memo to NDA 20,725 dated August 10, 2007, Dr. Jacobs noted the clear presence of systemic effects in both animals and humans. These effects include signs of liver toxicity and the incidence of thyroid concretions in dogs treated orally with pancrelipase (Pharmacology/Toxicology Review of NDA 20,725 dated September 4, 2003), liver effects and hyperglycemia in the submitted clinical studies, and published reports of hyperuricemia and uricosuria in humans. Given the evidence of systemic effects, it is reasonable to assume that pancrelipase has a potential to produce indirect harm to the fetus. Therefore, a “Pregnancy” subsection in the labeling is clearly warranted. Since no reproductive toxicity studies of pancrelipase have been performed, and there are no adequate and well-controlled studies in humans, the appropriate pregnancy category is “C”.
Recommended Pregnancy Labeling

“8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C

Animal reproduction studies have not been conducted with CREON. It is also not known whether CREON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CREON should be given to a pregnant woman only if clearly needed.”

David B. Joseph, Ph.D.  
Pharmacologist, HFD-180  
Date

Comment:

Sushanta K. Chakder, Ph.D.  
Acting Supervisory Pharmacologist, HFD-180  
Date
cc:
Orig NDA 20,725
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Choudary
HFD-180/Dr. Joseph
ONDIO/Dr. Jacobs

R/D Init.: S. Chakder 8/13/07

DJ/dbj: 8/13/07
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/s/
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David Joseph
8/13/2007 10:39:38 AM
PHARMACOLOGIST
New recommendation for pregnancy labeling.

Sushanta Chakder
8/13/2007 11:35:43 AM
PHARMACOLOGIST
PHARMACOLOGIST’S REVIEW OF NDA 20,725

(Amendment Dated November 17, 2006; Amendment Dated March 2, 2007; Amendment Dated April 18, 2007)

Reviewer: David B. Joseph, Ph.D.
Pharmacologist (HFD-180)

Sponsor and Address: Solvay Pharmaceuticals, Inc.
Marietta, Georgia

Drug: CREON®

Other Names: Pancrelipase Delayed-Release Capsules

Drug Class: digestive aid for treatment of exocrine pancreatic insufficiency/pancreatic enzyme preparation

Date of Submission: November 17, 2006
March 2, 2007
April 18, 2007

Date of CDER White Oak DR1 Receipt: November 20, 2006
March 5, 2007
April 19, 2007

Date of Review: June 25, 2007

Submission Contents: 4-Week oral toxicity study of phthalic acid in rats (submitted in the amendments dated March 2, 2007 and April 18, 2007); Summary report of toxicological information on phthalic acid and closely related compounds (submitted in the amendment dated November 17, 2006).

Introduction:

Creon® (Pancrelipase Delayed-Release Capsules) is a pancreatic enzyme product that was submitted for marketing approval under the amendment dated November 17, 2006 (Complete Response to Not Approvable Letter). Creon® is distinct from Creon® Minimicrospheres® (Pancrelipase Delayed-Release Capsules), a product that is marketed in the United States without a NDA or OTC monograph. Creon® Minimicrospheres® was deemed as not approvable after the initial review of NDA 20,725 (letter to Sponsor dated October 9, 2003). The Sponsor intends to discontinue marketing of Creon® Minimicrospheres®, after obtaining approval for Creon®. O-phthalic acid, also known as phthalic acid, has been identified as an impurity in Creon®. The presence of phthalic acid is due to degradation of the excipient, hydroxypropyl methylcellulose phthalate. The amount of phthalic acid in Creon® was shown to increase during storage of the drug product. The Sponsor conducted a 4-week oral toxicity study of phthalic acid in rats to
evaluate the potential for adverse effects due to phthalic acid ingestion associated with Creon® administration. This study was initially submitted in an IND amendment (IND 47,546), followed by its submission in the present application. The Sponsor also submitted a summary report of the available toxicology information on phthalic acid and closely related compounds.

The following study review was taken from the Pharmacologist’s review of IND 47,546 dated June 8, 2007.

4-Week Subchronic Toxicity Study of Phthalic Acid by Repeated Oral Administration to CD Rats

Key Study Findings: changes in urinalysis parameters occurred in the 250 and 1000 mg/kg/day groups; NOAEL in males was 62.5 mg/kg/day; tolerated dose in males and females was 250 mg/kg/day

Study # S245.7.002 (20303/06)

Vol. 1, Pg. 1

Conducting Laboratory and Location:

Date of Study Initiation: June 19, 2006 (report dated November 23, 2006)

GLP Compliance: A statement of compliance was included.

QA Report: yes (x) no ( )

Test Article: Phthalic acid; lot # 06811 ED; 99.6% pure

METHODS: Crl:CD®(SD) rats (males: 115-145 g, age 33 days; females: 102-144 g, age 34 days), were treated orally with 0 (vehicle), 62.5, 250, or 1000 mg/kg/day phthalic acid for 28 or 29 days (10 rats/sex/group). The animals were sacrificed in a randomized manner on days 29 and 30. The test and control articles were administered orally via gavage using a dose volume of 10 ml/kg. The test article was administered as a suspension in 0.8% hydroxypropyl methylcellulose. The authors stated that dose selection was based on “available toxicological data”. No additional information about dose selection was provided.

Observations and Times:

Mortality: twice daily

Clinical Signs: twice daily
Bodyweight: weekly starting on day 1

Food Consumption: weekly

Ophthalmoscopy: at study termination

Hematology: blood samples were collected on day 29

Clinical Chemistry: blood samples were collected on day 29

Urinalysis: urine samples were collected at study termination

Gross Pathology: at sacrifice

Organ Weights: adrenals, brain, heart, kidneys, liver, lungs, lymph nodes (cervical, mesenteric), ovaries, pituitary, prostate, spleen, testes, thymus, thyroid/parathyroids

Histopathology: The following organs/tissues were examined in the control and high-dose groups: adrenals, aorta, bone (femur with joint and marrow), brain (cerebrum, cerebellum, and brain stem), cecum, colon, duodenum, epididymides, esophagus, eyes (with optic nerve and Harderian gland), gross lesions, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (cervical, mesenteric), mammary gland, masses/tumors (with regional lymph nodes), ovaries, pancreas, pituitary, prostate, rectum, salivary glands (mandibular, parotid, sublingual), sciatic nerve, seminal vesicle, skeletal muscle, skin, spinal cord (3 sections), spleen, stomach, testes, thymus, thyroid (with parathyroids), tongue (with base), trachea (with larynx), ureters, urinary bladder, uterus (with cervix and oviducts), vagina.

Adequate Battery: yes (x) no ( )
Peer Review: yes ( ) no (x)

Other: A hearing test was performed in all animals on day 26.

RESULTS:

Mortality: None.

Clinical Signs: None.

Bodyweight: Weight gain in the 62.5, 250, and 1000 mg/kg/day females was decreased by 10-12%. Weight gain in males was unaffected. No significant effect on bodyweight in males or females was observed. The mean (± S.D.) weight of control males and females was 135 ± 5 g and 125 ± 6 g, respectively, on day 1, and 304 ± 24 g and 230 ± 15 g, respectively, on day 29.

Food Consumption: No treatment-related effects were observed.

Ophthalmoscopy: No lesions were observed.
**ECG:** Not performed.

**Hematology:** The results are shown in the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg/day)</th>
<th>Change</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>1000^m</td>
<td>51% increase (ns)</td>
<td>29</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1000^m</td>
<td>42% increase</td>
<td>29</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1000^m</td>
<td>27% increase (ns)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>62.5^f, 250^f, 1000^f</td>
<td>26%, 26%, 49% increase (ns)</td>
<td>29</td>
</tr>
<tr>
<td>Basophils</td>
<td>62.5^m, 1000^m</td>
<td>44%, 34% increase (ns)</td>
<td>29</td>
</tr>
<tr>
<td>Large unstained cells</td>
<td>62.5^m, 1000^m</td>
<td>52%, 35% increase (ns)</td>
<td>29</td>
</tr>
</tbody>
</table>

*ns: not significant

m: males

f: females

Increases in neutrophils, monocytes, eosinophils, basophils, and large unstained cells occurred in the 1000 mg/kg/day males. Eosinophils, basophils, and large unstained cells were also increased at lower dose levels. Thromboplastin time and activated partial thromboplastin time were unaffected.

**Clinical Chemistry:** No effects were observed.

**Urinalysis:** A small but statistically significant increase in specific gravity of urine occurred in the 1000 mg/kg/day males and females. A dose-dependent decrease in pH was observed, as shown in the table below.

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.92 ± 0.25</td>
<td>6.74 ± 0.21</td>
</tr>
<tr>
<td>62.5</td>
<td>6.92 ± 0.20</td>
<td>6.62 ± 0.11</td>
</tr>
<tr>
<td>250</td>
<td>6.48 ± 0.21*</td>
<td>6.35 ± 0.29*</td>
</tr>
<tr>
<td>1000</td>
<td>5.48 ± 0.16*</td>
<td>5.57 ± 0.41*</td>
</tr>
</tbody>
</table>

*p ≤ 0.01

The mean pH values in the 1000 mg/kg/day males and females were lower than the historical control range from the testing laboratory. Volume was reduced by 41% in the 1000 mg/kg/day males, and by 28% and 39% in the 250 and 1000 mg/kg/day females, respectively. Nitrite was not detected in urine from the 1000 mg/kg/day group. The absence of nitrite was observed in 4/10 males in each of the 62.5 and 250 mg/kg/day groups. In contrast, all control animals and all females in the 62.5 and 250 mg/kg/day groups exhibited a positive result in the nitrite test.

**Organ Weights:** Absolute weight and relative weight (organ/bodyweight ratio) were reported.
Adrenal (right): Relative weight was increased by 22%, 14%, and 18% in the 62.5, 250, and 1000 mg/kg/day females, respectively.

Lymph nodes (cervical): Relative weight was decreased by 33%, 17%, and 16% in the 62.5, 250, and 1000 mg/kg/day males, respectively. Relative weight was increased by 20%, 29%, and 30% in the 62.5, 250, and 1000 mg/kg/day females, respectively.

Pituitary: Relative weight was decreased by 17%, 15%, and 22% in the 62.5, 250, and 1000 mg/kg/day males, respectively. Relative weight was increased by 15%, 37%, and 20% in the 62.5, 250, and 1000 mg/kg/day females, respectively.

Prostate: Absolute weight was increased by 31%, 17%, and 13% in the 62.5, 250, and 1000 mg/kg/day males, respectively. Relative weight was increased by 36%, 15%, and 17% in the 62.5, 250, and 1000 mg/kg/day males, respectively.

Thyroid: Absolute weight was decreased by 21%, 16%, and 16% in the 62.5, 250, and 1000 mg/kg/day males, respectively. Relative weight was decreased by 22%, 14%, and 14% in the 62.5, 250, and 1000 mg/kg/day males, respectively.

**Gross Pathology:** No treatment-related effects were observed.

**Histopathology:**

- Adrenals: Cortical hypertrophy occurred in the 1000 mg/kg/day group (1/20 rats).
- Bone (femur): Myelofibrosis was observed in the 1000 mg/kg/day group (1/20 rats).
- Heart: Hemorrhage (minimal) occurred in the 1000 mg/kg/day group (1/20 rats).
- Optic nerve: Hemorrhage (slight) was observed in the 1000 mg/kg/day group (1/20 rats).
- Prostate: Mononuclear cell infiltrate, inflammation, and hemorrhage occurred in the 1000 mg/kg/day group (1/10 males for each lesion, three different animals).

**Toxicokinetics:** Not performed.

**Other:** All animals responded normally in the hearing test.

**Conclusions:** Changes in urinalysis parameters occurred in the 250 and 1000 mg/kg/day groups. These effects included increased specific gravity, decreased pH, and decreased volume. The authors considered the reduction in pH to be the result of excretion of phthalic acid in urine, although no information was provided or cited to support this viewpoint. The NOAEL (no observed adverse effect level) in males is considered to be 62.5 mg/kg/day, based on the changes in urinalysis parameters at 250 and 1000 mg/kg/day. A NOAEL was not established in females due to slight impairment of weight gain at all dose levels. The tolerated dose in males and females is considered to be 250 mg/kg/day, based on the severity of changes in urinalysis.
parameters at 1000 mg/kg/day. Some tissue lesions were observed in the high-dose group, but these occurred in no more than one animal. None of the lesions were considered to be treatment-related.

**Addendum:** The authors’ view that the decrease in urinary pH was the result of excretion of phthalic acid in urine is supported by information submitted in the present application (amendment dated November 17, 2006). Phthalic acid was shown to be excreted unchanged in urine after oral administration in rats (Williams and Blanchfield, Bull Environ Contam Toxicol, 12, pg. 109-112, 1974).

**Summary of Phthalic Acid Toxicology Information**

**Report # S0010.7.637X**

**Introduction:** The information in this report was presented in a summary format. The report includes pharmacokinetic and toxicology information from studies with o-phthalic acid, an impurity in Creon®. In addition, pharmacokinetic and toxicology information about p-phthalic acid and phthalic anhydride is also presented. The structures of these compounds are shown below.

![Chemical Structures](image)

o-phthalic acid  p-phthalic acid  phthalic anhydride

Information about p-phthalic acid was included in the report because of its structural similarity to o-phthalic acid. Data from studies of phthalic anhydride was also included, because this compound rapidly converts to o-phthalic acid in water and biological fluids. Thus, the information from studies of phthalic anhydride is considered to be relevant to the safety evaluation of o-phthalic acid. The Sponsor did not submit the references that were cited in this report.

**Pharmacokinetics:** The absorption of orally administered o-phthalic acid in rats was described as incomplete, whereas p-phthalic acid was almost completely absorbed (Williams and Blanchfield, Bull Environ Contam Toxicol, 12, pg. 109-112, 1974; Hoshi and Kuretani, Chem Pharm Bull, 15(12), pg. 1979-1984, 1967). Following oral administration of radiolabeled o- or p-phthalic acid in rats, radioactivity was rapidly and widely distributed. The greatest accumulation of radioactivity was seen in kidneys after administration of o-phthalic acid, and in liver after administration of p-phthalic acid. There was no radioactivity detectable in any tissue at 24 hr post-dose (Williams and Blanchfield, Bull Environ Contam Toxicol, 12, pg. 109-112, 1974; Hoshi and Kuretani, Chem Pharm Bull, 16(1), pg. 131-135, 1968). Distribution of
p-phthalic acid in fetal tissues was observed after oral administration to pregnant rats, but the amount was low in relation to maternal tissue concentrations (Wolkowski-Tyl et al., Drug Metab Disp, 10(5), pg. 486-490, 1982). O- and p-phthalic acid were excreted unchanged in urine within 24-48 hours after oral dosing in rats (Williams and Blanchfield, Bull Environ Contam Toxicol, 12, pg. 109-112, 1974; Hoshi and Kuretani, Chem Pharm Bull, 15(12), pg. 1979-1984, 1967). Unconjugated o-phthalic acid was detected in the urine of humans after exposure to phthalic anhydride (Ridgeway et al, “Health and Safety Executive. Acid Anhydrides: criteria document for an occupational exposure limit”, HSE Books, 1996). This was presumably due to the conversion of phthalic anhydride to o-phthalic acid via hydrolysis, followed by excretion in urine.

**General Toxicology:**

**Acute Toxicity:**

Oral LD₅₀ values of 1100 and 7900 mg/kg have been reported for o-phthalic acid in rats (BIBRA Toxicity Profile – ortho-phthalic acid and its sodium and potassium salts, 1989; Meleschenko et al, Hyg Sanit, 32, pg. 167-170, 1967). Oral LD₅₀ values in mice were reported to be 2530 and >5000 mg/kg for o-phthalic acid (Lin et al, J Am Coll Toxicol, 11(4), pg. 711, 1982; Schobeker et al, Food Chem Toxicol, 41, pg. 405-413, 2003) In acute toxicity studies with phthalic anhydride, oral LD₅₀ values in rats were in the range of 1530-4500 mg/kg, whereas the oral LD₅₀ values in mice were 1500-2210 mg/kg (Ridgeway et al, “Health and Safety Executive. Acid Anhydrides: criteria document for an occupational exposure limit”, HSE Books, 1996; Sax, “Dangerous Properties of Industrial Materials”, 6th ed., pg. 2226, Van Nostrand Reinhold, New York, NY, 1984; Bomhard et al, J Am Coll Toxicol, 15(Suppl 1), pg. 68, 1996).

**Subacute/Subchronic Toxicity:**

A 7-day study in male rats was performed to evaluate the liver toxicity of o-phthalic acid. Animals were treated orally with 0, 850, 1335, or 1425 mg/kg/day o-phthalic acid for seven days using gavage administration. Biochemical, histochemical, and electronmicroscopic examinations were carried out. O-phthalic acid treatment did not affect the relative liver weight or the biochemical parameters examined. No histochemical or ultrastructural changes were seen in the livers (Lake et al, Toxicol Appl Pharmacol; 32, pg. 355-367, 1975).

In another study of the effects of phthalic acid in the liver, rats were given 2% o-phthalic acid (approximately 1000 mg/kg/day) via the diet for two weeks. Livers were examined by electron microscopy. Peroxisomal, mitochondrial, and microsomal enzymes were evaluated in liver homogenate. No gross or microscopic changes in liver or effects on liver enzyme levels were observed. In addition, there was no evidence of peroxisome proliferation (Ganning et al, Acta Chemica Scandinavica, B36(8), pg. 563-565, 1982).

A 34-day oral toxicity study in rats was performed using dietary administration of 0.5% or 5% o-phthalic acid (approximately 250 and 2500 mg/kg/day, respectively). A control group was also included in the study. Histopathologic examination was limited to kidney, liver, and testes. No effects were observed in these organs. The results also showed no effects on bodyweight,
organ weights, or dehydrogenase and respiration activity in hepatic mitochondria (Murakami and Nishiyama, Jap J Hyg, 41(4), pg. 775-780, 1986).

The authors cited a 4-week oral toxicity study of pancrelipase in dogs, in which the currently marketed product, Creon® Minimicrospheres®, was administered at a dose level of 6000 mg/kg/day. Other groups were treated with multiple dose levels of pancrelipase, the drug substance. This study was reviewed in the Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003. O-phthalic acid is known to be an impurity in Creon® Minimicrospheres®. However, the amount of o-phthalic acid in the product used in the 4-week toxicity study in dogs was not measured at the time of the study. Current measurements of a reserve sample from this study, which was conducted in 1999, show an o-phthalic acid content of 0.6%. The authors assume that the amount of o-phthalic acid at the time of the study was about 0.1%, based on results from stability studies with Creon® Minimicrospheres®. Using this assumption, it is estimated that the daily dose of o-phthalic acid was approximately 6 mg/kg/day. Glandular dilatation in the small intestine and concretions in thyroid were observed in dogs treated with Creon® Minimicrospheres®. The relationship of these effects to o-phthalic acid exposure is uncertain. Given the relatively low estimated dose of o-phthalic acid (6 mg/kg/day) and the short duration of treatment, this study is of limited value in the safety assessment of o-phthalic acid intake associated with Creon® administration.

A 7-week oral toxicity study of phthalic anhydride in F344 rats and B6C3F1 mice were performed as dose range-finding studies for a NTP carcinogenicity bioassay. Groups of five male and five female animals were given diets containing 0, 6200, 12,500, 25,000, or 50,000 ppm phthalic anhydride. The estimated dose levels were 0, 310, 625, 1250, and 2500 mg/kg/day for rats and 0, 750, 1500, 3000, and 6000 mg/kg/day for mice. Bodyweight was recorded and tissues were examined microscopically. The only treatment-related effect was a reduction in bodyweight gain of rats in the highest dose group (2500 mg/kg/day). Microscopic examination did not reveal treatment-related effects. However, the authors did not indicate whether a complete set of tissues were examined (NTP Study Report, “Bioassay of phthalic anhydride for possible carcinogenicity”, Technical report No. 159, 1979).

The toxicity of p-phthalic acid was investigated in 28-day old F344 rats using dietary administration of 0%, 0.5%, 1.5%, 3%, 4%, or 5% p-phthalic acid (approximately 250, 750, 1500, 2000, and 2500 mg/kg/day) for 14 days. Bodyweight, food consumption, and water consumption were measured. Upon sacrifice on day 42, urine was collected and the entire urinary tract was examined for macroscopic calculi. Bodyweight and food consumption were significantly reduced in animals exposed to 4% or 5% p-phthalic acid in the diet. At 3% and higher, water consumption was significantly elevated and diarrhea was frequently observed. A dose-related trend in urinary bladder calculi formation was apparent in males at dietary levels
of 3-5% p-phthalic acid, and in females given 1.5-5% p-phthalic acid. In addition to dose-related decreases in urinary pH, there was also a decrease in urinary sodium, potassium, and sulfate excretion. Calculi were found to be principally composed of calcium p-phthalate and calcium phosphate. Histopathologic examination was performed in 10 males in each of the control and 4% dose groups. In 10/10 control rats and 4/10 treated rats without calculi, the histopathology of the urinary tract was normal. In six treated rats with bladder calculi, thickened transitional epithelium with diffuse hyperplasia was observed, but kidneys and ureters appeared normal in five of these animals (Chin et al, Toxicol Appl Pharmacol, 58(2), pg. 307-321, 1981).

A 90-day oral toxicity study of p-phthalic acid in Wistar and CD rats was performed using dietary administration of 0%, 0.03%, 0.125%, 0.5%, 2.0%, or 5.0% p-phthalic acid (approximately 15, 62.5, 250, 1000, and 2500 mg/kg/day). Rats were sacrificed on days 30, 60, and 90. Rats were assessed for clinical signs, bodyweight, and food consumption. At sacrifice, urine samples were taken for urinalysis and measurement of p-phthalic acid concentration, and histopathologic examination was performed on major internal organs with particular emphasis on kidney and lower urinary tract structures. Food consumption was significantly reduced in females given 2.0% (CD rats) and 5.0% (both strains) p-phthalic acid. A dose-dependent reduction in bodyweight gain was observed in animals given 0.5-5.0% in the diet. Diarrhea, urogenital discharge, and death were observed at the 5% dietary level. Urinalysis revealed a tendency towards increased urine acidity after 90 days in groups given dietary levels of 0.5% and higher. A dose-related increase in urinary excretion of calcium was observed at and above 0.5% p-phthalic acid, and increased urinary excretion of magnesium was found in males in the 2.0% and 5.0% groups. Phosphate excretion was increased at the 5% level. Urinary excretion of p-phthalic acid was highest in Wistar rats given 0.5-5.0% p-phthalic acid in the diet. No alteration of kidney weight was observed. Gross observation upon necropsy revealed bladder distension, calculi in the bladder, and distension of cecum and colon, primarily in the 5% groups. Histopathologic examination revealed little correlation between inflammatory lesions in the bladder and the presence of calculi. At terminal sacrifice, transitional cell hyperplasia in bladder and ureters was common in all groups exposed to 5.0% p-phthalic acid (unpublished data, U.S. EPA Environmental Criteria and Assessment Office, “Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-)”, EPA/600/x-86/292, August 1989).

A 90-day oral toxicity study of p-phthalic acid in Wistar rats was performed using dietary administration of 5.0% p-phthalic acid for one week followed by 3.0% in the diet until study termination. Bladder stones and hyperplasia of the bladder endothelium was observed in male and female animals. The presence of calculi was strongly correlated with the development of hyperplasia (unpublished data, U.S. EPA Environmental Criteria and Assessment Office, “Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-)”, EPA/600/x-86/292, August 1989).

Chronic Toxicity:

A 6-month oral toxicity study of o-phthalic acid in rats was performed using dose levels of 0 (distilled water), 0.0056, 0.056, or 0.56 mg/kg/day o-phthalic acid. The test article was administered by gavage. O-phthalic acid did not cause changes in appearance or behavior, and no alterations in red blood cell parameters or differential white blood cell counts occurred.
However, there was a tendency towards lower platelet count in the 0.56 mg/kg/day group at study termination. The weights of brain, liver, heart, kidneys, spleen, stomach, and intestines were unaffected by treatment. Animals treated with 0.56 mg/kg/day showed some dystrophic and reactive changes in the liver, kidneys, stomach, and intestines. However, the details of these findings were not presented in the publication (Meleschenko et al, Hyg Sanit, 32, pg. 167-170, 1967).

**Genetic Toxicology:**

O-phthalic acid tested negative in several genotoxicity studies, as shown in the table below (taken from the report).

<table>
<thead>
<tr>
<th>Assay</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ames test</td>
<td>S. typhimurium (TA100, 1535)</td>
<td>500 µg/plate</td>
<td>negative (with and without metabolic activation); cytotoxicity</td>
<td>[17]</td>
</tr>
<tr>
<td>Ames test</td>
<td>S. typhimurium (TA98, 100)</td>
<td>up to 1000 µg/plate</td>
<td>negative (with and without metabolic activation)</td>
<td>[18]</td>
</tr>
<tr>
<td>Ames test</td>
<td>S. typhimurium (TA98, 100)</td>
<td>30, 100, 300 µg/plate</td>
<td>negative (with and without metabolic activation)</td>
<td>[19]</td>
</tr>
<tr>
<td>Mutation test</td>
<td>S. typhimurium (TA98, 100); E. coli</td>
<td>10 mg/plate</td>
<td>negative (with metabolic activation)</td>
<td>[20]</td>
</tr>
<tr>
<td>Repair test</td>
<td>B. subtilis E. coli</td>
<td>10 mg/plate</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Chromosome aberration</td>
<td>Chinese hamster ovary cells</td>
<td>10, 20 50 mM</td>
<td>Negative</td>
<td>[21]</td>
</tr>
</tbody>
</table>


O-phthalic acid was also evaluated *in vivo* for the induction of dominant lethal mutations (40 or 80 mg/kg ip for five days) and sperm head abnormalities (50, 100, 150, 200, or 300 mg/kg ip as a single treatment) in male Swiss albino mice. The results of the dominant lethal assay indicated a positive dose-response relationship and induction of statistically significant dominant lethal mutations. Treatment with o-phthalic acid resulted in a statistically significant and dose-related increase in sperm head abnormalities at dose levels of 100 mg/kg and higher. No effects were observed at 50 mg/kg (Jha et al, Mutat Res, 422(2), pg. 207-212, 1998).

The genotoxic potential of phthalic anhydride was also investigated. No evidence of mutagenicity or clastogenicity was observed in the Ames tests or in assays using mammalian cells. One positive result was observed in a chromosome aberration assay at 10 mM without metabolic activation. However, severe cytotoxicity and precipitation were observed at this dose level. The results of genetic toxicology studies of phthalic anhydride are summarized in the following table (taken from the report).
Table 4: Genotoxicity results with phthalic acid anhydride

<table>
<thead>
<tr>
<th>Assay</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ames test (preincubation</td>
<td>S. typhimurium (TA98, 100, 1535,</td>
<td>3 to 3333 μg/plate</td>
<td>negative (with and without metabolic activation)</td>
<td>[23]</td>
</tr>
<tr>
<td>assay)</td>
<td>1537)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ames test</td>
<td>S. typhimurium (TA100)</td>
<td>up to 3 μmol/plate</td>
<td>negative (with and without metabolic activation)</td>
<td>[24]</td>
</tr>
<tr>
<td>Chromosome aberration</td>
<td>Chinese hamster ovary cells</td>
<td>30 – 300 mg/ml</td>
<td>negative (with and without metabolic activation)</td>
<td>[25]</td>
</tr>
<tr>
<td>Sister chromatid exchange</td>
<td>Chinese hamster ovary cells</td>
<td>10 300 mg/ml</td>
<td>negative (with and without metabolic activation)</td>
<td>[25]</td>
</tr>
<tr>
<td>Chromosome aberration</td>
<td>Chinese hamster ovary cells</td>
<td>6, 8, 10 mM</td>
<td>negative (with metabolic activation); positive at the cytotoxic dose level of 10 mM (without activation); precipitation at 10 mM</td>
<td>[26]</td>
</tr>
<tr>
<td>DNA-damage (alkaline elution)</td>
<td>primary rat hepatocytes</td>
<td>1, 3, 10 mM</td>
<td>negative; marginal cytotoxicity at 3 and 10 mM</td>
<td>[27]</td>
</tr>
<tr>
<td>Inhibition of DNA synthesis</td>
<td>HeLa cell</td>
<td>up to 100 mM</td>
<td>Negative</td>
<td>[28]</td>
</tr>
</tbody>
</table>


Carcinogenicity:

A 105-week carcinogenicity study of phthalic anhydride in F344 rats was performed using dietary administration of 0, 7500, or 15,000 ppm phthalic anhydride (approximately 375 and 750 mg/kg/day). Survival of rats was not affected by the test article. Weight gain was reduced in the high-dose males. No treatment-related neoplastic or non-neoplastic effects were observed (NTP Study Report, “Bioassay of phthalic anhydride for possible carcinogenicity”, Technical report No. 159, 1979).

A 104-week carcinogenicity study of phthalic anhydride in B6C3F1 mice was performed using dietary administration. The dose levels during the first 32 weeks of treatment were 0, 25,000, and 50,000 ppm (approximately 3000 and 6000 mg/kg/day). Because of excessive growth depression, dose levels were reduced to 12,500 and 25,000 ppm for males (equivalent to 1500 and 3000 mg/kg/day) and 6250 and 12,500 ppm for females (equivalent to 750 and 1500 mg/kg/day). These dose levels were administered for the remaining 72 weeks of the study. Survival of mice was unaffected by treatment. The results demonstrated lower mean body weight gain in the low- and high-dose mice compared to the control group. Depression of body weight gain was dose-related throughout the study. No treatment-related neoplastic or non-neoplastic effects were observed (NTP Study Report, “Bioassay of phthalic anhydride for possible carcinogenicity”, Technical report No. 159, 1979).
A 2-year carcinogenicity study of p-phthalic acid in Wag/Rij rats was performed using dietary administration of 0%, 1%, 2%, or 5% p-phthalic acid (approximately 500, 1000, and 2500 mg/kg/day). Upon terminal sacrifice, at least 13 tissues were microscopically examined and blood was taken for hematology and analysis of urea. Mortality was increased in the 5% dose group, with 69/100 rats dying before study termination. Bodyweight was significantly decreased in females at 5% and males at 2% and 5% p-phthalic acid. No treatment-related effects on hematology parameters or bone marrow were detected. Bladder urolith formation and renal nephropathy was observed in the 5% p-phthalic acid group. Kidneys from this group showed signs of chronic inflammation and the number of rats with blood urea levels above 40 mg% was significantly increased. Significantly greater incidences of hyperplastic lesions and tumors in bladder and ureters were observed in high-dose animals. The hyperplastic and neoplastic changes were considered secondary to the presence of stones (unpublished data, U.S. EPA Environmental Criteria and Assessment Office, “Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-)”, EPA/600/x-86/292, August 1989).

A 2-year carcinogenicity study of p-phthalic acid in F344 rats was performed using dietary administration of 0, 20, 142, or 1000 mg/kg/day p-phthalic acid. Groups of rats were sacrificed at 6, 12, 18, and 24 months. Bodyweight gain in the 1000 mg/kg/day group was reduced. No urinary tract calculi were noted in rats sacrificed after 6 or 12 months. After 18 and 24 months, the 1000 mg/kg/day females showed urinary tract calculi formation. No other groups sacrificed at 18 or 24 months showed this effect. At terminal sacrifice, only the 1000 mg/kg/day females had hyperplasia of the bladder epithelium. Bladder lesions were also observed in the 1000 mg/kg/day females sacrificed at 18 months. The incidence of transitional cell adenoma and carcinoma in the bladders was significantly increased only in the 1000 mg/kg/day females after 24 months of treatment. It was noted that the rats were exposed to constant illumination for an unknown period of time during the study due to a room light cycle malfunction (unpublished data, U.S. EPA Environmental Criteria and Assessment Office, “Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-)”, EPA/600/x-86/292, August 1989).

Reproductive and Developmental Toxicology:

An embryo-fetal developmental study (Segment II study) of o-phthalic acid in rats was performed using dietary administration of 0%, 1.25%, 2.5%, or 5% o-phthalic acid on days 7-16 of pregnancy. The average daily dose levels were determined to be 1021, 1763, and 2981 mg/kg/day. The dams were sacrificed on day 20 of gestation and C-sections were performed. Live fetuses were examined for external, visceral, and skeletal malformations. Maternal toxicity (reduced weight gain and food consumption) was observed in the 1763 and 2981 mg/kg/day groups. The weight of male fetuses in the 2981 mg/kg/day group was significantly reduced, but female fetuses were not affected. No other changes in reproductive parameters were observed. Since the reduction in weight of male fetuses occurred at a dose which produced maternal toxicity, the results indicate that o-phthalic acid did not produce embryo-fetotoxicity. No treatment-related external, visceral, or skeletal malformations were noted. The extent of caudal vertebrae ossification was significantly reduced in fetuses of the 2981 mg/kg/day group. This effect may also be secondary to maternal toxicity (Ema et al, Toxicol Lett, 93(2-3), pg. 109-115, 1997).
A reproductive study in Swiss albino mice was performed using a single intraperitoneal injection of 200 or 400 mg/kg o-phthalic acid on day 9 of pregnancy. A control group was also included in the study. C-sections were performed on day 18 of pregnancy. The results did not show an increase of the incidence of resorptions or fetal malformations in the treatment groups (Köhler et al, Experientia, 27/10, pg. 1149-1150, 1971). However, the study methods were grossly deficient due to administration of the test article only on day 9 of pregnancy. Therefore, this study has minimal value for the evaluation of teratogenicity or embryo-fetotoxicity.

A reproductive study of p-phthalic acid in Wistar and CD rats was performed. The rats that were used in this study had completed a 90-day oral toxicity study using dietary administration of 0%, 0.03%, 0.125%, 0.5%, 2%, or 5% p-phthalic acid (approximately 15, 62.5, 250, 1000, and 2500 mg/kg/day). The rats continued to receive dietary administration of these dose levels after termination of the 90-day oral toxicity study and throughout the mating, pregnancy, lactation, and post-weaning periods in the reproductive study. The dams were allowed to give birth and the offspring were evaluated for litter size, sex, viability, survival, bodyweight, clinical signs, morbidity, and mortality. At weaning, all litters were culled to two males and two females and maintained on the diet until day 51 post-partum. Necropsies were performed on culled pups, the remaining pups on day 51, and all F₀ and F₁ rats which died. Macroscopic examination of the thoracic and abdominal viscera was conducted with special emphasis on the urinary system.

Stillbirth was observed in the 2% and 5% dose groups. CD pups exposed to 2% p-phthalic acid during the peri-natal period showed a nearly 30% decrease in survival and a 20-25% decrease in bodyweight on post-partum day 21. Over 50% of the male and female CD pups in the 5% dose group did not survive to day 21. The viability of Wistar pups was reduced to 50% in the 5% dose group on day 1 after birth. Post-weaning mortality of pups among both strains was observed only in the 5% dose group. Significantly lower bodyweights were observed in the high-dose Wistar pups on day 1 after birth, and pup weight in both strains was reduced at the 5% dose level by day 21. No gross teratogenic effects were observed, but standard skeletal and visceral evaluations were not performed. Pooled necropsy data of all pups showed incidences of bladder abnormalities (i.e. discoloration, calculi, and thickened bladder wall) in males and females of both strains treated with 5% p-phthalic acid. Urinary tract lesions were more pronounced on day 51. The only other gross lesion related to treatment was enlarged cecum in the high dose pups (unpublished data, U.S. EPA Environmental Criteria and Assessment Office, “Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-)”, EPA/600/x-86/292, August 1989).

LABELING:

The proposed labeling was submitted in the format described in the final rule that revised the requirements for the content and format of labeling for human prescription drug and biological products (Federal Register, Vol. 71, No. 15, pg. 3922-3997, 2006). Under the new labeling rule, the established pharmacologic class of the product must be stated under the “INDICATIONS AND USAGE” section of the “HIGHLIGHTS OF PRESCRIBING INFORMATION” (Highlights). This requirement applies only to products that belong to an established pharmacologic class. Therefore, the “INDICATIONS AND USAGE” section of the Highlights is reviewed below. The preclinical subsections of the “FULL PRESCRIBING
INFORMATION” in the proposed labeling include “Mechanism Of Action” and “Carcinogenesis, Mutagenesis, Impairment of Fertility”, which are reviewed below. The “Pregnancy” subsection was omitted from the proposed labeling, based on the following statement under the “USE IN SPECIFIC POPULATIONS” section: “No specific population has been identified to limit the use by patients with maldigestion due to exocrine pancreatic insufficiency”. The acceptability of this statement will be determined by the reviewing medical officer. However, the pharmacology/toxicology reviewer agrees that a “Pregnancy” subsection is not needed in the labeling, since the drug fulfills the regulatory requirements for the omission of this subsection. 21 CFR 201.57 (April 1, 2007) states that the “Pregnancy” subsection “may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus”. It is reasonable to assume that the digestive enzymes present in the drug substance are not absorbed in their original state, given that these are large proteins. However, it is likely that the enzymes are digested in the small intestine and absorbed as short-chain peptides and individual amino acids. A preclinical study demonstrated that pancreatic lipase, procolipase/colipase, and trypsin were not absorbed after oral administration of Creon® Minimicrospheres® (the presently marketed product) in pancreatic duct-ligated pigs or in pancreatectomized pigs (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). These results support the omission of the “Pregnancy” subsection.

**Sponsor’s Proposed Version:**

**“HIGHLIGHTS OF PRESCRIBING INFORMATION”**

**“INDICATIONS AND USAGE**

CREON Capsules is a pancrelipase indicated for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency.”

**Evaluation:** The term “pancrelipase” is used inappropriately as the established pharmacologic class for Creon®. However, “pancrelipase” is an appropriate non-proprietary name for the drug substance. Pancrelipase is described by the USP Dictionary (2007) as a concentrate of pancreatic enzymes standardized for lipase content. Creon® and other products containing pancrelipase have a long history of successful treatment of patients with EPI (exocrine pancreatic insufficiency). The ability of pancrelipase to improve digestive function has also been demonstrated in preclinical studies. The Sponsor previously submitted two studies using the minipig model of EPI. In one study, Creon® Minimicrospheres® (the currently marketed product) produced a dose-dependent improvement in the digestion of fat and dry matter in pancreatic duct-ligated minipigs. In the other study, Creon® Minimicrospheres® produced a dose-dependent increase in the digestion of fat, protein, and starch in the same model of EPI. The increase in daily fecal output was partially reversed by Creon® Minimicrospheres® (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). The term “digestant” accurately describes the pharmacologic effect of pancreatic enzyme preparations such as Creon®, and is therefore considered to be a scientifically valid pharmacologic class. However, the term “pancreatic enzyme preparation” is commonly used as a classification for products that contain pancreatic enzymes of porcine or bovine origin. Since “pancreatic enzyme preparation” is an accurate description of the chemical nature and origin of the drug, this term is
also considered to be a scientifically valid pharmacologic class. Both “digestant” and “pancreatic enzyme preparation” are terms that provide useful information about Creon®, and are each considered as a clinically meaningful pharmacologic class. Therefore, it is recommended that the established pharmacologic class under the “INDICATIONS AND USAGE” section of the Highlights should be “pancreatic enzyme preparation digestant”.

**Recommended Version:**

“HIGHLIGHTS OF PRESCRIBING INFORMATION”

“INDICATIONS AND USAGE

CREON Capsules is a pancreatic enzyme preparation digestant indicated for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency.”

**Sponsor’s Proposed Version:**

“12 CLINICAL PHARMACOLOGY

12.1 Mechanism Of Action

Evaluation: The subsection heading, “Mechanism Of Action”, should be changed to “Mechanism of Action”. The information stated in this subsection is accurate. However, changes in the language are recommended, as shown below.

**Recommended Version:**

“12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The porcine pancreatic enzymes in CREON Capsules are enteric-coated to resist gastric destruction or inactivation. The enzymes catalyze the hydrolysis of fats to monoglycerol, glycerol, and fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars, thereby acting as a replacement for the digestive enzymes physiologically secreted by the pancreas.”

**Sponsor’s Proposed Version:**

“13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Evaluation: The sentence, should be deleted,

Recommended Version:

“13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed.”

SUMMARY AND EVALUATION:

Creon® (Pancrelipase Delayed-Release Capsules) is a pancreatic enzyme product that was submitted for marketing approval under the amendment dated November 17, 2006 (Complete Response to Not Approvable Letter). Creon® is distinct from Creon® Minimicrospheres® (Pancrelipase Delayed-Release Capsules), a product that was deemed as not approvable after the initial review of NDA 20,725 (letter to Sponsor dated October 9, 2003). Creon® Minimicrospheres® is marketed in the United States without a NDA or OTC monograph. The Sponsor intends to discontinue marketing of Creon® Minimicrospheres®, after obtaining approval for Creon®. O-phthalic acid, also known as phthalic acid, has been identified as an impurity in Creon®. The presence of phthalic acid is due to degradation of the excipient, hydroxypropyl methylcellulose phthalate. The amount of phthalic acid in Creon® was shown to increase during storage of the drug product. The Sponsor conducted a 4-week oral toxicity study of phthalic acid in rats to evaluate the potential toxicity of phthalic acid intake associated with Creon® administration. The preclinical studies in the present submission include the 4-week oral toxicity study of phthalic acid in rats and a summary report of toxicological information on phthalic acid and closely related compounds.

The 4-week oral toxicity study of phthalic acid in rats was performed using dose levels of 0 (vehicle), 62.5, 250, and 1000 mg/kg/day. Changes in urinalysis parameters occurred in the 250 and 1000 mg/kg/day groups. These effects included increased specific gravity, decreased pH, and decreased volume. The authors considered the reduction in pH to be the result of excretion of phthalic acid in urine, a view that is supported by published information. The NOAEL (no
observed adverse effect level) in males is considered to be 62.5 mg/kg/day, based on the changes in urinalysis parameters at 250 and 1000 mg/kg/day. A NOAEL was not established in females due to slight impairment of weight gain at all dose levels. The tolerated dose in males and females is considered to be 250 mg/kg/day, based on the severity of changes in urinalysis parameters at 1000 mg/kg/day.

The Sponsor also submitted a summary report of the available toxicology information on o-phthalic acid and the closely related compounds, p-phthalic acid and phthalic anhydride. Information about p-phthalic acid was included in the report because of its structural similarity to o-phthalic acid. Data from studies of phthalic anhydride was also included because this compound rapidly converts to o-phthalic acid in water and biological fluids. Thus, the information from studies of phthalic anhydride is considered to be relevant to the safety evaluation of o-phthalic acid. Information from this report is described below.

Radiolabeled o-phthalic acid was rapidly and widely distributed following oral administration in rats, with the highest levels observed in kidneys. O-phthalic acid was excreted unchanged in urine within 24-48 hours after oral administration in rats, and was detected in the urine of humans after exposure to phthalic anhydride.

Oral LD₅₀ values of 1100 and 7900 mg/kg have been reported for o-phthalic acid in rats. Oral LD₅₀ values in mice were reported to be 2530 and >5000 mg/kg for o-phthalic acid. Repeat-dose oral toxicity studies of o-phthalic acid ranging from seven to 34 days duration have been reported in publications. These studies were grossly deficient with respect to the standard parameters used in regulatory toxicology studies. Histopathologic examination was performed only for liver in two oral toxicity studies in rats (7- and 14-day duration). In a 34-day oral toxicity study in rats, histopathologic examination was limited to kidney, liver, and testes. No adverse effects were observed in the 7-day, 14-day, or 34-day rat studies, in which the maximum doses tested were 1425 mg/kg/day, 1000 mg/kg/day, and 2500 mg/kg/day, respectively. These studies are of limited value in assessing the safety of o-phthalic acid, given the deficiencies in the methods used.

The authors cited a 4-week oral toxicity study of pancrelipase in dogs, in which the currently marketed product, Creon® Minimicrospheres®, was administered at a dose level of 6000 mg/kg/day (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). O-phthalic acid is known to be an impurity in Creon® Minimicrospheres®, and the estimated daily dose of o-phthalic acid in this study was approximately 6 mg/kg/day. Glandular dilatation in the small intestine and concretions in thyroid were observed in dogs treated with Creon® Minimicrospheres®. The relationship of these effects to o-phthalic acid exposure is uncertain. Given the relatively low estimated dose of o-phthalic acid (6 mg/kg/day), this study is of limited value in the safety assessment of o-phthalic acid intake associated with Creon® administration.

A 6-month oral toxicity study of o-phthalic acid in rats was performed using dose levels of 0 (distilled water), 0.0056, 0.056, or 0.56 mg/kg/day o-phthalic acid. The test article was administered by gavage. Platelet count tended to be lower in the 0.56 mg/kg/day group at study termination. The 0.56 mg/kg/day group showed some dystrophic and reactive changes in the liver, kidneys, stomach, and intestines. However, the details of these findings were not presented
in the publication. Given that details of the study methods and results were not provided, the results of this study should be viewed with caution.

Two oral toxicity studies of phthalic anhydride in rats have been conducted. A 4-week oral (dietary) study was performed without microscopic examination of tissues. The maximum dose in this study was approximately 319.6 mg/kg/day. Bodyweight was unaffected, and no macroscopic lesions were observed. This study is of limited value due to the absence of histopathology data. A 7-week oral (dietary) toxicity study of phthalic anhydride in F344 rats was performed as a dose range-finding study for a NTP carcinogenicity bioassay. The estimated dose levels were 0, 310, 625, 1250, and 2500 mg/kg/day. Bodyweight was recorded and unspecified tissues were examined microscopically. The only treatment-related effect was a reduction in bodyweight gain of rats in the highest dose group (2500 mg/kg/day). Microscopic examination did not reveal treatment-related effects. However, the authors did not indicate whether a complete set of tissues was examined.

Three oral (dietary) toxicity studies of p-phthalic acid have been performed in rats (14 days, 90 days, and 90 days). The major findings in these studies included urinary bladder calculi (750-2500 mg/kg/day), distension of urinary bladder, cecum, and colon (2500 mg/kg/day), and transitional cell hyperplasia in urinary bladder and ureters (2500 mg/kg/day). Death occurred at 2500 mg/kg/day in a 90-day study. Changes in urine parameters were also observed (e.g., reduced pH, reduced excretion of sodium, potassium, and sulfate). The presence of calculi in urinary bladder was strongly correlated with the development of hyperplasia. Calculi were found to be principally composed of calcium p-phthalate and calcium phosphate.

O-phthalic acid was negative in the bacterial reverse mutation test, DNA repair test in B. subtilis and E. coli, and the chromosome aberration test in CHO (Chinese hamster ovary) cells. However, a positive result was obtained for the in vivo induction of dominant lethal mutations and sperm head abnormalities in male Swiss albino mice. Phthalic anhydride was negative in the bacterial reverse mutation test, chromosome aberration test in CHO cells, sister chromatid exchange test, DNA damage test in rat hepatocytes, and DNA synthesis inhibition test in HeLa cells.

A 105-week carcinogenicity study of phthalic anhydride in F344 rats was performed using dietary administration of 0, 7500, or 15,000 ppm phthalic anhydride (approximately 375 and 750 mg/kg/day). Survival of rats was not affected by the test article. Weight gain was reduced in the high-dose males. No treatment-related neoplastic or non-neoplastic effects were observed.

A 104-week carcinogenicity study of phthalic anhydride in B6C3F1 mice was performed using dietary administration. The dose levels during the first 32 weeks of the study were 0, 25,000, and 50,000 ppm (approximately 3000 and 6000 mg/kg/day). Because of excessive growth suppression, dose levels were reduced to 12,500 and 25,000 ppm for males (equivalent to 1500 and 3000 mg/kg/day) and 6250 and 12,500 ppm for females (equivalent to 750 and 1500 mg/kg/day). These dose levels were administered for the remaining 72 weeks of the study. Survival of mice was unaffected by treatment. The results demonstrated lower mean body weight gain in the low- and high-dose mice compared to the control group. Reduction of body weight gain was dose-related throughout the study. No treatment-related neoplastic or
non-neoplastic effects were observed.

The carcinogenic potential of p-phthalic acid was evaluated in Wag/Rij rats and F344 rats in two separate studies, both of which utilized dietary administration for two years. In both studies, the high-dose levels (2500 and 1000 mg/kg/day) produced significant increases in neoplasia and hyperplasia in the urinary bladder. However, these effects appeared to be secondary to the formation of urinary tract calculi.

O-phthalic acid produced no teratogenic or embryo-fetotoxic effects in rats after oral (dietary) administration of up to 2981 mg/kg/day (average daily dose) in pregnant rats on days 7-16 of gestation. Maternal toxicity was observed in the 1763 and 2981 mg/kg/day groups, as indicated by reduced weight gain and food consumption.

A reproductive study in Swiss albino mice was performed using a single intraperitoneal injection of 200 or 400 mg/kg o-phthalic acid on day 9 of pregnancy. A control group was also included in the study. C-sections were performed on day 18 of pregnancy. The results did not show an increase in the incidence of resorptions or fetal malformations in the treatment groups. However, the study methods were grossly deficient due to administration of the test article only on day 9 of pregnancy. Therefore, this study has minimal value for the evaluation of teratogenicity or embryo-fetotoxicity.

A reproductive study of p-phthalic acid in Wistar and CD rats was performed using dietary administration of 0%, 0.03%, 0.125%, 0.5%, 2%, or 5% p-phthalic acid (approximately 15, 62.5, 250, 1000, and 2500 mg/kg/day). Male and female rats were given dietary administration of p-phthalic acid for at least 90 days prior to mating and throughout the mating, pregnancy, lactation, and post-weaning periods. The dams were allowed to give birth and the offspring were evaluated for litter size, sex, viability, survival, bodyweight, clinical signs, morbidity, and mortality. At weaning, all litters were culled to two males and two females and maintained on the diet until day 51. Post-weaning mortality of pups among both strains was observed only in the 5% dose group. Significantly lower bodyweights were observed in the high-dose Wistar pups on day 1 after birth, and pup weight in both strains was reduced at the 5% dose level by day 21. No gross teratogenic effects were observed, but standard skeletal and visceral evaluations were not performed. Pooled necropsy data of all pups showed incidences of bladder abnormalities (i.e. discoloration, calculi, and thickened bladder wall) in males and females of both strains treated with 5% p-phthalic acid. The only other gross lesion related to treatment was enlarged cecum in the high dose pups. The relevance of this study, in which p-phthalic acid was tested, to the reproductive and developmental toxicity of o-phthalic acid exposure associated with Creon® administration is uncertain.

Safety assessment of phthalic acid intake associated with Creon® administration is based on an estimated maximum dose of 21,000 lipase U/kg/day (6000 lipase U/kg/meal, 3.5 meals/day). It is assumed that this extremely high dose level would be administered using Creon® 24, which contains the highest pancreatic enzyme quantity (24,000 lipase U/capsule) of the three capsule strengths (6, 12, and 24). Creon® capsules are filled with delayed-release pellets, which contain pancrelipase, excipients, and several impurities including phthalic acid. Creon® 24 contains mg of pellets, as indicated in the acceptance criteria. For phthalic acid, the acceptance
criterion during shelf life is not more than \( \frac{250}{w/w} \) mg/kg/day. The maximum dose of phthalic acid from Creon® administration is estimated to be \( \frac{21,000}{w/w} \) mg/kg/day, based on the following assumptions: a target dose of 21,000 lipase U/kg/day, \( \frac{50}{w/w} \) mg pellets per capsule, and a phthalic acid content of \( \frac{250}{w/w} \) mg/kg/day, which exceeds the estimated maximum dose level of phthalic acid by 19-fold. Therefore, the 4-week oral toxicity study provides a reasonable assurance of safety for Creon®, with respect to phthalic acid intake. It is expected that Creon® will be used as a long-term therapy given the irreversible nature of exocrine pancreatic insufficiency, a condition that is associated with chronic pancreatitis, cystic fibrosis, and alcoholism. Therefore, a chronic toxicity study of at least six months duration would have been more useful for the safety assessment of phthalic acid intake associated with Creon® administration. However, the 4-week oral toxicity of phthalic acid was submitted as an impurity qualification study, and the recommended duration of such studies are 14 to 90 days (ICH Guidance Q3B(R), “Impurities in New Drug Products”, November 2003).

Oral (dietary) administration of phthalic anhydride produced no neoplastic or non-neoplastic changes in a 2-year carcinogenicity study in rats. The survival of treatment groups was unaffected. The results of this study are considered to be representative of the effects of lifetime exposure to phthalic acid, because phthalic anhydride is converted to phthalic acid in water or biological fluids. This study provides an additional assurance of safety for phthalic acid intake associated with Creon® administration, given that highest tested dose of phthalic anhydride, 750 mg/kg/day, exceeds the estimated maximum dose level of phthalic acid by 58-fold. It should be noted that 750 mg/kg/day phthalic anhydride is equivalent to 841 mg/kg/day phthalic acid, assuming that phthalic anhydride is completely converted to phthalic acid after dosing. In a 2-year carcinogenicity study in mice, oral (dietary) administration of phthalic anhydride produced no neoplastic or non-neoplastic changes. The treatment had no effect on the survival of animals. The initial dose levels, 3000 and 6000 mg/kg/day, were reduced to 1500 and 3000 mg/kg/day in males and 750 and 1500 mg/kg/day in females on week 33 due to suppression of bodyweight gain. This study provides an additional assurance of safety for phthalic acid intake associated with Creon® administration, given that highest tested dose of phthalic anhydride, 6000/3000 mg/kg/day in males and 6000/1500 mg/kg/day in females, markedly exceeds the estimated maximum dose level of phthalic acid \( \frac{841}{w/w} \) mg/kg/day. Based on results of the submitted 4-week oral toxicity study of o-phthalic acid in rats, the 2-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride, the estimated maximum dose of o-phthalic acid resulting from Creon® administration is not considered to be a safety concern.

Because of the long history of clinical use of pancreatic enzyme products, toxicology studies of the drug substance are usually not needed, particularly for porcine-derived pancrelipase. The preclinical review of pancreatic enzyme products is generally directed to safety information about the excipients, given that patients with exocrine pancreatic insufficiency may require daily ingestion of a large quantity of product (e.g. capsules) to achieve adequate digestion. Preclinical information about the excipients in Creon® Minimicrospheres® was previously reviewed. No major safety issues were identified, and the product was recommended for approval (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). However, the Sponsor is now seeking approval of a new formulation, Creon®, which is distinguished from
Creon® Minimicrospheres® by qualitative and quantitative differences in the excipient content. Therefore, the preclinical information in the original NDA submission cannot be used as the sole basis for supporting the approval of Creon®, from a preclinical viewpoint. A safety evaluation of the excipients in Creon® is needed.

The table below shows the major excipients in Creon®, and the maximum daily dose for each excipient based on the estimated maximum daily dose of Creon® (21,000 lipase U/kg/day).

<table>
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<tr>
<th>Excipient</th>
<th>% w/w</th>
<th>Maximum Dose* (mg/day)</th>
<th>Maximum Dose* (mg/kg/day)</th>
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<tr>
<td>Polyethylene glycol 4000</td>
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<tr>
<td>Hydroxypropyl methylcellulose phthalate</td>
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<tr>
<td>Cetyl alcohol</td>
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<td></td>
<td></td>
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<tr>
<td>Triethyl citrate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dimethicone 1000</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on administration of Creon® 24 containing 21,000 lipase U/kg/day, a target dose of 21,000 lipase U/kg/day, and a 60-kg bodyweight.

Polyethylene glycol 4000, hydroxypropyl methylcellulose phthalate, and dimethicone 1000 are major excipients in both Creon® and Creon® Minimicrospheres®. The maximum dose level for these excipients is similar in both products. The safety of polyethylene glycol 4000, hydroxypropyl methylcellulose phthalate, and dimethicone 1000 at the maximum dose levels associated with Creon® administration is supported by preclinical information in the original submission of NDA 20,725 (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003).

Cetyl alcohol is an excipient in Creon®, but not in Creon® Minimicrospheres®. This compound is a primary alcohol containing 16 carbons (CH₃(CH₂)₁₅OH). The maximum daily dose of cetyl alcohol in patients treated with Creon® is estimated to be mg/kg/day, equivalent to mg/day in a 60-kg patient. The maximum level of cetyl alcohol among all approved oral formulations is 59 mg (FDA Inactive Ingredients Database), which is present in Voltaren-XR® tablets. Based on the approved dose levels, the maximum daily intake of cetyl alcohol associated with the administration of Voltaren-XR® is mg/day, which is nearly equal to that estimated for Creon® (mg/day in a 60-kg patient). Toxicity information about cetyl alcohol is extremely limited, particularly for oral administration. Cetyl alcohol, along with other long-chain aliphatic alcohols, was described as “at most, only slightly toxic when administered orally at doses of 5 g/kg and greater” (Anonymous, J Am Coll Toxicol, 7(3), pg. 359-413, 1988). Cetyl alcohol is classified as a synthetic flavoring substance and adjuvant for use as a direct food additive (21 CFR 172.515). Based on the regulatory information, previous human experience, and the limited toxicity information about cetyl alcohol, the estimated maximum dose for cetyl alcohol resulting from Creon® administration is not considered to be a safety concern.
The inclusion of triethyl citrate in Creon® and its absence in Creon® Minimicrospheres® also distinguishes these two drug products. The maximum daily dose of triethyl citrate in patients treated with Creon® is estimated to be \( \text{mg/kg/day} \), equivalent to \( \text{mg/day} \) in a 60-kg patient. Published information about the toxicity of triethyl citrate is extremely limited. In an oral toxicity study in rats of unstated duration, no adverse effects were observed at a dose of 2000 mg/kg/day, given through dietary administration (WHO Food Additives Series, 19, pg. 115-116, 1984). Triethyl citrate has been used in oral pharmaceutical formulations and as a direct food additive. The maximum level among approved oral drug formulations is 20.2 mg (FDA Inactive Ingredients Database). Triethyl citrate is classified as GRAS for use as a direct food substance, with no limitation on its use other than current good manufacturing practice (21 CFR 184.191). The Joint FAO/WHO Expert Committee on Food Additives designated 0-20 mg/kg bodyweight as the ADI (acceptable daily intake) for triethyl citrate in 1984 and again in 1999. The estimated maximum daily dose associated with Creon® administration falls within the ADI range. Based on the regulatory information and previous human experience, the ingestion of triethyl citrate due to Creon® administration is not considered to be a safety concern.

Creon® also contains gelatin and several minor excipients, which are present in the capsule shell and imprinting ink. Most of these excipients are also contained in Creon® Minimicrospheres®. Safety and regulatory information about these excipients was previously reviewed (Pharmacology/Toxicology review of NDA 20,725 dated September 4, 2003). Sodium lauryl sulfate is present in the capsule shell in Creon®, but not in Creon® Minimicrospheres®. However, this excipient has been used extensively in approved oral formulations. The maximum level of sodium lauryl sulfate among all approved oral formulations is 51.7 mg (FDA Inactive Ingredients Database). It is likely that the daily intake of sodium lauryl sulfate associated with the maximum dose of Creon® will be less than 51.7 mg, given that it is a minor excipient present only in the capsule shell.

The submitted preclinical information was related to the safety of phthalic acid in Creon®. The maximum dose of phthalic acid associated with Creon® administration is estimated to be \( \text{mg/kg/day} \). The tolerated dose of phthalic acid in the 4-week oral toxicity study in rats was 250 mg/kg/day, which exceeds the estimated maximum dose by 19-fold. Therefore, the 4-week oral toxicity study provides a reasonable assurance of safety for phthalic acid intake associated with Creon® administration. Additional support for the safety of phthalic acid intake from Creon® is provided by the 2-year carcinogenicity studies of phthalic anhydride in rats and mice, and other preclinical studies of o-phthalic acid, p-phthalic acid, and phthalic anhydride.

**RECOMMENDATIONS:**

From a preclinical viewpoint, the application is recommended for approval, with the provision that the labeling be changed as described in the “LABELING” section of this review.
David B. Joseph, Ph.D.  
Pharmacologist, HFD-180

Comment:

Jasti B. Choudary, B.V.Sc., Ph.D.  
Supervisory Pharmacologist, HFD-180

cc:  
Orig NDA 20,725
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Choudary
HFD-180/Dr. Joseph

R/D Init.: S. Chakder 6/20/07

DJ/dbj: 6/25/07

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/s/

David Joseph
6/25/2007 03:33:30 PM
PHARMACOLOGIST

Sushanta Chakder
6/25/2007 05:15:09 PM
PHARMACOLOGIST
Signed for Dr. Choudary
PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 20-725

Product Name: CREON® MINIMICROSHERES®
(Pancrelipase Delayed-Release Capsules, USP)

Sponsor: Solvay Pharmaceuticals, Inc.

Indication: Exocrine pancreatic insufficiency associated with but not limited to cystic fibrosis, chronic pancreatitis, postpancreatectomy, postgastrointestinal bypass surgery, or ductal obstruction of pancreas or common bile duct.

Division: Gastrointestinal and Coagulation Drug Products, HFD-180

Reviewer: David B. Joseph, Ph.D.

Date: September 4, 2003
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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability

The application is recommended for approval.

1.2 Recommendation for nonclinical studies

None.

1.3 Recommendations on labeling

Statements should be included in the “Carcinogenesis, Mutagenesis, Impairment of Fertility” section to indicate that genetic toxicology studies have not been performed, and that fertility studies in animals have not been performed.

2. Summary of nonclinical findings

2.1 Pharmacologic Activity

The pharmacologic activity of Creon® Minimicrospheres® was demonstrated in the minipig model of exocrine pancreatic insufficiency. Creon® produced improvement in the digestion of fat, protein, and starch. No evidence of enzyme absorption was observed in pancreatic duct-ligated pigs after oral administration the drug product. The drug substance produced no effect on gastrointestinal motility mice.

2.2 Toxicological Findings

Oral toxicity studies of the drug substance were performed in dogs, using treatment periods of one and nine months. Changes in small intestine and thyroid were observed in the 1-month study. Administration of 4000 mg/kg/day in the 9-month study produced an increased incidence and severity of fat accumulation in liver. Lesions in the large intestine and thyroid were also observed in the treatment groups. Toxicology studies of the excipients were also submitted. The results of the toxicity studies on the drug substance and excipients do not present a significant safety concern.

2.3 Nonclinical safety issues relevant to clinical use

None.
3. Administrative

A. Reviewer signature: ______________________________

B. Supervisor signature: Concurrence: ______________________________

Non-Concurrence: ______________________________
(see attached memo)

C. cc: list

NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Joseph
HFD-180/Dr. Choudary

R/D Init.: J. Choudary 8/26/03
3.1 INTRODUCTION AND DRUG HISTORY

Pancreatic enzyme preparations (PEPs) of porcine or bovine origin have been marketed in the United States since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938, for treatment of exocrine pancreatic insufficiency in children and cystic fibrosis and chronic pancreatitis in adults. With the exception of one PEP approved in 1996, PEPs have been marketed as OTC products without NDAs. Creon® Microspheres, a delayed-release capsule formulation of pancreatic enzymes, was initially marketed in Germany starting in 1982, followed by approval in over 50 countries. This product was marketed in the United States from 1987 to 1993. Creon® Minimicrospheres® was subsequently developed and has been marketed in the United States since 1993 following the withdrawal of the microsphere formulation. Creon® Minimicrospheres® was initially approved in 1990 in Germany. The Sponsor is seeking approval of Creon® Minimicrospheres® (Pancrelipase Delayed-Release Capsules, USP) in the present application. This application was submitted on July 31, 1997, and was placed under AIP (Application Integrity Policy) shortly thereafter. The review of the application was suspended until the Sponsor was removed from AIP on April 9, 2003.
NDA number: 20-725

Review number: 1

Sequence number/date/type of submission: 000/July 31, 1997/Original submission
000/December 16, 2002/Amendment

Information to Sponsor: ( )Yes (x)No

Sponsor and/or agent: Solvay Pharmaceuticals, Inc.
Marietta, Georgia

Manufacturer of drug substance: Scientific Protein Laboratories
Division of American Home Products
Waunakee, Wisconsin

Reviewer name: David B. Joseph, Ph.D.

Division name: Gastrointestinal and Coagulation Drug Products

HFD #: 180

Review completion date: September 4, 2003

Drug:
Trade name: CREON® MINIMICROSPHERES®
Generic name: Pancrelipase Delayed-Release Capsules, USP
Code name: none
Chemical names: Triacylglycerol lipase; Lipase of pancreas
CAS registry number: 9001-62-1
Molecular formula/molecular weight: not applicable
Structure: not applicable

Relevant INDs/NDAs/DMFs: IND 47,546 (Creon® (Pancrelipase) Delayed Release MINIMICROSPHERES™ Capsules); Solvay Pharmaceuticals, Inc./DMF 9649

Drug class: digestive aid for treatment of exocrine pancreatic insufficiency

Indication: Exocrine pancreatic insufficiency associated with but not limited to cystic fibrosis, chronic pancreatitis, postpancreatectomy, postgastrointestinal bypass surgery, or ductal obstruction of pancreas or common bile duct.

Dose: The maximum recommended dose is 6000 USP lipase units/kg/meal (equal to 90 mg pancrelipase/kg/meal, based on the Sponsor’s information). The dose levels for the major product ingredients are listed in the following table. These dose levels were estimated based on an assumed maximum daily ingestion of 60 capsules of Creon® 5, Creon® 10, or Creon® 20 in
a 60-kg adult (equivalent to 20 capsules in a 20-kg child). Ingestion of 60 Creon® 20 capsules daily would result in a daily dose of 20,000 USP lipase units/kg/day, which is equal to the maximum recommended dose of 6000 USP lipase units/kg with each of three meals, plus 2000 USP lipase units/kg with snacks.

<table>
<thead>
<tr>
<th>Drug Substance</th>
<th>Creon® 5 mg/kg/day</th>
<th>Creon® 10 mg/kg/day</th>
<th>Creon® 20 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancrelipase</td>
<td>(b)</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>Amylase</td>
<td>USP U/kg/day</td>
<td>USP U/kg/day</td>
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<tr>
<td>Lipase</td>
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<tr>
<td>Excipients</td>
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<td></td>
<td>Dibutyl phthalate</td>
<td>Dimethicone 1000</td>
<td>Iron oxide</td>
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<tr>
<td></td>
<td>Titanium dioxide</td>
<td>FD&amp;C Blue No. 2</td>
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Clinical formulation: Creon® Minimicrospheres® are capsules containing porcine-derived pancrelipase (concentrate of pancreatic enzymes) in enteric-coated Minimicrospheres®. This formulation is resistant to gastric inactivation. The ingredients are listed in the following table (taken directly from the Sponsor’s submission).
It is noteworthy that “Pancreatin” is listed as the drug substance in the above table. However, the actual drug substance is pancrelipase. Both of these terms refer to a powder concentrate of pancreatic enzymes derived from pigs. Pancrelipase contains standardized levels of lipase activity (USP Dictionary of USAN and International Drug Names, 1995). It is likely that “Pancreatin” is listed in the above table because “pancrelipase” is not a recognized term in Europe, and Creon® Minimicrospheres® are manufactured in Germany. The term “FIP” in the

**Route of administration:** oral

**Proposed use:** Treatment of exocrine pancreatic insufficiency in adults and cystic fibrosis in pediatric patients.

**Disclaimer:** Tabular and graphical information were constructed by the reviewer unless cited otherwise.

**Publication List:** In a pre-NDA meeting on June 14, 1994, the Division of Gastrointestinal and Coagulation Drug Products requested that the Sponsor provide all available toxicology information on each excipient. In response to this request, the Sponsor submitted the following publications in IND 47,546 and in the present NDA.


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Hodge, J Pharmacol, 80, pg. 250, 1944.
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vан Velzen et al., Postgrad Med J, 72(Suppl. 2), pg. 539, 1996.
Studies reviewed within this submission:

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<tr>
<td>Effects of Creon® 10,000 Minimicrospheres on Fat Digestion in a Minipig Model of Exocrine Pancreatic Insufficiency** Solvay Pharmaceuticals Hannover, Germany</td>
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</tr>
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<td>Effects of Kreon® 10,000 Minimicrospheres on Nutrient Digestibility in a Minipig Model of Exocrine Pancreatic Insufficiency** Institute of Animal Nutrition School of Veterinary Medicine Hannover, Germany</td>
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</tr>
<tr>
<td><strong>SAFETY PHARMACOLOGY:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Charcoal Propulsion Test in Mice** Solvay Pharmaceuticals GmbH Hannover, Germany.</td>
<td>0031</td>
<td>20</td>
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<tr>
<td><strong>PHARMACOKINETICS/TOXICOKINETICS:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancrelipase</td>
<td></td>
<td></td>
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<tr>
<td>Absorption and Plasma Kinetics of Pancreatic Enzymes in Pigs Treated with Creon® Minimicrospheres**</td>
<td>0070</td>
<td>21</td>
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<tr>
<td>Hydroxypropylmethylcellulose Phthalate</td>
<td></td>
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<tr>
<td>Absorption of $^{14}$C-Hydroxypropylmethylcellulose Phthalate (HPMCP) After Oral Administration*</td>
<td></td>
<td>23</td>
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<tr>
<td>Distribution of $^{14}$C-Hydroxypropylmethylcellulose Phthalate (HPMCP) After Oral Administration*</td>
<td></td>
<td>24</td>
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<tr>
<td>Identification of HPMCP Metabolites in Urine and Feces After Oral Administration*</td>
<td></td>
<td>24</td>
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<tr>
<td>Excretion of $^{14}$C-Hydroxypropylmethylcellulose Phthalate After Oral Administration*</td>
<td></td>
<td>25</td>
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<tr>
<td>Dibutyl Phthalate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Summary of ADME Information*</td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>
### Dimethicone 1000

**Brief Summary of ADME Information**

#### Light Mineral Oil

- Distribution of $^{3}$H-Mineral Oil After Single-Dose or Multiple-Dose I.P. Administration in Rats
- Distribution of $^{3}$H-Mineral Oil After Single-Dose or Multiple-Dose Oral Administration in Rats
- Identification of $^{3}$H-Mineral Oil and $^{3}$H-Non-Mineral Oil in Tissues and Feces After I.V. and Oral Administration of $^{3}$H-Mineral Oil
- Excretion of $^{3}$H-Mineral Oil After Single-Dose or Multiple-Dose I.P. Administration in Rats
- Excretion of $^{3}$H-Mineral Oil After Single-Dose or Multiple-Dose Oral Administration in Rats

#### TOXICOLOGY:

**Pancrelipase**

- 4-Week Subchronic Toxicity Study of Pancreatin Powder and Pellets by Oral Administration (Twice Daily) to Beagle Dogs

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Code 1</th>
<th>Code 2</th>
<th>Code 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Week Subchronic Toxicity Study of Pancreatin Powder</td>
<td>0012</td>
<td>0057</td>
<td></td>
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<tr>
<td>and Pellets by Oral Administration (Twice Daily) to</td>
<td>(powder)</td>
<td>(pellets)</td>
<td></td>
</tr>
<tr>
<td>Beagle Dogs**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Code 1</th>
<th>Code 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-Month Chronic Toxicity Study of Pancreatin Powder</td>
<td>0122, 0146</td>
<td></td>
</tr>
<tr>
<td>by Oral Administration (Twice Daily) to Beagle Dogs**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hydroxypropylmethylcellulose Phthalate**

- Acute Oral Toxicity Study in Rats
- 1-Month Oral Toxicity Study of HPMCP (Rats)
- 6-Month Oral Toxicity Study of HPMCP (Rats)

**Dibutyl Phthalate**

- Brief Summary of General Toxicology
- Brief Summary of Reproductive Toxicology

**Dimethicone 1000**

- Acute Oral Toxicity Study in Rats
3.2 PHARMACOLOGY

3.2.1 Brief summary

The efficacy of the drug product was demonstrated in the minipig model of exocrine pancreatic insufficiency. The drug substance had no effect on gastrointestinal motility in mice.

3.2.2 Primary pharmacodynamics

Mechanism of action: The pancreatic enzymes catalyze the following digestive reactions: hydrolysis of fats to monoglycerol, glycerol, and fatty acids; hydrolysis of protein into short-chain peptides (2-5 amino acids); hydrolysis of starch into dextrins and short-chain sugars.

Drug activity related to proposed indication: Increased digestion of fat, protein, and starch, as shown in the following studies.
Effects of Creon 10,000 Minimicrospheres on Fat Digestion in a Minipig Model of Exocrine Pancreatic Insufficiency

Methods: This study was conducted by Solvay Pharmaceuticals (Hannover, Germany). Seven female Götttingen minipigs (approximately 25 kg) were used. This species was chosen for this study for the following reasons: a large animal was necessary to test the clinical formulation; the pig is a good model for human digestion/absorption and nutrition; the pig has a digestive system that is most similar to that of humans. The pancreatic duct was surgically ligated in three of the study animals to achieve exocrine pancreatic insufficiency. Sham-operations were performed in the four remaining animals. All minipigs were implanted with T-cannulae in jejunum and ileum. A period of at least two weeks was allowed for recovery from surgery, prior to the initiation of studies. Pancreatic exocrine status was monitored before and during the study through the measurement of chymotrypsin in stool. Fluid samples were collected from jejunum and ileum for measurement of pH. For the digestibility studies, one unoperated control minipig was compared with the four sham-operated controls to assess the influence of the fistulation on digestibility. All minipigs were fed twice daily with 250 g of 3%, 20%, or 40% fat diet, with eight hours between feedings. Administration of the 40% fat diet in pancreatic insufficient minipigs was combined with the oral administration of 2, 4, 8, or 16 Creon 10,000 minimicrospheres capsules. The enzyme dose levels were equivalent to approximately 800, 1600, 3200, or 6400 FIP lipase units/kg, respectively (FIP units are the same as USP lipase units). The declared enzyme activity of the test article was 8,000 FIP amylase units, 10,000 FIP lipase units, and 600 FIP protease units per capsule (see “Clinical Formulation” section for explanation of FIP units). Stool was collected for three days for each diet mixture. The dry matter and fat content in stool samples were measured. The calculation of digestibility for dietary dry matter and fat was done using the following equation:

\[
\text{Digestibility (\%) = } \frac{(g/\text{day in feed}) - (g/\text{day in stool})}{(g/\text{day in feed})} \times 100
\]

Results: The stool chymotrypsin content was reduced by approximately 97% in the pancreatic insufficient minipigs at a minimum of nine days after ligation of the pancreatic duct, in comparison to the control group value or the mean value measured prior to duct ligation. Jejunal and ileal lipase activity was reduced by approximately 99% in the P.I. (pancreatic insufficient) animals.

The pH values that were measured in fluid collected from jejunum are shown in the following table (taken directly from the study report).
A small reduction in pH was observed prior to diet consumption and at 5 min after feeding in the P.I. animals, presumably due to the loss of pancreatic bicarbonate secretion. Supplementation of the 40% fat diet with Creon had no effect on the reduction in jejunal pH. The reduction of ileal pH values in the P.I. animals was minimal.

The effects of pancreatic duct ligation on the digestibility of dry matter and fat was evaluated.

The digestibility of dry matter and fat were significantly reduced in the diets containing 20% and 40% fat, whereas no significant changes occurred with the 3% fat diet. The effect of Creon 10,000 minicapsules on the digestibility of the 40% fat diet in pancreatic insufficient animals is shown in the following table (taken directly from the study report).

### Table 2c

<table>
<thead>
<tr>
<th>Group</th>
<th>Diet - ½ h</th>
<th>+ 5 min</th>
<th>+ ½ h</th>
<th>+ 1 h</th>
<th>+ 2 h</th>
<th>+ 4 h</th>
<th>+ 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 25) Mean of all diets</td>
<td>6.40 ± 0.64 (n = 21)</td>
<td>6.66 ± 0.39 (n = 25)</td>
<td>6.30 ± 0.34 (n = 25)</td>
<td>5.85 ± 0.26 (n = 25)</td>
<td>5.68 ± 0.38 (n = 25)</td>
<td>5.84 ± 0.61 (n = 22)</td>
<td>6.24 ± 0.55 (n = 21)</td>
</tr>
<tr>
<td>P.I. (n = 24) Mean of all diets</td>
<td>5.96 ± 0.55* (n = 21)</td>
<td>6.02 ± 0.68*** (n = 19)</td>
<td>6.13 ± 0.44 (n = 23)</td>
<td>5.96 ± 0.41 (n = 23)</td>
<td>5.87 ± 0.27 (n = 24)</td>
<td>6.05 ± 0.34 (n = 23)</td>
<td>5.94 ± 0.48 (n = 20)</td>
</tr>
</tbody>
</table>

* P < 0.05, *** P < 0.001 (Student t test)

n = number of observations

### INFLUENCE OF CREON 10,000 MMS ON APPARENT DIGESTIBILITY OF A 40% FAT DIET IN PANCREATIC EXOCRINE INSUFFICIENT MINIPIGS

<table>
<thead>
<tr>
<th>Creon 10,000 capsules/meal</th>
<th>MEAN APPARENT DIGESTIBILITY (%)</th>
<th>Dry Matter</th>
<th>Total Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>54.29 ± 2.13</td>
<td>36.84 ± 1.46</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>51.27 ± 5.64</td>
<td>44.61 ± 4.08 a</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61.16 ± 5.22 b</td>
<td>57.80 ± 5.38 ab</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>64.72 ± 6.19 b</td>
<td>60.68 ± 6.46 ab</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>75.09 ± 1.80 abc</td>
<td>74.88 ± 3.98 abc</td>
<td></td>
</tr>
</tbody>
</table>

Results are mean ± S.D.

a, b, c = P < 0.05 (paired t test) versus 0, 2, 4 caps/meal respectively

Creon produced a dose-dependent increase in the digestibility of dry matter and fat.

**Conclusions:** Supplementation of the high-fat diet with Creon 10,000 minicapsules in pancreatic insufficient minipigs produced a dose-dependent improvement in the digestibility of fat and dry matter. The adequacy of the model of exocrine pancreatic insufficiency in this study was well supported by the study results.
Effects of Kreon® 10,000 Minimicrospheres on Nutrient Digestibility in a Minipig Model of Exocrine Pancreatic Insufficiency (Tabeling et al., J Anim Physiol Anim Nutr, 82, pg. 251, 1999)

**Methods:** This study was conducted at the Institute of Animal Nutrition, School of Veterinary Medicine (Hannover, Germany). Six adult Göttingen minipigs (mean weight of 30 kg) were fitted with an ileo-cecal re-entrant fistula. In three of the minipigs, the pancreatic duct was ligated, which resulted in very low to zero activity of chymotrypsin in feces and no activity in ileal chyme. The animals were allowed to adapt to the study diet for at least 10 days prior to collection of feces and 7 days prior to collection of ileal chyme. The diet was given at regular 12-hr intervals starting at least three days prior to and during collection of ileal chyme. Chromic oxide was added to the diet (2.5 g/kg fresh matter) to enable correction for a 100% recovery rate of ileal chyme. Total ileal chyme was collected during 2-hr intervals, 12 hr/day, for three days. Feces was collected for five days. The collection of ileal chyme and feces occurred during separate periods. The estimated losses of NaCl and KCl in ileal chyme was replaced by infusion in the large intestine. Intact (non-ligated) minipigs were used as the control group. PL (pancreatic duct-ligated) minipigs were given the study diet without enzyme supplementation, or with escalating doses of Kreon® 10,000 mms (minimicrospheres) during separate experiments. The declared enzyme activity of Kreon® 10,000 mms was 11,200 FIP amylase units, 14,000 FIP lipase units, and 665 FIP protease units per capsule (see “Clinical Formulation” section for explanation of FIP units). Ileal chyme and feces were collected from the control minipigs, PL minipigs with no enzyme supplementation, PL minipigs treated with 8 capsules/meal, PL minipigs treated with 16 capsules/meal, and PL minipigs treated with 24 capsules/meal. The estimated enzyme dose levels of Kreon® 10,000 mms were 3733, 7467, and 11,200 FIP lipase units/kg bodyweight/meal in minipigs given 8, 16, and 24 capsules/meal, respectively (FIP units are the same as USP lipase units).

**Results:** The results of the analysis of ileal chyme samples are shown in the following table (taken directly from the study report).

![Table 2. Composition of ileal chyme](Best Possible Copy)
The DM (dry matter) content in chyme was increased in the PL-0 group (pancreatic duct ligation with no enzyme supplementation). However, supplementation with Kreon® 10,000 mms in the pancreatic duct-ligated minipigs (PL-8, PL-16, and PL-24) produced a dose-dependent reduction in DM content to levels that were slightly lower than the control group. Viscosity was unaffected in the PL-0 group, but was reduced with each dose level of Kreon® 10,000 mms. The LPS (lipopolysaccharide) content was increased by 22-fold in the PL-0 group, indicative of an increased gram-negative bacterial presence. LPS levels were markedly reduced in the Kreon®-treated minipigs, with values in the PL-16 and PL-24 groups that were similar to the control value.

The results of fecal analysis are shown in the following table (taken directly from the study report).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Amount (FM, g/day)</th>
<th>DM-content (%)</th>
<th>LPS-content (ng/g FM)</th>
<th>Total bacterial count (CFU/g faeces)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83.3 ± 20.5</td>
<td>68.7 ± 2.4</td>
<td>85.4 ± 28.3</td>
<td>8.8 ± 10^7 ± 5.5 ± 10^7</td>
</tr>
<tr>
<td>PL-0</td>
<td>351.7 ± 50.6</td>
<td>50.1 ± 3.3</td>
<td>2700 ± 796.7</td>
<td>9.8 ± 10^8 ± 9.3 ± 10^8</td>
</tr>
<tr>
<td>PL-8</td>
<td>294.1 ± 54.5</td>
<td>50.7 ± 3.6</td>
<td>2440 ± 1247</td>
<td>3.5 ± 10^8 ± 1.5 ± 10^8</td>
</tr>
<tr>
<td>PL-16</td>
<td>265.6 ± 63.4</td>
<td>49.4 ± 5.8</td>
<td>2440 ± 1247</td>
<td>not analysed</td>
</tr>
<tr>
<td>PL-24</td>
<td>208.0 ± 42.9</td>
<td>51.4 ± 2.2</td>
<td>1980 ± 1093</td>
<td></td>
</tr>
</tbody>
</table>

The amount of feces (FM, g/day) was increased by 4-fold in the PL-0 group. Supplementation with Kreon® produced only a partial reversal of this effect. At the highest dose level, the daily output of feces was still increased by over 2-fold. DM content was similarly reduced in the PL-0 group and the Kreon®-treated PL groups. The LPS content was increased by 31-fold in the PL-0 group, indicative of an increased gram-negative bacterial number. Kreon® supplementation produced a minimal reduction of LPS in the PL minipigs. E. coli and gram negative anaerobes were increased in the PL-0 group.

The nutrient content in ileal chyme and feces was measured to assess the pre-cecal digestibility and total digestibility of nutrients, respectively. The results are shown in the following tables (taken directly from the study report). The data are expressed as the percent digestibility.
The PL-0 group exhibited reduced pre-cecal digestibility for the following dietary components: DM (dry matter), OM (organic matter), CP (crude protein), CF (crude fat), CFI (crude fiber), NfE (nutrient-free extract), and starch (table 5). Treatment with Kreon® produced a dose-dependent increase in pre-cecal digestibility for each of these dietary components. The results from the measurement of pre-cecal and total digestibility were generally similar, with respect to the effect of Kreon®. However, the pre-cecal digestibility in the PL-0 group was reduced by a greater magnitude, as compared with the reduction in total digestibility. The only exception to this difference was crude fat digestion.

**Conclusions:** In pancreatic duct-ligated minipigs, Kreon® 10,000 mms produced a dose-dependent increase in nutrient digestibility, expressed as either pre-cecal or total digestibility. Daily fecal output was strongly increased in the pancreatic duct-ligated minipigs, and treatment with Kreon® 10,000 mms produced only a partial reversal of this effect. The depletion of pancreatic enzymes in this model of exocrine pancreatic insufficiency resulted in an increased number of gram-negative bacteria in ileal chyme, as indicated by the marked increase in LPS concentration. The elevated LPS concentration in chyme was restored to the control level by supplementation with Kreon®. However, elevated LPS levels in feces were minimally affected by Kreon®.

### 3.2.3 Secondary pharmacodynamics

No information was provided.

### 3.2.4 Safety pharmacology

**Neurological effects:** No studies were submitted.
Cardiovascular effects: No studies were submitted. Heart rate and systolic pressure were unaffected in the 1-month and 9-month oral toxicity studies of pancreatin in dogs.

Pulmonary effects: No studies were submitted.

Renal effects: No studies were submitted.

Gastrointestinal effects: See study below.

**Charcoal Propulsion Test in Mice**

**Methods:** This study was conducted by Solvay Pharmaceuticals GmbH (Hannover, Germany). Male NMRI mice (about 14 days old, 22-30 g) were fasted overnight. The mice were treated orally with 0 (vehicle), 1500 mg/kg pancreatin, or 0.05 mg/kg clonidine HCl as a positive control (10 mice/group). The dose level of pancreatin was equal to approximately 200,000 FIP lipase units/kg (FIP units are the same as USP lipase units), which is 10-fold higher than the estimated maximum daily dose in humans. It is assumed that the test article was actually pancrelipase, but was referred to as “pancreatin” by the authors since “pancrelipase” is not a recognized term in Europe. The dose volume for each group was 10 ml/kg. Saline was used as the vehicle for pancreatin. At 45 min after drug administration, the mice were treated orally with 0.25 ml of a 5% charcoal suspension. The vehicle used for the charcoal suspension and clonidine HCl was 1% methylhydroxyethylcellulose + 1% poloxamer. The mice were sacrificed at 40 min after administration of the charcoal suspension. The stomach to cecum segment of the gastrointestinal tract was removed and the distance traversed by the charcoal bolus was measured, starting from the pyloric sphincter. The data was expressed as the relative distance of charcoal propulsion (RDC), calculated from the distance traversed and the total length of the small intestine.

**Results:** No clinical signs were observed in any of the study groups. The RDC values are shown in the following table.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RDC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>63.5 ± 11.3</td>
</tr>
<tr>
<td>1500 mg/kg Pancreatin</td>
<td>68.1 ± 10.2</td>
</tr>
<tr>
<td>0.05 mg/kg Clonidine</td>
<td>40.0 ± 9.9*</td>
</tr>
</tbody>
</table>

Values are the mean ± S.D.  
*p<0.01 (t-test)

Pancreatin had no effect on charcoal propulsion, whereas clonidine produced a significant reduction. The mean RDC value in the vehicle control group was within the expected range of 45-75%.

**Conclusions:** Pancreatin did not affect gastrointestinal motility.

**Abuse liability:** No studies were submitted.

**Other:** No studies were submitted.
3.2.5 Pharmacodynamic drug interactions

No information was provided.

3.3 PHARMACOKINETICS/TOXICOKINETICS:

3.3.1 Pancrelipase

3.3.1.1 Brief Summary

No evidence of enzyme absorption was observed in pancreatic duct-ligated pigs treated with the drug product.

3.3.1.2 Absorption

**Absorption and Plasma Kinetics of Pancreatic Enzymes in Pigs Treated with Creon® Minimicrospheres®**

**Methods:** This study was performed using 32 pigs (13.6 ± 1.9 kg, age eight weeks) for measurement of pancreatic enzyme absorption following oral administration of Creon® 10,000 mms (Minimicrospheres®), and six pigs (13.7 ± 1.4 kg) for measurement of plasma kinetics following intravenous administration of pancreatic juice. Pancreatic duct ligation was performed on 30 pigs. Total pancreatectomy was performed on five pigs and three pigs were sham-operated. Blood sugar levels were monitored in the pancreatectomized pigs, and insulin was administered when the blood sugar exceeded 10-15 mmol/l. The pigs were maintained on a regular diet and fed twice daily. In the absorption study, a total of four oral doses of Creon® 10,000 mms or placebo were administered to each animal. Each dose was administered during the first feeding of each dosing period (48 hr). Blood was collected at 30 and 0 min before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hr post after dosing. Pancreatic lipase activity in plasma was measured using [3H]triolein as the substrate. Plasma levels of procolipase + colipase and IRCT (immunoreactive cationic trypsin) were measured using an ELISA method. The dosing schedule is shown in the following table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Surgery</th>
<th>N</th>
<th>Creon 10,000 mms (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Sham</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ascending Dose</td>
<td>Pancreatectomy</td>
<td>5</td>
<td>0 0 4 8</td>
</tr>
<tr>
<td>Control</td>
<td>Pancreatic Duct Ligation</td>
<td>6</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Ascending Dose</td>
<td>Pancreatic Duct Ligation</td>
<td>8</td>
<td>0 2 4 8</td>
</tr>
<tr>
<td>Descending Dose</td>
<td>Pancreatic Duct Ligation</td>
<td>6</td>
<td>8 4 2 0</td>
</tr>
<tr>
<td>Latin Square</td>
<td>Pancreatic Duct Ligation</td>
<td>1</td>
<td>8 0 4 2</td>
</tr>
<tr>
<td>Latin Square</td>
<td>Pancreatic Duct Ligation</td>
<td>1</td>
<td>2 4 0 8</td>
</tr>
<tr>
<td>Latin Square</td>
<td>Pancreatic Duct Ligation</td>
<td>1</td>
<td>0 2 8 4</td>
</tr>
<tr>
<td>Latin Square</td>
<td>Pancreatic Duct Ligation</td>
<td>1</td>
<td>4 8 2 0</td>
</tr>
</tbody>
</table>
The declared enzyme activity was 52,128 FIP amylase units, 52,441 FIP lipase units, and 3,202 FIP protease units per gram of minicapsules (see “Clinical Formulation” section for explanation of FIP units).

In the plasma kinetics study, six pigs were treated intravenously with sterile pancreatic juice (392 FIP lipase units/ml). This treatment was performed twice before and twice after pancreatic duct ligation. A washout period of two days was allowed between each dose. The dosing schedule is shown in the following table.

<table>
<thead>
<tr>
<th>Pig</th>
<th>Dose # 1</th>
<th>Dose # 2</th>
<th>Dose # 3</th>
<th>Dose # 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>B</td>
<td>16</td>
<td>8</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>16</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>16</td>
<td>8</td>
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<td>16</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Blood was collected at 30 and 0 min before dosing, and at 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hr post-dose. Pancreatic lipase activity in plasma was measured.

**Results:** All pigs maintained normal eating habits. However, weight gain was strongly reduced in the pancreatic-duct ligated and pancreatectomized pigs (data not shown in report). The pancreatectomized pigs displayed signs of diabetes mellitus (i.e. elevated glucose levels). Sporadic increases in plasma pancreatic lipase activity were observed in the pancreatic duct-ligated control group (before and after administration of placebo), but not in the sham-operated control group. Peaks of pancreatic lipase activity also occurred in the pancreatic duct-ligated pigs given ascending doses of Creon®, most often at 30 min before and at 12, 24, and 48 hr after dosing. Similar results were observed for the pancreatectomized ascending-dose group, the pancreatic duct-ligated descending dose group, and the pancreatic duct-ligated group dosed according to a Latin Square design. The increases in plasma pancreatic lipase activity following Creon® administration were not dose-related, and were consistent with the sporadic increases that occurred in the pancreatic duct-ligated control group. Plasma levels of procolipase + colipase and IRCT (immunoreactive cationic trypsin) were about 50 ng/ml and 150 ng/ml, respectively, in the pancreatic-duct ligated control group. These levels did not change substantially after feeding. Creon® administration had no effect on the plasma concentration of procolipase + colipase or IRCT in the pancreatic duct-ligated ascending dose group or the pancreatectomized ascending dose group (plasma enzyme levels from the remaining groups were not reported).

The plasma kinetic parameters for pancreatic lipase activity in pigs treated intravenously with pancreatic juice could not be estimated in four of the six animals due to extremely low activity in the plasma samples. In the other two pigs, the range of \( t_{1/2} \) values prior to surgical ligation of the pancreatic duct was 4.3-12.4 min. The \( t_{1/2} \) values were 2.5-9.9 min after ligation. The plasma \( t_{1/2} \) was not dependent on dose level. The short \( t_{1/2} \) value for pancreatic lipase activity is a further
indication that the peak plasma lipase activities associated with late time-points in the absorption study were not related to Creon® administration. The pancreatic juice that was used in the plasma kinetics study contained about 120 U/ml of pancreatic lipase activity. Upon addition of the pancreatic juice to blood samples, the recovery of lipase activity was 80-134%. The assay for measuring pancreatic lipase activity involved the use of \(^{3}H\)triolein as the substrate. This assay appeared to be highly specific for pancreatic lipase, based on the extremely low sensitivity for the detection of lipoprotein lipase and hepatic lipase activity.

**Conclusions:** Pancreatic lipase, procolipase/colipase, and trypsin were not absorbed after oral administration of Creon® 10,000 mms in pancreatic duct-ligated pigs or in pancreatectomized pigs. A sporadic incidence of increased plasma pancreatic-like lipase activity was observed with and without Creon® administration. The authors suggested that the extra-pancreatic source of lipase activity may have been the duodenal bulb, antrum, gastroesophageal junction, esophagus, leukocytes, adipose tissue, lung, brain, or the entire small intestine, based on published reports.

### 3.3.2 Hydroxypropylmethylcellulose Phthalate (HPMCP)

#### 3.3.2.1 Brief summary

Orally administered \(^{14}C\)HPMCP was poorly absorbed in rats. The gastrointestinal contents contained most of the radioactive dose at 6 hr post dose (93.3% in males, 81.5% in females). Phthalic acid was identified as a major metabolite. Excretion occurred mostly in feces (94.8% in males, 91.4% in females).

#### 3.3.2.2 Absorption

The following study was reported in: Kitagawa et al., Pharmacometrics, 8(8), pg. 1123, 1974.

1. **Absorption of \(^{14}C\)-Hydroxypropylmethylcellulose Phthalate (HPMCP) After Oral Administration (Ref. 20 Provided by Sponsor).**

   **Animals:** Male and female Wistar rats (160-180 g; ages were not provided).

   **Methods:** Rats were orally administered 1.3 g/kg of HPMCP diluted with \(^{14}C\)-HPMCP (specific activity of 700 μCi/ng); vehicle was 1.5% sodium bicarbonate. Radioactivity was measured by a liquid scintillation counter. Detailed methodology was not provided.

   **Results:** Peak plasma level of HPMCP (converted from dpm/ml to μg/ml by authors) was approximately 15 μg/ml in males at 2 hr after dosing and approximately 15 μg/ml in females at 6 hr after dosing. Thereafter, plasma levels gradually diminished and were near zero at 72 hr after dosing. More detailed results were not provided.
3.3.2.3 Distribution

The following study was reported in: Kitagawa et al., Pharmacometrics, 8(8), pg. 1123, 1974.

1. Distribution of $^{14}$C-Hydroxypropylmethylcellulose Phthalate (HPMCP) After Oral Administration (Ref. 20 Provided by Sponsor).

**Animals:** Male and female Wistar rats (160-180 g; ages were not provided).

**Methods:** Rats were orally administered 1.3 g/kg of HPMCP diluted with $^{14}$C-HPMCP (specific activity of 700 μCi/mg); vehicle was 1.5% sodium bicarbonate. Subgroups of animals (numbers were not specified) were sacrificed at 1, 6, 12, 24, 48 and 72 hr after dosing. Distribution of radioactivity was determined in tissue samples from cerebrum, cerebellum, heart, liver, lungs, kidneys, adrenals, thyroid, spleen, fat, testicles and prostate. Radioactivity was measured with a scintillation counter. Authors converted radioactivity values to percent of total dose.

**Results:** Concentrations of HPMCP in the above tissue samples were very low. For example, the highest concentration of HPMCP was in the liver, being 0.02% of the total dose at 1 hr after dosing in males; 0.03% of the total dose in females. In contrast, 93.3% of the total dose was located in gastrointestinal contents in males at 6 hr after dosing; 81.5% in females.

3.3.2.4 Metabolism

The following study was reported in: Kitagawa et al., Pharmacometrics, 8(8), pg. 1123, 1974.

1. Identification of HPMCP Metabolites in Urine and Feces After Oral Administration (Ref. 20 Provided by Sponsor).

**Animals:** Male and female Wistar rats (160-180 g; ages were not provided).

**Methods:** Rats were orally administered 1.3 g/kg of HPMCP diluted with $^{14}$C-HPMCP (specific activity of 700 μCi/mg); vehicle was 1.5% sodium bicarbonate. Animals were placed in metabolism cages; urine was collected for 24 hr and feces were collected for 12 to 24 hrs. Urine samples were acidified with HCl and extracted with ethyl ether. Extracts were dehydrated, concentrated under vacuum and analyzed with thin-layer chromatography. Comparative standards were phthalic acid, monomethyl phthalate, and dimethyl phthalate. Feces were lyophilized, acidified with acetic acid and extracted with acetone. The acetone extract was concentrated under vacuum and analyzed on a Sephadex LH-20 column. Comparative standard was $^{14}$C-HPMCP.
**Results:** The major metabolite in urine was phthalic acid. Two other relatively minor metabolites were not identified. In the case of feces, the acetone extract was identified as being entirely \(^{14}\text{C}\)-HPMCP.

### 3.3.2.5 Excretion

The following study was reported in: Kitagawa et al., Pharmacometrics, 8(8), pg. 1123, 1974.

1. **Excretion of \(^{14}\text{C}\)-Hydroxypropylmethylcellulose Phthalate After Oral Administration (Ref. 20 Provided by Sponsor).**

**Animals:** Male and female Wistar rats (160-180 g; ages were not provided).

**Methods:** Rats were orally administered 1.3 g/kg of HPMCP diluted with \(^{14}\text{C}\)-HPMCP (specific activity of 700 \(\mu\text{Ci/mg}\)); vehicle was 1.5% sodium bicarbonate. Animals were placed in metabolism cages. Urine was collected at intervals of 0-6, 6-12, 12-24, 24-48 and 48-72 hrs. Feces were collected at intervals of 0-24, 24-48 and 48-72 hrs. Radioactivity was measured with a scintillation counter.

**Results:** In males at 72 hrs after dosing, 0.7% and 94.8% of total radioactivity was accounted for in the urine and feces, respectively. In females at 72 hrs after dosing, 1.2% and 91.4% of total radioactivity was accounted for in the urine and feces, respectively.

### 3.3.3 Dibutyl Phthalate

#### 3.3.3.1 Brief summary


Since the results of preclinical ADME studies for dibutyl phthalate were summarized in the reviews, full descriptions of methods and presentations of quantitated data were not provided.

Orally administered dibutyl phthalate was rapidly absorbed in rats and hamsters.

Orally administered \(^{14}\text{C}\)-dibutyl phthalate in rats was distributed throughout the body. At 48 h after oral administration of a single dose, no organ contained more than 0.7% of the administered dose. When rats were fed 0.1% of dibutyl phthalate in the diet for up to 12 weeks, there was no accumulation of dibutyl phthalate in any organ that was studied.
Final metabolic products of dibutyl phthalate included phthalic acid, monobutyl phthalate glucuronide, 3-keto-butyl phthalate and 4-carboxypropyl phthalate. In vitro studies demonstrated that dibutyl phthalate is metabolized by liver homogenates from rats and is hydrolyzed by liver and intestinal-mucosal cell homogenates from the rat, ferret and baboon.

When dibutyl phthalate was orally administered to rats, 63% to 97% of the administered dose was accounted for in the urine during the first 24 h after dosing. In the case of orally administered [\(^{14}\)C]-dibutyl phthalate in the rat, 85% to 100% of the administered dose was accounted for in the urine during the first 24 h. When dibutyl phthalate was orally administered to hamsters, 79% of the administered dose was accounted for in the urine during the first 24 h after dosing.

3.3.4 Dimethicone 1000

3.3.4.1 Brief summary

The following study was reported in: Anonymous, J Amer Coll Toxicol, 1(4), pg. 33, 1982.

Full descriptions of pharmacokinetic methods and presentations of quantitated data were not provided. Silicone compounds do not easily cross membranes and, thus, are not readily absorbed from the gastrointestinal tract. When [\(^{14}\)C]-dimethicone fluid was injected into the hind limbs of rats, dimethicone was not metabolized, but was stored primarily in the gastrointestinal tract. When [\(^{14}\)C]-dimethicone (15 and 100 \(\mu\)Ci) was intraperitoneally administered to rats, 51% of the administered dose was accounted for in adipose tissue at 25 days after dosing; 27% and 15% in gastrointestinal tissues and liver, respectively.

3.3.5 Light Mineral Oil

3.3.5.1 Brief summary

The distribution of total radioactivity was mostly limited to the gastrointestinal tract contents following oral administration of \([\(^3\)H]mineral oil in rats (80% at 8 hr post-dose). Both \([\(^3\)H]mineral oil and \([\(^3\)H]metabolites with increased polarity were detected in tissue extracts. At two days after oral administration of \([\(^3\)H]mineral oil in rats, about 80% of the total radioactivity was recovered in feces. The cumulative urinary excretion was 7-8% during one week post-dose. Following intraperitoneal administration, 11% of the total radioactivity was excreted in feces and 8% was excreted in urine at eight days post-dose. These results suggest that \([\(^3\)H]mineral oil is poorly absorbed following oral administration in rats.

3.3.5.2 Absorption

No information (i.e. plasma level measurements) from animal studies was provided.
3.3.5.3 Distribution

The following study was reported in: Ebert et al., J Pharmaceut Studies, 55(9), pg. 923, 1966.

1. Distribution of \(^3\)H-Mineral Oil After Single-Dose or Multiple-
   Dose I.P. Administration in Rats (Ref. 15 Provided by Sponsor).

   Animals: Male and female Sprague-Dawley rats (body weights and
   ages were not provided).

   Methods: In a single-dose study, rats were intraperitoneally
   administered 0.66 ml/kg of \(^3\)H-mineral oil (liquid petrolatum
   U.S.P.; specific activity of 1.52 mc/ml). In a multiple-dose
   study, rats received 0.66 ml/kg/day of unlabeled mineral oil for
   31 days and 0.66 ml/kg of \(^3\)H-mineral oil on the 32nd day. Rats
   were sacrificed at various times after \(^3\)H-mineral oil
   administration (number of rats per group and times of sacrifice
   after \(^3\)H-mineral oil administration were not clearly described in
   the article). Radioactivity in gastrointestinal tract and
   contents, and carcass was measured with scintillation counters.
   Radioactivity in tissues from liver, kidney, brain and fat was
   also measured.

   Results: Data were not provided in the article for distribution
   of radioactivity in gastrointestinal tract and contents, and
   carcass after i.p. administration of \(^3\)H-mineral oil.

   At 24 hr after single-dose i.p. administration, there were 432.5,
   174.9, 6.5 and 20,235.2 \(\mu\)g/g of \(^3\)H-mineral oil in liver, kidney,
   brain and fat, respectively. At 24 hr after single-dose i.p.
   administration, there were 31.2, 70.8, 2.9 and <1.0 \(\mu\)g/g of
   \(^3\)H-non-mineral oil substances in liver, kidney, brain and fat,
   respectively. Data were not provided in the article for
   distribution of \(^3\)H-mineral oil in liver, kidney, brain and fat
   after multiple-dose administration.

The following study was reported in: Ebert et al., J Pharmaceut Studies, 55(9), pg. 923, 1966.
2. Distribution of $^3$H-Mineral Oil After Single-Dose or Multiple-Dose Oral Administration in Rats (Ref. 15 Provided by Sponsor).

**Animals:** Male and female Sprague-Dawley rats (body weights and ages were not provided).

**Methods:** In a single-dose study, rats were orally administered 0.66 ml/kg of $^3$H-mineral oil (liquid petrolatum U.S.P.; specific activity of 1.52 mc/ml). In a multiple-dose study, rats received 0.66 ml/kg/day of unlabeled mineral oil for 31 days and 0.66 ml/kg of $^3$H-mineral oil on the 32nd day. Rats were sacrificed at various times after $^3$H-mineral oil administration (number of rats per group and times of sacrifice after $^3$H-mineral oil administration were not clearly described in the article). Radioactivity in gastrointestinal tract and contents, and carcass was measured with scintillation counters. Radioactivity in tissues from liver, kidney, brain and fat was also measured.

**Results:** After either single-dose or multiple-dose oral administration of $^3$H-mineral oil, about 80% of the total radioactivity was located in the gastrointestinal tract plus contents at 8 hr after administration. At 24 hr after administration, about 4.5% of the total radioactivity was located in the gastrointestinal tract plus contents and about 0.6% in the carcass.

After single-dose oral administration of $^3$H-mineral oil, the amount of total radioactivity in the carcass dropped sharply over 2 days. Thereafter, there was a much slower elimination of $^3$H-mineral oil from the carcass; 0.1% of total radioactivity was found in the carcass at 21 days after administration.

At 24 hr after single-dose oral administration, there were 21.7, 3.3, 3.4 and 21.4 µg/g of $^3$H-mineral oil in liver, kidney, brain and fat, respectively. At 24 hr after acute oral administration, there were 19.3, 6.2, 2.7 and 4.0 µg/g of $^3$H-non-mineral oil substances in liver, kidney, brain and fat, respectively.

### 3.3.5.4 Metabolism

The following study was reported in: Ebert et al., J Pharmaceut Studies, 55(9), pg. 923, 1966.
Addendum:
The study title indicates that “I.V. and Oral” administration was used in this study. However, the routes of administration that were actually used were intraperitoneal and oral, as stated in the Methods section.

3.3.5.5 Excretion

The following study was reported in: Ebert et al., J Pharmaceut Studies, 55(9), pg. 923, 1966.

1. Excretion of $^3$H-Mineral Oil After Single-Dose or Multiple-Dose I.P. Administration in Rats (Ref. 15 Provided by Sponsor).

Animals: Male and female Sprague-Dawley rats (body weights and ages were not provided).

Methods: In a single-dose study, rats were intraperitoneally administered 0.66 ml/kg of $^3$H-mineral oil (liquid petrolatum U.S.P.; specific activity of 1.52 mc/ml). In a multiple-dose study, rats received 0.66 ml/kg/day of unlabeled mineral oil for 31 days and 0.66 ml/kg of $^3$H-mineral oil on the 32nd day. Rats were placed in metabolism cages where food and water were available ad libitum. Urine and feces were collected daily. Radioactivity in samples of urine and feces was measured with scintillation counters.
3.4 TOXICOLOGY

3.4.1 Pancrelipase

3.4.1.1 Overall toxicology summary

General toxicology: The toxicity of pancrelipase was evaluated in studies of four weeks and nine months duration in dogs. Oral administration of 1000, 3000, and 6000 mg/kg/day produced glandular dilatation in the small intestine in the 4-week study. Thyroid concretions occurred in the 6000 mg/kg/day group. In the 9-month study, administration of 4000 mg/kg/day produced an increased incidence and severity of fat accumulation in liver. Treatment with 1000, 2000, and 4000 mg/kg/day produced a low incidence of hemorrhage in large intestine. Concretions and cysts in thyroids were observed in all drug-treated groups.

Genetic Toxicology: No studies were submitted.

Carcinogenicity: No studies were submitted.

Reproductive toxicology: No studies were submitted.
Special toxicology: No studies were submitted.

3.4.1.2 Repeat-dose toxicity

4-Week Subchronic Toxicity Study of Pancreatin Powder and Pellets by Oral Administration (Twice Daily) to Beagle Dogs

Key Study Findings: NOAEL was not established; small intestine and thyroid were target organs of toxicity

Study # 11746/98

Testing Laboratory:

Study Dates: 1/28/99-9/20/99

GLP Compliance: A statement of compliance was included.

QA Report: (x)Yes ( )No

Drug: Lot # 0122 (Pancreatin powder)
Amylase: 87,850 FIP units/g
Lipase: 94,460 FIP units/g
Proteases: 6,150 FIP units/g
Expiration Date: 1/31/02

Lot # 0057 (Pancreatin pellets)
Amylase: 56,892 FIP units/g
Lipase: 53,654 FIP units/g
Proteases: 2,870 FIP units/g
Expiration Date: 3/15/00

Formulation/Vehicle: gelatin capsules, size 0, containing pancreatin powder or pancreatin pellets

Animals: Beagle dogs, age 12 months
Males: 7.1-8.9 kg
Females: 5.2-7.1 kg

METHODS: Dogs were treated orally with pancreatin for four weeks, as described in the following table.
<table>
<thead>
<tr>
<th>Group #</th>
<th>Dose (mg/kg/day)</th>
<th>Formulation</th>
<th># Capsules/Administration</th>
<th># Dogs/Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Placebo</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
<td>Powder</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3000</td>
<td>Powder</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>6000</td>
<td>Powder</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6000</td>
<td>Pellets*</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*Pellets were composed entirely of pancreatin.

It is assumed that the test article was actually pancrelipase, but was referred to as “pancreatin” by the authors since “pancrelipase” is not a recognized term in Europe. Each group was dosed twice daily, with the doses separated by 5 hr. The drug-treated groups were given 500, 1500, 3000, or 3000 (pellets) mg/kg b.i.d. pancreatin. The pancreatin dose levels were equal to 94,460, 283,380, and 566,760 FIP lipase units/kg/day for the groups treated with the powder formulation, and 321,924 FIP lipase units/kg/day for the group treated with the pellet formulation (FIP units are the same as USP lipase units). The dose selection was designed to achieve the maximum feasible dose, based on the assumption that a maximum of six capsules/administration can be used in a 4-week study, with a maximum capacity of approximately 5 g/capsule. The authors stated that a single oral administration of 15.8 g/kg in dogs produced only mild vomiting and hyperpnea in a previous study. In the present study, the following parameters were included:

**Clinical Signs:** at least twice daily, before and after dosing

**Bodyweight:** once weekly

**Food Consumption:** daily

**Ophthalmoscopy:** pre-study and on day 29; adnexae, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body, and fundus were examined

**EKG:** before dosing and 2 hr after the first daily dose on days 1 and 28

**Hematology:** pre-study and on day 28; blood smears were examined in cases of anemia, enlarged thymus, and lymphadenopathy

**Clinical Chemistry:** pre-study and on day 28

**Urinalysis:** pre-study and on day 28

**Organ Weights:** adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, submandibular glands, testes, thymus, thyroids/parathyroids

**Gross Pathology:** at necropsy

**Histopathology:** The following organs/tissues were examined in each animal: adrenals, aorta (abdominal), bone/bone marrow, brain, cecum, colon, duodenum, epididymides, esophagus, eyes (with optic nerve), gall bladder, gross lesions, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (cervical, mandibular, mesenteric), mammary gland, ovaries, pancreas, pituitary, prostate,
rectum, salivary glands (submandibular), sciatic nerve, skeletal muscle, spinal cord, spleen, stomach, testes, thymus, thyroids/parathyroids, tissue masses, trachea, tumors, urinary bladder, uterus.

Adequate Battery: (x)Yes ( )No
Peer Review: ( )Yes (x)No

Other: Blood pressure was measured before dosing and at 2 hr 5 min after the first daily dose on days 1 and 28. A hearing test was performed prior to study initiation and on day 29.

RESULTS:

Mortality: No deaths occurred.

Clinical Signs: No signs were observed.

Bodyweight: Weight gain was unaffected. The control males and females weighed 7.9 ± 0.56 kg and 5.93 ± 0.59 kg, respectively, at study initiation, and 7.88 ± 0.46 kg and 6.13 ± 0.49 kg, respectively, at study termination.

Food Consumption: Results were reported as g/kg bodyweight/day. Food intake in the 6000 mg/kg/day powder group was significantly reduced on week 4 (19% in males, 22% in females). Reductions in food intake (6-17%, not statistically significant) were also observed in the 6000 mg/kg/day powder group on weeks 1-3, and in the 6000 mg/kg/day pellets group on weeks 1 and 4. The decreased food consumption was considered to be a non-specific effect related to the high caloric value of the pancreatin dose. Water consumption was not affected.

Ophthalmoscopy: There were no effects.

EKG: Heart rate was the only data reported. No treatment-related changes in heart rate were observed. The authors stated that no abnormalities in electrical complexes were observed.

Hematology: Hemoglobin was reduced by 11% in the 6000 mg/kg/day pellets males (not significant). WBC count was decreased by 33% and 26% in the 6000 mg/kg/day powder males and females, respectively (not significant). Thromboplastin time and partial thromboplastin time were not affected.

Clinical Chemistry: Total bilirubin was increased by 52% and 69% in the 3000 and 6000 (powder) mg/kg/day males. Males in the 6000 mg/kg/day pellets group exhibited a 40% increase in total bilirubin (not significant). Females in the 3000 and 6000 (powder) mg/kg/day powder groups exhibited a 39% and 43% increase in bilirubin, respectively (not significant). Triglycerides was increased by 52% and 75% in the 3000 and 6000 (powder) mg/kg/day females, respectively (not significant). Urea was increased by 43% (not significant) in the 6000 (powder) mg/kg/day powder males, and by 53% in the 6000 (pellets) mg/kg/day males. Females in the 6000 (powder) mg/kg/day group and 6000 (pellets) mg/kg/day group exhibited a 28% and 19% increase in urea, respectively (not significant). One male in the 1000 mg/kg/day
group exhibited a 3.4-fold increase in ALT, relative, to the mean control value. One male in the 3000 mg/kg/day group exhibited a 10.8-fold increase in ALT.

**Urinalysis:** The following parameters were unaffected: specific gravity, pH, protein, glucose, bilirubin, urobilirubin, ketones, hemoglobin, nitrite, and microscopic examination.

**Organ Weights:** Absolute weight and organ/bodyweight ratio were reported. There were no effects.

**Gross Pathology:**

Stomach: Reddened fundus was observed in the 1000 mg/kg/day group (2/8 dogs).

Prostate: Reduction in size occurred in 1/4 males in each of the 3000 and 6000 (powder) mg/kg/day groups.

**Histopathology:** Lesions occurred sporadically in the drug-treated groups. These lesions occurred in the following organs and were considered as incidental: adrenals, brain, epididymides, kidneys, large intestine, liver, lungs, pancreas, prostate, skeletal muscle, stomach, testes, trachea, urinary bladder, and uterus. Those lesions which were considered as drug-related are described below.

Small Intestine: Glandular dilatation occurred in the 1000, 3000, 6000 (powder), and 6000 (pellets) mg/kg/day groups (1/8, 2/8, 1/8, and 2/8 dogs, respectively). Mineralization was observed in the 3000 mg/kg/day group (1/8 dogs).

Thyroid: Concretions occurred in the 6000 (pellets) mg/kg/day group (3/8 dogs).

**Toxicokinetics:** Not performed.

**Other:** No treatment-related changes in systolic pressure were observed. Hearing was unaffected.

**Conclusions:** A NOAEL (no observed adverse effect level) was not established. Glandular dilatation in the small intestine occurred in all treatment groups, whereas no incidence was observed in the control group. Therefore, the small intestine is considered to be a target organ of toxicity in all treatment groups. Thyroid was also a target organ of toxicity, based on the incidence of concretions in the 6000 mg/kg/day pellets group (3/8 dogs). Immature testes and epididymides were observed in all treatment groups, especially in the 6000 mg/kg/day pellets group. These changes were considered as incidental and age-related (dogs were 13 months old at study termination).
**9-Month Chronic Toxicity Study of Pancreatin Powder by Oral Administration (Twice Daily) to Beagle Dogs**

**Key Study Findings:** liver, large intestine, and thyroid were target organs of toxicity; a NOAEL was not established

**Study #** 11751/98 (K.223.4002)

**Testing Laboratory:**

**Study Dates:** 1/28/99-2/28/01

**GLP Compliance:** A statement of compliance was included.

**QA Report:** (x)Yes ( )No

**Drug:** Lot # 0122 (Pancreatin powder, administered on weeks 1-8)
- Amylase: 87,850 FIP units/g
- Lipase: 94,460 FIP units/g
- Proteases: 6,150 FIP units/g
- Expiration Date: 1/31/02

Lot # 0146 (Pancreatin powder, administered on weeks 9-39)
- Amylase: 98,100 FIP units/g
- Lipase: 98,700 FIP units/g
- Proteases: 4,590 FIP units/g
- Expiration Date: 6/13/02

**Formulation/Vehicle:** gelatin capsules, size 0, containing pancreatin powder

**Animals:** Beagle dogs, age 6 months
- Males: 6.7-8.2 kg
- Females: 5.0-6.8 kg

**METHODS:** Dogs were treated orally with 0 (placebo), 1000, 2000, or 4000 mg/kg/day pancreatin for 39 weeks (4 dogs/sex/group). It is assumed that the test article was actually pancrelipase, but was referred to as “pancreatin” by the authors since “pancrelipase” is not a recognized term in Europe. Each group was dosed twice daily, with the doses separated by 5 hr. The drug-treated groups were given 500, 1000, or 2000 mg/kg b.i.d. pancreatin. The pancreatin dose levels were equal to 98,700, 197,400, and 394,800 FIP lipase units/kg/day (FIP units are the same as USP lipase units). The dose selection was designed to achieve the maximum feasible dose, based on the assumption that no more than four capsules (maximum capacity of 5 g/capsule) can be administered for each dose in a 9-month study. The following parameters were reported:
Clinical Signs: at least twice daily, before and after dosing

Bodyweight: once weekly

Food Consumption: daily

Ophthalmoscopy: pre-study and on days 273/274; adnexae, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body, and fundus were examined

EKG: before dosing and 2 hr after the first daily dose on days 1, 27/28, 83, 138, 196, and 272

Hematology: blood was collected before study initiation and on weeks 4, 12, 20, 28, and 39

Clinical Chemistry: blood was collected before study initiation and on weeks 4, 12, 20, 28, and 39

Urinalysis: urine was collected before study initiation and on weeks 4, 12, 20, 28, and 39

Organ Weights: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, submandibular glands, testes, thymus, thyroids/parathyroids

Gross Pathology: at necropsy

Histopathology: The following organs/tissues were examined in each animal: adrenals, aorta (abdominal), bone/bone marrow, brain, cecum, colon, duodenum, epididymides, esophagus, eyes (with optic nerve), gall bladder, gross lesions, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (cervical, mandibular, mesenteric), mammary gland, ovaries, pancreas, pituitary, prostate, rectum, salivary glands (submandibular), sciatic nerve, skeletal muscle, spinal cord, spleen, stomach, testes, thymus, thyroids/parathyroids, tissue masses, trachea, tumors, urinary bladder, uterus. In addition to tissue staining with hematoxylin and eosin, frozen sections of heart, liver, and kidneys were stained with Scarlet red for detection of fat.

Adequate Battery: (x)Yes ( )No
Peer Review: ( )Yes (x)No

Other: Blood pressure was measured before dosing and at 2 hr 5 min after the first daily dose on days 1, 27/28, 83, 138, 196, and 272. A hearing test was performed prior to study initiation and on days 273/274.

RESULTS:

Mortality: No deaths occurred.

Clinical Signs: No signs were observed.
**Bodyweight:** Weight gain was increased by 43-78% in all treatment groups, except for the 1000 mg/kg/day males, which exhibited no substantial change in weight gain. The authors considered this effect to be related to the high caloric value of the test article at the given dose levels. The mean bodyweight of the control males and females was 7.45 ± 0.71 kg and 6.00 ± 0.62 kg, respectively, at study initiation, and 9.33 ± 1.27 kg and 7.80 ± 2.03 kg, respectively, at termination.

**Food Consumption:** The daily food allotment was 40 g/kg bodyweight. The results were reported as the mean daily values from one week (g/kg bodyweight). Complete food consumption was observed in the control group on most days. Food intake was reduced by 6-27% in the 2000 mg/kg/day females during weeks 20-28 (significant on week 20). Food consumption was reduced by 5-31% in the 4000 mg/kg/day males on weeks 12-39, and by 2-21% in the 4000 mg/kg/day females during the same period. The reduced food consumption was considered as an effect of the high caloric value of the test article at the given dose levels. Water consumption was unaffected, based on observation.

**Ophthalmoscopy:** No abnormalities were observed.

**Electrocardiography:** Heart rate was the only parameter reported. The drug had no effect on heart rate. The authors stated that no drug-related abnormalities were observed in the visual examination of the EKG tracings.

**Hematology:** The results are shown in the following table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose(s)</th>
<th>Change</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mg/kg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>2000f, 4000f</td>
<td>12%, 14% increase (ns)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>4000f</td>
<td>11% increase (ns)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2000m, 4000</td>
<td>11-17% increase (ns)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2000m, 4000</td>
<td>13-19% increase (ns)</td>
<td>39</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>2000f, 4000f</td>
<td>13% increase (ns)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>4000</td>
<td>9-12% increase (ns)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1000f, 2000, 4000</td>
<td>11-21% increase (ns)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2000, 4000</td>
<td>10-22% increase (ns)</td>
<td>39</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>4000f</td>
<td>9% increase (ns)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1000f, 2000f, 4000f</td>
<td>10-15% increase (ns)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1000f, 4000</td>
<td>11-12% increase (ns)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1000, 2000, 4000</td>
<td>10-21% increase (ns)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>1000f, 2000, 4000f</td>
<td>10-24% increase*</td>
<td>39</td>
</tr>
<tr>
<td>WBC</td>
<td>1000f, 2000m, 4000f</td>
<td>33%, 45%, 53% increase (ns)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2000f, 4000f</td>
<td>26%, 17% increase (ns)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1000f, 2000f, 4000f</td>
<td>19-24% increase (ns)</td>
<td>39</td>
</tr>
</tbody>
</table>

* significant in the 4000 mg/kg/day males only (24% increase, p<0.01)

m: males
f: females

ns: not significant
RBC count was slightly increased in the 2000 and 4000 mg/kg/day groups from week 12 onward. Slight increases in hemoglobin and hematocrit were observed at 1000, 2000, and 4000 mg/kg/day beginning at week 12. None of these changes were statistically significant, except for the increased hematocrit in the 4000 mg/kg/day males on week 39. Sporadic increases in WBC count were observed in all treatment groups. APTT (activated partial thromboplastin time) was reduced by 22% and 14% in the 2000 and 4000 mg/kg/day males, respectively, on week 39 (significant in the 2000 mg/kg/day males). Thromboplastin time was unaffected.

**Clinical Chemistry:** The results are shown in the following table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose(s)</th>
<th>Change</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>2000(^f), 4000(^f)</td>
<td>41%, 20% increase (ns)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1000(^m), 4000(^m)</td>
<td>22%, 24% increase (ns)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>1000(^f), 2000(^f)</td>
<td>20%, 26% increase (ns)</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>4000(^f)</td>
<td>22% increase (ns)</td>
<td>39</td>
</tr>
<tr>
<td>α₂-globulin</td>
<td>2000(^m)</td>
<td>24% increase (ns)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>4000(^m)</td>
<td>21% increase (ns)</td>
<td>39</td>
</tr>
<tr>
<td>Calcium</td>
<td>4000(^m)</td>
<td>9% increase</td>
<td>28</td>
</tr>
<tr>
<td>Potassium</td>
<td>4000(^m)</td>
<td>12% decrease</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>4000(^m)</td>
<td>11% decrease</td>
<td>20</td>
</tr>
</tbody>
</table>

ns: not significant
m: males
f: females

The observed changes occurred sporadically during the study, and were not clinically significant.

**Urinalysis:** No changes were observed.

**Organ Weights:** Absolute weight and organ/bodyweight ratio were reported. Absolute weight of organs was unaffected. Brain/bodyweight ratio was reduced by 18-23% in the 1000, 2000, and 4000 mg/kg/day females (not significant). Liver/bodyweight ratio was decreased by 26% in the 4000 mg/kg/day females (not significant). Lungs/bodyweight ratio was reduced by 25-35% in the 1000, 2000, and 4000 mg/kg/day females (not significant).

**Gross Pathology:**

Lungs: Blue discoloration of left lobe was observed in one female in each of the 2000 and 4000 mg/kg/day groups.

**Histopathology:** Lesions occurred sporadically in the drug-treated groups. These lesions occurred in the following organs and were considered as incidental: adrenals, brain, epididymides, heart, lungs, ovaries, parathyroids, salivary glands, skeletal muscle, small intestine, testes, urinary bladder, and uterus. Those changes which appeared to be drug-related are described below.
Large Intestine: Hemorrhage occurred in the 1000, 2000, and 4000 mg/kg/day groups (1/8, 2/8, and 1/8 dogs, respectively). Mononuclear cell infiltration was observed in the 4000 mg/kg/day group (1/8 dogs).

Liver: The incidence and severity of lipid accumulation in hepatocytes was increased in the 4000 mg/kg/day group (7/8 dogs compared to 3/8 dogs in the control group). The severity of lipid accumulation in sinusoidal cells and the accumulation of lipofuscin pigment in liver cells was increased in the 4000 mg/kg/day group. Hepatocyte hypertrophy occurred in the 4000 mg/kg/day group (1/8 dogs).

Thyroid: Cysts were observed in the 1000, 2000, and 4000 mg/kg/day groups (1/8, 2/8, and 1/8 dogs, respectively). Mononuclear cell infiltration occurred in the 4000 mg/kg/day group (1/8 dogs). Concretions were observed in the 1000, 2000, and 4000 mg/kg/day groups (2/8, 1/8, and 2/8 dogs, respectively).

Other: Systolic arterial pressure was unaffected. Hearing was normal in each animal.

Conclusions: Liver was a target organ of toxicity in the 4000 mg/kg/day group, as indicated by the enhanced accumulation of fat. The effect in liver may have been the consequence of nutritional and/or metabolic imbalances, as food consumption was reduced in the 4000 mg/kg/day group. The authors attributed the decreased food consumption to the high caloric value of the test article at the given dose level. Despite the reduction in food consumption at the 2000 and 4000 mg/kg/day dose levels, weight gain was increased by 43-78% in all treatment groups, except for the 1000 mg/kg/day males. The target organs of toxicity also included large intestine (hemorrhage) and thyroid (concretions and cysts). Lesions in these organs were observed in all drug-treated groups. A NOAEL was not established.

3.4.2 Hydroxypropylmethylcellulose Phthalate (HPMCP)

HPMCP is a component of the enteric coating in Creon® Minimicrospheres®.

3.4.2.1 Overall toxicology summary

General toxicology: Oral administration of up to 15000 mg/kg produced no deaths in rats. Oral toxicity studies of one month (1300, 2000, 3000, 4500, and 10000 mg/kg/day) and six months (1500, 3000, and 6000 mg/kg/day) duration in rats were submitted. The NOAEL was 4500 mg/kg/day in the 1-month study. All animals in the 10000 mg/kg/day group and the vehicle control group (1.5% sodium bicarbonate, same dose volume) died between days 10-16. Thus, the deaths in the high-dose group may have been related to the vehicle. The NOAEL in the 6-month study was 6000 mg/kg/day.

Genetic toxicology: No studies were submitted.

Carcinogenicity: No studies were submitted.

Reproductive toxicology: No studies were submitted.
Special toxicology: No studies were submitted.

3.4.2.2 Single-dose toxicity

The following study was reported in: Kitagawa et al., Pharmacometrics, 4(6), pg. 1017, 1970.

**Acute Oral Toxicity Study in Rats**

Four groups of 20 Wistar rats each (10 males and 10 females) were orally administered 0, 5, 10 and 15 g/kg of HPMCP, respectively by intubation; vehicle was phosphate buffer, pH 7.4 (Ref. 18 provided by sponsor). Observation period was 1 week. There were no mortalities. Some degree of behavioral inactivity and ataxia was produced by all doses of HPMCP. The 10 and 15 g/kg doses produced diarrhea.

3.4.2.3 Repeat-dose toxicity

The following study was reported in: Kitagawa et al., Pharmacometrics, 4(6), pg. 1017, 1970.

1. **1-Month Oral Toxicity Study of HPMCP (Ref. 18 Provided by Sponsor).**

   **Animals:** Male and female Wistar rats (130-190 g; ages were not provided).

   **Methods:** Five groups of 10 rats each (5 males and 5 females) were orally administered 1.3, 2.0, 3.0, 4.5 and 10.0 g/kg/day of HPMCP, respectively, via intubation for 1 month; vehicle was 1.5% sodium bicarbonate solution; dosing volumes were 1.63, 2.45, 3.68, 5.52 and 12.5 ml/100 g, respectively. The 10 g/kg/day dose was divided and given 2 times a day. Five groups of 10 rats each (5 males and 5 females) were orally administered 1.63, 2.45, 3.68, 5.52 and 12.5 ml/100 g of the vehicle daily, respectively, via intubation for 1 month.
Body weights and food consumption were recorded twice weekly. After 30 days of HPMCP administration, blood samples were withdrawn from the tail vein, and hematology assessments were made. Urine samples were subjected to analysis at this time.

Animals were sacrificed by decapitation and subjected to gross pathological examination. Organ weights of liver, kidneys, spleen, heart, lungs, gonads, adrenals and thyroids were recorded. Tissue samples from these organs were subjected to histopathological examination.

Results:

1. **Observed Effects**: The 10 g/kg/day dose of HPMCP produced diarrhea.

2. **Mortality**: All animals in the 10 mg of HPMCP/kg/day group and the 12.5 ml/100 g vehicle control group died between 10 and 16 days after initiation of HPMCP treatment. Animals displayed a gradual emaciation and shock symptoms.

3. **Body Weight**: Body weight gain (% of body weight on Day 0) of males on Day 16 was 32.5% in control rats receiving no treatment and 12.5% in rats receiving 12.5 ml of 1.5% sodium bicarbonate solution/100 g/day. Body weight gain in males on Day 10 was 22% in rats receiving 1.3 g HPMCP/kg/day and 15% in rats receiving 10.0 g HPMCP/kg/day. (Data were estimated from a figure.)

   Body weight gain (% of body weight on Day 0) of females on Day 16 was 20% in control rats receiving no treatment and 5% in rats receiving 12.5 ml of 1.5% sodium bicarbonate solution/100 g/day. Body weight gain in females on Day 10 was 7.5% in rats receiving 1.3 g HPMCP/kg/day and 2% in rats receiving 10.0 g HPMCP/kg/day.

   Thus, the vehicle (12.5 ml of 1.5% sodium bicarbonate solution/100 g/day) reduced body weight gain. Therefore, reductions in body gain at higher doses of HPMCP may have not be due to HPMCP per se.

4. **Food Consumption**: Food consumption (% of food intake on Day 0) of males on Day 16 was 115% in control rats receiving no treatment and 103% in rats receiving 12.5 ml of 1.5% sodium bicarbonate solution/100 g/day. Food consumption in males on Day 10 was 110% in rats receiving 1.3 g HPMCP/kg/day and 101% in rats receiving 10.0 g HPMCP/kg/day. (Data were estimated from a figure.)

   Food consumption (% of food intake on Day 0) of females on Day 16 was 100% in control rats receiving no treatment and 125% in rats receiving 12.5 ml of 1.5% sodium bicarbonate solution/100 g/day. Thus, there were no treatment-related effects on food consumption.
5. **Hematology:** There were no treatment-related effects.

6. **Urinalysis:** There were no treatment-related effects.

7. **Organ Weights:** There were no treatment-related effects.

8. **Gross Pathology:** There were no treatment-related gross pathological lesions.

9. **Histopathology:** There were no treatment-related histopathological lesions.

In summary, the apparent no effect oral dose of HPMCP was 4.5 g/kg/day. Administration of both 10 g/kg/day of HPMCP and 12.5 ml/100 g of vehicle (1.5% sodium bicarbonate solution) were lethal. Therefore, since the 1.5% sodium bicarbonate solution at a dosing volume of 12.5 ml/100 g was lethal, HPMCP per se at the 10 g/kg/day dose may not have been lethal.

The following study was reported in: Kitagawa et al., Pharmacometrics, 7, pg. 1, 1973.

2. **6-Month Oral Toxicity Study of HPMCP** (Ref. 19 Provided by Sponsor).

**Animals:** Male and female Wistar rats (90-100 g; ages were not provided).

**Methods:** Three groups of 10 rats each (5 males and 5 females) were orally administered 1.5, 3.0, and 6.0 g/kg/day of HPMCP, respectively, via intubation for 6 months; vehicle was 1.5% sodium bicarbonate solution; dosing volumes were 1.88, 3.75, and 7.50 ml/100 g, respectively. The 6 g/kg/day dose was divided and given 2 times a day. Three groups of 10 rats each (5 males and 5 females) were orally administered 1.88, 3.75, and 7.50 ml/100 g of the vehicle daily, respectively, via intubation for 6 months.

Rats were observed daily for clinical signs of toxicity. Body weights were recorded daily. At 3 and 6 months, blood samples were collected via the tail vein, and hematological parameters were studied. At 3 and 6 months, urine samples were collected for analysis. When animals were sacrificed by decapitation, blood samples were collected for blood chemistry determinations. Animals were subjected to gross pathological examination and organ weights were recorded for liver, kidneys, heart, spleen, brain, lungs, adrenals and testes or ovaries. Tissue samples from these organs were subjected to histopathological examination.
Results:

1. **Observed Effects:** There were no treatment-related clinical signs of toxicity.

2. **Mortality:** There were no treatment-related deaths.

3. **Body Weight:** Mean body weights of males during Week 1 were 96.6, 98.6, 97.0 and 105.7 g in the 0, 1.5, 3 and 6 g/kg/day groups, respectively. Mean body weights of males during Week 26 were 470.7, 475.3, 475.3 and 498.5 g in the 0, 1.5, 3 and 6 g/kg/day groups, respectively.

Mean body weights of females during Week 1 were 94.8, 93.6, 93.6 and 101.4 g in the 0, 1.5, 3 and 6 g/kg/day groups, respectively. Mean body weights of females during Week 26 were 262.2, 272.9, 286.2 and 317.4 g in the 0, 1.5, 3 and 6 g/kg/day groups, respectively.

Thus, there were no treatment-related effects on body weight.

4. **Hematology:** There were no treatment-related effects.

5. **Blood Chemistry:** There were no treatment-related effects.

6. **Urinalysis:** There were no treatment-related effects.

7. **Organ Weights:** There were no treatment-related effects.

8. **Gross Pathology:** There were no treatment-related gross pathological lesions.

9. **Histopathology:** There were no treatment-related histopathological lesions.

In summary, the no effect oral dose of HPMCP was 6 g/kg/day. Organs of toxicity were not identified.

### 3.4.3 Dibutyl Phthalate

Dibutyl phthalate is a component of the enteric coating in Creon® Minimicrospheres®. It is used as a plasticizer.

#### 3.4.3.1 Overall toxicology summary

**General toxicology:**

Since the results of preclinical toxicity studies of dibutyl phthalate were summarized in the reviews, full descriptions of methods and presentations of quantitated data were not provided. The following table summarizes toxic effects of orally administered dibutyl phthalate in animal studies. The oral no effect dose of dibutyl phthalate ranged from 120 mg/kg/day to 1 g/kg/day. Since 750 mg/kg/day produced deaths in a 1-year dietary study, the average oral no effect dose appears to be greater than 120 mg/kg/day, but lower than 750 mg/kg/day.

**Summary of Oral Toxicity Studies of DIBUTYL PHTHALATE in Mice and Rats.**

<table>
<thead>
<tr>
<th>Oral Dose</th>
<th>Duration</th>
<th>Species</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml/kg (1 g/kg)</td>
<td>6 weeks</td>
<td>Rats</td>
<td>No effect dose.</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>80 days</td>
<td>Rats</td>
<td>Leukocytosis in rats.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mice</td>
<td>Inhibited growth in mice.</td>
</tr>
<tr>
<td>0.12 and 1.2 g/kg in olive oil</td>
<td>3 months</td>
<td>Rats</td>
<td>120 mg/kg was no effect dose. 1.2 g/kg produced death in 6/50 animals.</td>
</tr>
<tr>
<td>2.5 mg/kg</td>
<td>6 months</td>
<td>Rats</td>
<td>No effect dose.</td>
</tr>
<tr>
<td>0.125% (75 mg/kg/day) in food</td>
<td>1 year</td>
<td>Rats</td>
<td>No effect dose.</td>
</tr>
<tr>
<td>0.01, 0.05, 0.25, and 1.25% (6, 30, 150 and 750 mg/kg) in food</td>
<td>1 year</td>
<td>Rats</td>
<td>150 mg/kg was no effect dose. 750 mg/kg/day produced death in 5/10 animals.</td>
</tr>
<tr>
<td>1 ml/kg (1 g/kg) in oil</td>
<td>1½ years</td>
<td>Rats</td>
<td>No effect dose.</td>
</tr>
</tbody>
</table>

Genetic toxicology: No studies were submitted.

Carcinogenicity: No studies were submitted.

Reproductive toxicology: The following study were incorporated from the Pharmacologist’s Review of IND 47,546 dated May 23, 1997, and was reviewed from the following reference: Anonymous, J Amer Coll Toxicol, 4(3), pg. 267, 1985.

Since the results of a reproductive toxicity study for dibutyl phthalate (DBP) was summarized in one of the reviews, a full description of methods and presentation of quantitated data were not provided. Five pregnant females per group were intraperitoneally administered DBP on Days 5, 10 and 15 of gestation and sacrificed on Day 20.

As shown in the following table, there were treatment-related increases in number of skeletal abnormalities in all DBP groups. The high-dose DBP group had treatment-related increases in number of resorptions, decreases in number of live fetuses and increases in number of skeletal abnormalities. Since data on maternal toxicity were not provided, interpretation of fetal toxicity is limited.
3.4.4 Dimethicone 1000

Dimethicone 1000 is a component of the enteric coating in Creon® Minimicrospheres®. Dimethicones are linear chains of dimethylpolysiloxane (DMPS) which have terminal trimethylsilyl groups, and are generally used for their antifoaming properties. Dimethicone 1000 has a viscosity 1000 cs (centistokes).

### 3.4.4.1 Overall toxicology summary

**General toxicology:** The submitted studies included a 76-week dietary study in mice, a 28-day oral study in female rats (brief summary), a 90-day dietary study in rats (brief summary), a 2-year study in rats (brief summary), and a 6-month dietary study in dogs. The test articles used in these studies were dimethicones of various sizes and viscosities, most of which were not identical to dimethicone 1000. The no effect dose in the 76-week mouse study was about 580 mg/kg/day (0.25% of diet). Increased mortality in females occurred at 5800 mg/kg/day. No drug-related lesions were observed. The no effect dose levels in the 28-day, 90-day, and 2-year rat studies were 20,000, 500, and 150 mg/kg/day, respectively. No treatment-related effects were observed at any dose level in these studies. A no-effect dose was not established in the 6-month dog study, in which the animals were treated with 300, 1000, or 3000 mg/kg/day. Deposits of bile were observed in all animals treated with DC antifoam A (dimethicone). The severity of this change was dose-related.

**Genetic toxicology:** No studies were submitted.

**Carcinogenicity:** No formal studies were submitted. However, a limited examination of tumors was reported in the 76-week dietary study in mice. No treatment-related incidence of neoplasms was observed.

**Reproductive toxicology:** Dimethicone 360 produced no effects in a Segment I study in rats, a Segment II study in rats, or a Segment II study in rabbits. In a Segment III study, administration of 200 and 1000 mg/kg/day in pregnant rats produced a decrease in the number of live pups. No effects were observed at 20 mg/kg/day.

**Special toxicology:** No studies were submitted.
3.4.4.2 Single-dose toxicity

The following study was incorporated from the Pharmacologist’s Review of IND 47,546 dated May 23, 1997. No reference was cited for this study.

**Acute Oral Toxicity Study in Rats**

The minimal lethal oral dose of DC 200 (50 cs), DC 550 (75 cs), DC 702 (35 cs) and DC 200 (350 cs) in rats was greater than 30 mg/kg.

3.4.4.3 Repeat-dose toxicity

The following study was reported in: Cutler et al., Food Cosmet Toxicol, 12, pg. 443, 1974.

1. **76-Week Dietary Toxicity Study of a Polydimethylsiloxane** (Ref.: 12 Provided by Sponsor).

**Animals:** Male and female mice (species not identified; body weights were not provided; 4-5 weeks of age).

**Methods:** Three groups of 80-100 mice each (40-50 males and 40-50 females) were given 0, 0.25% and 2.5% of a silicone antifoam compound (94% polydimethylsiloxane silicone oil and 6% finely divided silicone dioxide) in the diet on a daily basis for 76 weeks. For comparative purposes, 2 groups of 80-100 mice (40-50 males and 40-50 females) were subcutaneously injected with a single dose of the silicone antifoam compound (0.2 ml; estimated by the authors to be about 201 mg) and a single dose of liquid paraffin (0.2 ml), respectively.

All mice that died or that were sacrificed in a moribund condition were examined for gross pathological and histopathological lesions. All surviving animals were sacrificed by ether overdose at week 80. All mice were examined for gross pathological lesions and histopathological examinations were performed on all tissues that appeared abnormal. In addition, tissue samples from lung, heart, stomach, small intestine, spleen, liver and kidney were histopathologically examined in 10 males and 10 females from each treatment group.

Analyses for silicone were carried out on the liver, kidney, spleen and perirenal fat of 5 mice after 76 weeks at the 2.5% dose. Ten rats from the 2.5% groups were continued on control diet for 8 days, sacrificed and subjected to gross pathological examination, and analyzed for whole-body silicone content. Limit of detection was 20 μg of silicone in 1 mg of tissue.
Results:

1. Achieved Doses: The authors estimated that the mice received an average dose of 580 and 5800 mg/kg/day at the 0.25% and 2.5% concentrations, respectively.

2. Mortality: As shown in the following table, there was a significant increase in incidence of cumulative mortality of females at the 5800 mg/kg/day dose.

Cumulative Mortality in Rats Receiving 5800 mg/kg/day of a Silicone Antifoam Compound.

<table>
<thead>
<tr>
<th>Silicone antifoam compound (mg/kg/day)</th>
<th>Cumulative Incidence of Mortality Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Males (0)</td>
<td>0/50</td>
</tr>
<tr>
<td>Males (5800)</td>
<td>0/50</td>
</tr>
<tr>
<td>Females (0)</td>
<td>0/50</td>
</tr>
</tbody>
</table>
3. Non-Neoplastic Pathology: As shown in the following table (from page 446 of Ref. 12), there was a significant decrease in the incidence of proteinaceous plug in the urinary bladder of males given a single injection of silicone (0.2 ml, s.c.).

<table>
<thead>
<tr>
<th>Histo-pathological findings</th>
<th>Dietary silicone (0% control)</th>
<th>Injection of</th>
<th>No. of mice</th>
<th>0</th>
<th>0.25</th>
<th>2.5</th>
<th>Paraffin</th>
<th>Silicone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>43</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial ulcers</td>
<td>1</td>
<td>6*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>0</td>
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<tr>
<td>Lung</td>
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<td>Chronic respiratory disease</td>
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<td>Kidney</td>
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<td>Urinary bladder</td>
<td>Proteinaceous plug</td>
<td>10</td>
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<td>1</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Cyst at injection site</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Values marked with asterisks differ significantly (Student's t test) from that of the corresponding control group: *P < 0.05; **P < 0.01.

As shown in the following table (from page 447 of Ref. 12), there was a significant decrease in incidence of uterine atrophy in females given dietary silicone (2.5%).
4. Neoplastic Pathology: As shown in the following table (from page 447 of Ref. 12), there was a significant decrease in incidence of lung papillary adenoma in males given dietary silicone (0.25%).
As shown in the following table (from page 448 of Ref. 12), there were significant decreases in incidence of lung papillary adenoma in females given silicone (0.25% and 2.5%, respectively).

<table>
<thead>
<tr>
<th>Site and type of tumour</th>
<th>Effective no. of mice/group...</th>
<th>No. of mice bearing tumours in group given Dietary silicone (1x cone)</th>
<th>Injection of Paraffin</th>
<th>Paraffin</th>
<th>Silicone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.25</td>
<td>2.5</td>
<td>Paraffin</td>
<td>Silicone</td>
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<tr>
<td>Mammary gland</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>9 (21)</td>
<td>2 (5)**</td>
<td>1 (3)**</td>
<td>8 (17)</td>
<td>5 (11)</td>
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<tr>
<td>Papillary adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ovary</td>
<td>1 (3)</td>
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<td>0</td>
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<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>0</td>
<td>0</td>
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<td></td>
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<tr>
<td>Squamous carcinoma</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
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<tr>
<td>Fibromyxoma</td>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Cervix</td>
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<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (2)</td>
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<td>0</td>
<td>3 (9)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
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<td>Lymphoepithelioma</td>
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<tr>
<td>Reticulum-cell sarcoma</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<td>Fibroma</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Total no. with tumours... 12 (29) 3 (7)** 5 (15) 10 (21) 10 (23)

*No. of animals surviving to 80 wk plus tumour-bearing animals that died or were killed earlier.

Values in parentheses denote the numbers of mice affected expressed as a percentage of the effective no. of mice/group. Values marked with asterisks differ significantly (Student's t test) from that of the corresponding control group. **P < 0.01.

Thus, the no effect dose of the silicone antifoam compound was 580 mg/kg/day. The 5800 mg/kg/day dose produced increased cumulative mortality in females. There were no treatment-related incidences of either non-neoplastic or neoplastic pathologies.

The following studies were reported in: Anonymous, J Amer Coll Toxicol, 1(4), pg. 33, 1982; Rowe et al., Arch Indust Hyg Occup Med, 1, pg. 539, 1950.

Rats

Summaries of oral toxicity studies in rats, for which full descriptions of methods and presentations of quantitated data were not provided, follow:

When female rats were orally administered DC 200 fluid (350 cs) (1, 2, 5, 10, 12 and 20 g/kg, respectively) by gavage for 20 of 28 days, there were no treatment-related effects on body weight and hematological parameters, and there were no treatment-related gross pathological lesions or histopathological lesions.

When rats were given 1% (approximately 500 mg/kg) DMPS (50, 350, 1000, 10,000, and 60,000 cs, respectively) in the diet for 90 days, there were no treatment-related effects on body weight, hematological parameters and organ weights, and there were no treatment-related gross pathological lesions or histopathological lesions.
When rats were given 0.3% DC antifoam A (approximately 150 mg/kg/day) admixed in the diet for 2 years, there were no treatment-related effects on body weight and hematological parameters, and there were no treatment-related gross pathological lesions and histopathological lesions.

The following study was reported in: Child et al., Indus Hyg Occup Med, 3, pg. 479, 1951.
Dogs

1. **6-Month Dietary Toxicity Study of the Methyldiphenylsiloxane "DC Antifoam A" (Ref. 9 Provided by Sponsor)**

**Animals:** Mongrel dogs (sex, body weights and ages were not provided).

**Methods:** Four groups of 2 dogs each received 0, 0.3, 1 and 3 g/kg/day of DC antifoam A in the diet, respectively, for 6 months. During the first 3 months, the DC antifoam A was placed in about 50 or 60 g of ground horsemeat. During the final 3 months, the DC antifoam A was placed in about 50 g of palatable commercial dog food.

Blood samples were withdrawn from the saphenous vein at monthly intervals for hematology assays. 24-hr urine samples were obtained at monthly intervals for analysis.

Dogs were sacrificed by intracardial injection of air. Organ and tissues (unspecified) were examined for gross pathological lesions. Selected tissues (unspecified) were subjected to histopathological examination.

**Results:** Detailed data were not presented in this article.

1. **Observed Effects:** When dogs received DC antifoam A in either horsemeat or dog food, they chewed excessively and apparently were attempting to remove the contents from their mouths. Small amounts of the DC antifoam A were seen in the feces of the 3 g/kg/day group.

2. **Body Weight:** There were no treatment-related effects.

3. **Hematology:** There were no treatment-related effects.

4. **Urinalysis:** There were no treatment-related effects.

5. **Gross Pathology:** Both dogs in the 3 mg/kg/day group had a thin layer of viscid, gray-white material that covered the mucosa of the entire gastrointestinal tract.

6. **Histopathology:** The livers of all dogs fed DC antifoam A had deposits of bile; there was no iron. Quantities of bile deposited in Kupffer and hepatic cells were dose-related. In the 3 mg/kg/day group, the bile was also deposited in the interlobular bile ducts.

In summary, the minimal effect dietary dose of DC antifoam A was 3 g/kg/day. Dose-related deposits of bile were found in Kupffer and hepatic cells; the significance of the bile deposits is not known. Organs of toxicity were not identified.
Addendum: The Gross Pathology and Histopathology sections in this review include observations from the “3 mg/kg/day” group. This dose level was not used in the study, and the effects that were described for the “3 mg/kg/day” group were actually observed in the 3 g/kg/day group.

3.4.4.4 Reproductive and developmental toxicology

The following studies were reported in: Kennedy et al., J Toxicol Environ Health, 1, pg. 909, 1976.

Summaries of reproductive toxicity studies, for which full descriptions of methods and presentations of quantitated data were not provided, follow:

In a Segment I reproductive toxicity study in rats, DC 360 (0, 20 and 200 mg/kg) was subcutaneously administered 3 times a week for 10 weeks prior to mating in males, and 7 times during 2 weeks prior to mating in females. One-half of the pregnant females were sacrificed on Day 13 of gestation and the other one-half of the pregnant females were allowed to give birth and nurse their pups for 21 days. DC 360 had no effects in any dam, fetuses or pups.

In Segment II reproductive toxicity studies in rats and rabbits, DC 360 (0, 20, 200 and 1,000 mg/kg/day from Day 6 to Day 16 of gestation in rats and from Day 6 to 18 in rabbits) did not produce any treatment-related maternal toxicity and was not teratogenic.

In a Segment III reproductive toxicity study in rats, DC 360 (0, 20, 200 and 1,000 mg/kg/day from Day 15 of gestation to Day 21 of lactation) produced a decrease in number of live pups at the 200 and 1,000 mg/kg/day doses. Thus, the no effect dose of DC 360 was 20 mg/kg/day.

3.4.5 Polyethylene Glycol 4000

Polyethylene glycol 4000 is Polyethylene glycols with molecular weights above 3500 are commonly used as binders, plasticizers, and stiffening agents. PEG 4000 (polyethylene glycol 4000) was tested in each of the studies described below.

3.4.5.1 Overall toxicology summary

General toxicology: The no effect dose in a 3-month dietary study in rats was 4% (about 2400 mg/kg/day). Reduced bodyweight was observed at 8% PEG 4000 (about 4800 mg/kg/day). In a 4-month dietary study in rats, the no effect dose was 5% (about 3000 mg/kg/day). Decreased bodyweight and increased liver weight occurred in rats given 10% PEG 4000 (about 6000 mg/kg/day). The no effect dose in a 2-year dietary study in rats was 4% (about 2400 mg/kg/day), with reduced bodyweight occurring at 8% (about 4800 mg/kg/day). The no effect dose in a 1-year dietary study in dogs was 2% (about 800 mg/kg/day), the only dose tested.
In a 12-month intravenous study in dogs (with interim sacrifices at two and six months), the no effect dose was 90 mg/kg/day, the highest dose tested.

**Genetic toxicology:** No studies were submitted.

**Carcinogenicity:** No studies were submitted.

**Reproductive toxicology:** No studies were submitted.

**Special toxicology:** PEG 4000 did not produce sensitization in guinea pigs following administration of eight intradermal injections.

### 3.4.5.2 Single-dose toxicity

The following study was reported in: Rowe and Wolf, “Patty’s Industrial Hygiene and Toxicology”, J. Wiley & Sons, Vol. 2C, pg. 3817, 1982.

**Acute Oral Studies in Rats, Rabbits, and Guinea Pigs**

Acute oral LD₅₀ values for PEG 4000 were >50 g/kg in rats, rabbits and guinea pigs. Methods and data were not described in any detail.

### 3.4.5.3 Repeat-dose toxicity

The following study was reported in: Rowe and Wolf, “Patty’s Industrial Hygiene and Toxicology”, J. Wiley & Sons, Vol. 2C, pg. 3817, 1982.

**Rats**

In a review of the toxicology of polyethylene glycols (Ref. 27 provided by sponsor), summaries of repeated oral dose toxicity of PEG 4000 were included. For example, in a 3-month dietary toxicity study of PEG 4000 in rats, the no effect dose was 4% PEG 4000 (approximately 2.4 g/kg/day); the first noted sign of toxicity with 8% PEG 4000 (approximately 4.8 g/kg/day) was a decrease in body weight. In a 4-month dietary toxicity study of PEG 4000 in rats, the no effect dose was 5% PEG 4000 (approximately 3 g/kg/day); the first noted signs of toxicity with 10% PEG 4000 (approximately 6 g/kg/day) were a decrease in body weight and an increase in liver weight. In a 2-year dietary toxicity study of PEG 4000 in rats, the no effect dose was 4% PEG 4000 (approximately 2.4 mg/kg/day); the first noted sign of toxicity with 8% PEG 4000 (approximately 4.8 g/kg/day) was a decrease in body weight. In a 1-year dietary toxicity study of PEG 4000 in dogs, the only dose studied (2% PEG 4000 or approximately 800 mg/kg/day) was the no effect dose.
The following study was reported in: Carpenter et al., Toxicol Appl Pharmacol, 18, pg. 35, 1971.

Dogs

1. 2-Month, 6-Month and 12-Month I.V. Toxicity Study of Polyethylene Glycol (PEG) 4000 (Ref. 8 Provided by Sponsor).

Animals: Male and female (body weights were not provided in the article; 7 months to 5 years of age) Beagle dogs.

Methods: Four groups of 9 dogs each (random distribution by sex and age) were intravenously administered PEG 4000 (0, 10, 30 and 90 mg/kg/day) via the cephalic veins of the foreleg or the saphenous veins of the hindleg; 10% PEG 4000 was prepared in 0.85% saline solution. Two dogs in each group were sacrificed at 2 months after initiation of PEG 4000 administration, 2 dogs in each group at 6 months, and 5 dogs in each group at 12 months.

Dogs were observed daily for clinical signs of toxicity. Body weights were recorded on a weekly basis during the first 8 weeks of the study, and on a monthly basis thereafter.

Blood samples were withdrawn from the jugular vein. Hematologic and biochemical assessments were done after 2, 4 and 6 weeks and after 2, 6 and 12 months in the 0 and 90 mg/kg/day groups; after 2, 6 and 12 months in the 10 and 30 mg/kg/day groups.

After termination, organ weights of kidneys, liver and spleen were recorded. Gross pathological examinations were done; specific organs and tissues that were examined were not identified. Representative (unspecified) tissues from cranial, thoracic and abdominal viscera were subjected to histopathological examination.
Full complement data from all 36 dogs were statistically analyzed by chi-square and F tests. Data from the 0 and 90 mg/kg/day groups were analyzed with F and Fisher’s t tests.

Results:

1. **Body Weight:** There were no treatment-related effects.
2. **Hematology:** There were no treatment-related effects.
3. **Blood Chemistry:** There were no treatment-related effects.
4. **Organ Weights:** There were no treatment-related effects.
5. **Gross Pathology:** There were no treatment-related gross pathological lesions.
6. **Histopathology:** There were no treatment-related histopathological lesions.

In addition, summaries of an excretion study in rats and a sensitization study in guinea pigs were included in this article. In the excretion study, rats were either intravenously or orally administered $^{14}$C-PEG 4000 (approximately 70 mg/kg). At 7 days after i.v. injection, 81% of the total radioactivity was recovered; of this, 61% was accounted for in the urine, 20% in the feces and none in CO$_2$. At 7 days after oral administration, 86% of the total radioactivity was recovered; of this, 4.1% was accounted for in the urine, none in CO$_2$, and the remainder in the feces.

### 3.4.5.4 Special Toxicology

The following study was reported in: Carpenter et al., Toxicol Appl Pharmacol, 18, pg. 35, 1971.

**Sensitization Study in Guinea Pigs**

In the sensitization study, 20 male albino guinea pigs (430-530 g) were intradermally given 8 doses of 0.1 ml of 0.1% PEG 4000 in 0.85% saline solution; injections were given on alternate days, 3 injections per week. Following a 3-week incubation period, each animal was given a 0.05 ml challenge dose of the PEG 4000 solution. There were no reactions to the challenges.

### 3.4.6 Light Mineral Oil

Light mineral oil is a component of the enteric coating in Creon® Minimicrospheres®. It is commonly used as a food additive and as an excipient.
3.4.6.1 Overall toxicology summary

General toxicology: Chronic inhalation studies in mice, rats, gerbils, dogs, and rabbits were submitted. Oil accumulation in bronchiolar and alveolar macrophages was the most common effect in these studies.

Genetic toxicology: No studies were submitted.

Carcinogenicity: No studies were submitted.

Reproductive toxicology: No studies were submitted.

Special toxicology: No studies were submitted.

3.4.6.2 Repeat-dose toxicity

The following study was reported in: Stula and Kwon, Amer Indust Hyg Assoc J, 39(5), pg. 393, 1978.

1. Inhalation Toxicity of Complex Mineral Oil Mist (Ref. 28 Provided by Sponsor).

Animals: Beagle dogs, Charles River/CD rats, gerbils, Charles River-CD mice and CAF/JAX mice (see following table). Body weights and ages were not provided.

Methods: All animals were exposed to a complex oil mist for 6 hr per day, 5 days per week, for at least 12 months. Procedural details are summarized in the following table. The complex oil mist consisted of 70% paraffinic oil with a Saybolt viscosity of 48-52 at 38°C, 16% vegetable oils, 2% sulfated vegetable oils, 5% quaternary salts of alkyl phosphate esters, 4% polyalkyl oxide waxes and 3% polyalkyl oxide resins, along with 1000 ppm of acetone.

Hematology and blood chemistry assessments were conducted at 3-month intervals in dogs and rats. Urinalysis tests were conducted at 3-month intervals in dogs. Procedural details were not provided.

All animals found in extremis were sacrificed and subjected to histopathological examination. Rat, gerbils and mice were sacrificed by chloroform inhalation, while dogs were sacrificed by electrocution. Selected (not specified by authors) organs were weighed and organ tissues were fixed. Lung tissue was examined in all animals.
### Species, Sex, Number of Animals Per Group, Exposure Time, Recovery Time and Exposure Chamber Concentration of Complex Oil Mist

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex</th>
<th>Test Duration (mo)</th>
<th>Recovery Time (mo)</th>
<th>Number of Animals exposed to Complex Oil Mix (mg/M³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 mg/M³</td>
</tr>
<tr>
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<td>M</td>
<td>12</td>
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<td>4</td>
</tr>
<tr>
<td>Rat</td>
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<td>12</td>
<td>0.5</td>
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</tr>
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<td>M</td>
<td>12</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Gerbil</td>
<td>M</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mouse (Chr-CD)</td>
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<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Mouse (CAF/JAX)</td>
<td>M</td>
<td>12</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

**Results:** Experimental results were summarized with no numerical data. In dogs, there were no treatment-related clinical signs of toxicity. There were no treatment-related effects on hematology or blood chemistry parameters. There were no gross pathological lesions. In dogs of the 5 mg/cubic meter (M³) group, histological examinations revealed a few oil-containing macrophages in the lungs as well as in the hilar lymph nodes. At the 100 mg/M³ concentration, there were oil microgranulomas in the lungs measuring up to 1.0 mm in diameter. The microgranulomas consisted of oil-containing macrophages, a few lymphocytes, a few fibroblasts, and some collagen fibers.
In rats, there were no treatment-related clinical signs of toxicity. There were no treatment-related effects on hematology or blood chemistry parameters. There were no gross pathological lesions. In rats of the 5 mg/M³ group, there were a few vacuolated macrophages in the lungs. At the 100 mg/M³ concentration, there were microgranulomas in the lungs. Oil-containing macrophages were seen in alveoli and hilar lymph nodes. In male rats exposed to the 100 mg/M³ concentration for 1 year, there was some recovery from histopathological lesions in the lungs during the 10-month recovery period.

In mice and gerbils exposed to 5 or 100 mg/M³ of oil mist for up to 1 year, there were a few oil-containing macrophages in the bronchiolar lumen. There were no treatment-related differences between the 2 strains of mice.

The following study was reported in: Wagner et al., Indust Hyg J, 2, pg. 158, 1964.

2. Inhalation Toxicity of White Mineral Oil (Ref. 29 Provided by Sponsor).

**Animals:** Male mongrel dogs, Dutch rabbits, Golden-Syrain hamsters, Sprague-Dawley rats, CF No. 1 mice and CAF₁/JAX mice (see following table). Body weights and ages were not provided.

**Methods:** All animals were exposed to a mineral oil mist for 6 hr per day, 5 days per week. Petroleum base, "light" mineral oil (Saybolt viscosity 85-95) was employed as the aerosol. Subgroups of dogs were exposed for 6, 12, 18 and 26 months; subgroups of rabbits for 6, 12 and 18 months; subgroups of rats for 6, 12 and 16 months; subgroups of hamsters for 6, 12 and 15 months.

Body weight, respiratory function, and hematologic and blood chemistry parameters were monitored; procedural details were not provided by the authors.

Dogs and rabbits were sacrificed by i.v. pentobarbital overdose; rats, hamsters and mice by i.p. pentobarbital overdose. Organs were grossly examined and selected tissues (including lungs, hilar lymph nodes, spleen, stomach, duodenum, adrenals, liver, kidney and heart) were prepared for histopathological examination. Oil-red-O propylene glycol and oil-red-O carbowax 400 stains were utilized for specific identification of oil-droplet deposition in selected tissues (lung, hilar lymph nodes, spleen).
Species, Sex, Number of Animals Per Group and Exposure Chamber Concentration of Oil-Mist

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex</th>
<th>Number of Animals Exposed to Oil-mist (mg/M³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>0 mg/M³</td>
</tr>
<tr>
<td>Dog</td>
<td>M</td>
<td>9</td>
</tr>
<tr>
<td>Rabbit</td>
<td>M</td>
<td>26</td>
</tr>
<tr>
<td>Rat</td>
<td>M</td>
<td>85</td>
</tr>
<tr>
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<td>M</td>
<td>110</td>
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<tr>
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<td>M</td>
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</tr>
<tr>
<td>(CF No. 1)</td>
<td></td>
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<tr>
<td>Mouse</td>
<td>M</td>
<td>250</td>
</tr>
<tr>
<td>(CAP/JAX)</td>
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</tbody>
</table>

Results:

1. **Body Weight**: There were no treatment-related effects on body weight in rats, dogs, rabbits and hamsters.

2. **Respiratory Function**: There were no treatment-related effects on minute ventilation or oxygen consumption in rabbits.

3. **Hematology**: There were no treatment-related effects on hematology parameters. Specific data were not provided.

4. **Blood Chemistry**: Authors reported increases in sera and lung basic alkaline phosphatase (BAP) and magnesium alkaline phosphatase levels. Specific data were not provided.

4. **Histopathology**: Incidences of histopathological lesions were not quantitated; histopathological lesions were described in a general manner. There were increases in alveolar and hilar lymph node oil deposition and/or lipid granuloma formation after 12 months of oil mist exposure at the 100 mg/M³ concentration in rats and dogs.
3.5 LABELING

The preclinical sections of the Sponsor’s draft labeling include “Carcinogenesis, Mutagenesis, Impairment of Fertility”, “Pregnancy”, and “Nursing Mothers”. The “Pregnancy” and “Nursing Mothers” sections are acceptable. The “Carcinogenesis, Mutagenesis, Impairment of Fertility” section is reviewed below.

**Sponsor’s Version:**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Evaluation:** This section should include statements to indicate that genetic toxicology studies have not been performed, and that fertility studies in animals have not been performed.

**Proposed Version:** “Long-term animal studies for carcinogenesis and studies evaluating the potential for impairment of fertility or mutagenesis have not been performed with CREON® MINIMICROSPHERES® (Pancrelipase Delayed-Release Capsules, USP).”

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

EPI (exocrine pancreatic insufficiency) is associated with cystic fibrosis, chronic pancreatitis, postpancreatectomy, and other conditions. Inadequate secretion of pancreatic enzymes in patients with EPI causes malabsorption, leading to inadequate absorption of fats, proteins, and carbohydrates, as well as fat-soluble vitamins and vitamin B₁₂. The malabsorption of fats is the most clinically significant aspect of EPI, since this leads to steatorrhea and eventually to wasting in adults and failure to thrive in infants and children.

The Sponsor’s drug product, Creon® Minimicrospheres®, is a delayed-release capsule formulation of pancrelipase, a digestive enzyme product derived from porcine pancreas. The major classes of pancreatic enzymes in pancrelipase include lipase, protease, and amylase. These enzymes provide a therapeutic benefit to EPI patients by improving the digestion of fats, proteins, and starch. The minimicrospheres in the Sponsor’s drug product are enteric-coated pellets that contain a pancrelipase and PEG 4000. Thus, the formulation is designed to resist inactivation of the enzyme preparation that would occur in the acidic environment of the stomach, prior to delivery into the duodenum. Once in the duodenum, the enteric coating ruptures in response to the increased pH (5.5 or greater) and the enzymes are released to aid in digestion. The protection of enzymes from destruction in the gastric medium is especially important for lipase, which is the most sensitive to low pH among the pancreatic enzymes. The lipase activity is needed to resolve the steatorrhea associated with EPI.

The following indication for Creon® Minimicrospheres® is stated in the Sponsor’s draft labeling:
The Sponsor submitted the following preclinical studies of the drug substance: gastrointestinal motility study in mice, 1-month oral toxicity study in dogs, 9-month oral toxicity study in dogs. Preclinical studies of the drug product included two pharmacology studies in minipigs with exocrine pancreatic insufficiency, and a pharmacokinetics study in pigs with exocrine pancreatic insufficiency.

The pancreatic enzymes present in Creon® Minimicrospheres® act as a digestive aid in patients with EPI through catalysis of the following digestive reactions: hydrolysis of fats into monoglycerol, glycerol, and fatty acids; hydrolysis of protein into short-chain peptides (2-5 amino acids); hydrolysis of starch into dextrins and short-chain sugars. The pharmacological activity of the drug product was demonstrated in two studies using the minipig model of EPI. In one study, Creon® 10,000 mms (minimicrospheres) produced a dose-dependent improvement in the digestibility of fat and dry matter in pancreatic duct-ligated minipigs. In the other study, Kreon® 10,000 mms (same product as Creon®) was shown to produce a dose-dependent increase in the digestibility of fat, protein, and starch in the same model of EPI. The increase in daily fecal output was partially reversed by Kreon® 10,000 mms. The drug substance had no effect on gastrointestinal charcoal propulsion in mice at a dose of 1500 mg/kg p.o., the only dose tested. A pharmacokinetic study demonstrated the lack of absorption of pancreatic lipase, procolipase/collipase, and trypsin after oral administration of Creon® 10,000 mms in pancreatic duct-ligated pigs or in pancreatectomized pigs.

A 4-week oral toxicity study of pancreatin in Beagle dogs was performed using dose levels of 0 (placebo), 1000, 3000, or 6000 mg/kg/day (pancreatin powder in capsules). An additional group was treated with 6000 mg/kg/day pancreatin pellets in capsules. It is assumed that the test article was actually pancrelipase, but was referred to as “pancreatin” by the authors. Four males and four females were assigned to each group, and dosing was performed twice daily. The pancreatin dose levels were equal to 94,460, 283,380, and 566,760 FIP lipase units/kg/day for the groups treated with the powder formulation, and 321,924 FIP lipase units/kg/day for the group treated with the pellet formulation (FIP units are the same as USP lipase units). A NOAEL (no observed adverse effect level) was not established. Oral administration of 1000, 3000, 6000 (powder), and 6000 (pellets) mg/kg/day produced glandular dilatation in the small intestine. Thyroid concretions occurred in the 6000 mg/kg/day pellets group.
A 9-month oral toxicity study of pancreatin in Beagle dogs was performed using dose levels of 0 (placebo), 1000, 2000, or 4000 mg/kg/day (4 dogs/sex/group). Dosing was performed twice daily. The pancreatin dose levels were equal to 98,700, 197,400, and 394,800 FIP lipase units/kg/day. As with the preceding study, it assumed that the test article was actually pancrelipase. Liver was a target organ of toxicity in the 4000 mg/kg/day group, as indicated by an increased incidence and severity of fat accumulation. The effect in liver may have been the consequence of nutritional and/or metabolic imbalances, as food consumption was reduced in the 4000 mg/kg/day group. Treatment with 1000, 2000, and 4000 mg/kg/day produced a low incidence of hemorrhage in the large intestine. Concretions and cysts in thyroids were observed in all drug-treated groups. Despite the signs of reduced food consumption at the 2000 and 4000 mg/kg/day dose levels, weight gain was increased by 43-78% in all treatment groups, except for the 1000 mg/kg/day males. The authors attributed these conflicting observations to the high caloric value of the test article at the given dose level. However, this proposal seems unlikely, given that protein is the major component of pancreatin, and the relatively low calorie content of protein. Pancreatin contained an extremely low level of fat (0.2%). Hypothetically, the high doses of pancreatic enzymes (i.e. lipase) may have enhanced the digestion and absorption of fat, which could have resulted in the increased weight gain.

The submitted toxicity studies of pancrelipase provide useful safety information on the drug substance. However, the clinical use of the drug product may require the ingestion of a large number of capsules, which would result in the intake of high dose levels of certain excipients. The Sponsor estimates that as much as 60 Creon® 20 capsules will be ingested daily in a 60-kg patient, based on a maximum recommended dose of 6000 lipase units/kg/meal. Therefore, any adverse effect that is associated with the clinical use of the drug product may be caused by the drug substance, one or more of the excipients, or an interaction between the drug substance and the excipients. Thus, the information provided by the 1-month and 9-month oral toxicity studies of pancrelipase in dogs is of limited value in the evaluation of the potential toxicity associated with the drug product. Clearly, the results of these studies would have been more relevant to the potential human toxicity if the drug product had been used.

The Sponsor previously submitted pharmacokinetic and toxicology studies on the major excipients present in Creon® Minimicrospheres®, in compliance with a request from the Division of Gastrointestinal and Coagulation Drug Products. These studies were reviewed in the Pharmacologist’s Review of IND 47,546 dated May 23, 1997, and were also submitted in the present application. The preclinical studies of excipients included information on hydroxypropylmethylcellulose phthalate, dibutyl phthalate, dimethicone 1000, polyethylene glycol 4000, and light mineral oil. In some cases, the information consisted of summaries of ADME or toxicology studies, with few details provided.

Pharmacokinetic studies of hydroxypropylmethylcellulose phthalate (HPMCP) were performed in rats. HPMCP was poorly absorbed following oral administration. Most of the radioactive dose was present in the gastrointestinal contents at 6 hr after oral administration of [14C]HPMCP (93.3% in males, 81.5% in females). Phthalic acid was identified as a major metabolite excreted in urine. The proportion of unchanged drug and phthalic acid in urine was not stated. All of the radioactivity in feces was associated with unchanged drug. Following oral administration of
[¹⁴C]HPMCP, approximately 93% of the total radioactivity was excreted in feces at 72 hr post-dose. Excretion in urine accounted for about 1% of the total radioactivity.

Oral administration of up to 15,000 mg/kg HPMCP produced no deaths in rats. Oral toxicity studies of one month (1300, 2000, 3000, 4500, and 10,000 mg/kg/day) and six months (1500, 3000, and 6000 mg/kg/day) duration in rats were submitted. The NOAEL was 4500 mg/kg/day in the 1-month study. No target organs of toxicity were identified. All animals in the 10,000 mg/kg/day group and the vehicle control group (1.5% sodium bicarbonate, same dose volume) died between days 10-16. Thus, the deaths in the high-dose group may have been related to the vehicle. The NOAEL in the 6-month rat study was 6000 mg/kg/day. Target organ toxicity was not observed. These studies are of limited usefulness in assessing the toxicity of HPMCP, due to the small number of organs examined in each study. No segment of the gastrointestinal tract was examined in these studies.

Dibutyl phthalate was rapidly absorbed in rats and hamsters after oral administration. Radioactivity was distributed throughout the body following oral administration of [¹⁴C]dibutyl phthalate in rats. At 48 hr after administration, no organ contained more than 0.7% of the radioactive dose. When rats were given a diet containing 0.1% dibutyl phthalate for up to 12 weeks, there was no accumulation in any organ that was studied. Metabolism of dibutyl phthalate was demonstrated in rat liver homogenate, and intestinal mucosal cell homogenates from rat, ferret, and baboon. The metabolites included phthalic acid, monobutyl phthalate glucuronide, 3-keto-butyl-phthalate, and 4-carboxypropyl phthalate. Following oral administration of [¹⁴C]dibutyl phthalate in rats, 85-100% of the dose was excreted in urine at 24 hr post-dose. Urinary excretion accounted for 79% of the dose following oral administration in hamsters.

Brief summaries of the following toxicity studies of dibutyl phthalate were submitted: 6-week oral study in rats, 80-day oral study in rats and mice, 3-month oral study in rats, 6-month oral study in rats, two 1-year dietary studies in rats, and a ½-year oral study in rats. The oral no effect doses were the following: 1000 mg/kg/day in the 6-week rat study (only dose tested), 120 mg/kg/day in the 3-month rat study, 2.5 mg/kg/day in the 6-month rat study (only dose tested), 75 mg/kg/day in a 1-year dietary study in rats (only dose tested), 150 mg/kg/day in a 1-year dietary study in rats, and 1000 mg/kg/day in the ½-year rat study (only dose tested). A high incidence of deaths occurred at 750 mg/kg/day in a 1-year dietary study in rats. Death also occurred in rats treated orally with 1200 mg/kg/day in the 3-month study. Because no details of the study methods were provided for the toxicity studies, it is difficult to assess the quality of these studies.

A brief summary of a teratogenicity (Segment II) study of dibutyl phthalate in rats was submitted. Pregnant females were treated by intraperitoneal administration of 0, 320, 640, or 1180 mg/kg/day on days 5, 10, and 15 of gestation. The incidence of fetal skeletal abnormalities was increased in all treatment groups. The high-dose group exhibited an increased number of resorptions and a decreased number of live fetuses. Since no information about maternal toxicity was provided, it is difficult to interpret these results.
Dimethicones are linear chains of dimethylpolysiloxane (DMPS) which have terminal trimethylsilyl groups. Dimethicone 1000, a component of the enteric coating in the drug product, has a viscosity 1000 cs (centistokes). The dimethicones used in the toxicity studies varied in size and viscosity. Dimethicone 1000 was tested in only one of these studies. Silicone compounds are not readily absorbed from the gastrointestinal tract. Following injection of $[^{14}\text{C}]$dimethicone fluid in the hind limb of rats, the radioactivity was distributed primarily in the gastrointestinal tract, and no evidence of metabolism was observed. When $[^{14}\text{C}]$dimethicone was administered through i.p. injection in rats, the following distribution of radioactivity was observed at 25 days after dosing: 51% in adipose tissue, 27% in gastrointestinal tissues, and 15% in liver.

The minimum lethal oral dose of dimethicone 200 (50 cs), dimethicone 550 (75 cs), dimethicone 702 (35 cs), and dimethicone 200 (350 cs) in rats greater than 30 mg/kg.

A 76-week dietary toxicity study of a silicone antifoam compound (94% polydimethylsiloxane silicone oil and 6% silicone dioxide) was performed in mice. Three groups were given diet containing 0, 0.25%, or 2.5% of the test article. The dose levels in the treatment groups were estimated to be 580 and 5800 mg/kg/day. Mortality was increased in the 5800 mg/kg/day females. No target organs of toxicity were observed. The no effect dose was 580 mg/kg/day. This study is of limited usefulness for assessing the toxicity of dimethicones, due to the small number of organs/tissues that were examined.

Brief summaries of oral toxicity studies of dimethicone in rats were submitted. Female rats were treated with 1, 2, 5, 10, 12, and 20 g/kg/day dimethicone 200 fluid (350 cs), administered by gavage. The animals were dosed 20 times during a 28-day period. No treatment-related effects were observed at any dose. A 90-day dietary study in rats was performed using dimethicones with viscosity values of 50, 350, 1000, 10,000, and 60,000 cs. The rats were given a diet containing 1% dimethicone. No treatment-related effects were observed. A 2-year dietary study in rats was performed using dimethicone antifoam A. The rats were given a diet containing 0.3% of the test article, yielding an estimated dose of 150 mg/kg/day. No treatment-related effects occurred. Since no detail of the methods used in the above studies were provided, it is difficult to assess the quality of these studies.

A 6-month dietary study of dimethicone antifoam A in dogs was performed using dose levels of 0, 300, 1000, and 3000 mg/kg/day. The livers from all dimethicone-treated dogs had deposits of bile. The amount of bile present in Kupffer cells and hepatocytes was dose related. In the 3000 mg/kg/day group, bile was also deposited in the interlobular bile ducts. The significance of the bile deposits is unknown. A no effect dose was not established in this study, due to the bile deposits in liver. However, dimethicone antifoam A was well tolerated at all dose levels. Although histopathology was performed in this study, the authors did not state which organs were examined. Thus, it is difficult at assess the quality of this study.
Brief summaries of reproductive toxicology studies of dimethicone 360 were submitted. In a Segment I study, rats were treated subcutaneously with 0, 20, or 200 mg/kg/dose, administered three times per week. One half of the pregnant females were sacrificed on day 13 of gestation and the remaining pregnant females were allowed to give birth and nurse their pups for 21 days. Dimethicone 360 had no effects on the dams, fetuses, or pups. Segment II studies were performed in rats and rabbits using dose levels of 0, 20, 200, and 1000 mg/kg/day (route of administration was not stated). Pregnant rats were treated on days 6-16 of gestation, and pregnant rabbits were treated on days 6-18 of gestation. Dimethicone 360 was not teratogenic in either species. No signs of maternal toxicity were observed. In a Segment III study, rats were treated from day 15 of gestation through day 21 of lactation with 0, 20, 200, or 1000 mg/kg/day (route of administration was not stated). A decrease in the number of live pups was observed at 200 and 1000 mg/kg/day.

Limited information on the pharmacokinetics of PEG 4000 (polyethylene glycol 4000) was provided. The absorption of orally administered PEG 4000 is known to be extremely low. At seven days after oral administration of $[^{14}\text{C}]$PEG 4000 in rats, 4.1% of the total radioactivity was recovered in urine and 81.9% was recovered in feces. Following intravenous administration of $[^{14}\text{C}]$PEG 4000 in rats, the excretion of total radioactivity was 61% and 20% in urine and feces, respectively, at seven days post-dose. Brief summaries of repeat-dose toxicity studies of PEG 4000 were submitted. In a 3-month dietary toxicity study in rats, the no effect dose was 4% (approximately 2400 mg/kg/day). Reduced body weight was observed in rats given 8% PEG 4000 (approximately 4800 mg/kg/day). The no-effect dose in 4-month dietary toxicity study in rats was 5% (approximately 3000 mg/kg/day). Reduced bodyweight and increased liver weight occurred in rats given 10% PEG 4000 (approximately 6000 mg/kg/day) in this study. In a 2-year dietary toxicity study in rats, the no-effect dose was 4% (approximately 2400 mg/kg/day). Reduced bodyweight was observed in the group given 8% PEG 4000 (approximately 4800 mg/kg/day). In a 1-year dietary toxicity study in dogs, the no-effect dose was 2% PEG 4000 (approximately 800 mg/kg/day), which was the only dose tested. A 12-month intravenous toxicity study in dogs was performed using dose levels of 0, 10, 30, or 90 mg/kg/day PEG 4000. The no-effect dose was 90 mg/kg/day. The above studies are of limited usefulness in evaluating the toxicity of PEG 4000, due to the small number of organs/tissues examined in these studies.

Studies on the distribution, metabolism, and excretion of mineral oil in rats were submitted. The distribution of total radioactivity was mostly limited to the gastrointestinal tract contents following oral administration of $[^{3}\text{H}]$mineral oil in rats (80% at 8 hr post-dose). Both $[^{3}\text{H}]$mineral oil and its metabolites with increased polarity were detected in tissue extracts. At two days after oral administration of $[^{3}\text{H}]$mineral oil in rats, about 80% of the total radioactivity was recovered in feces. The cumulative urinary excretion was 7-8% during one week post-dose. Following intraperitoneal administration, 11% of the total radioactivity was excreted in feces and 8% was excreted in urine at eight days post-dose. These results suggest that $[^{3}\text{H}]$mineral oil is poorly absorbed following oral administration in rats.

The submitted toxicology studies of mineral oil consisted of chronic inhalation studies in mice, rats, gerbils, dogs, and rabbits. Oil accumulation in bronchiolar and alveolar macrophages was the most common effect in these studies. It is unlikely that these observations are relevant to the potential toxicity associated with oral administration of mineral oil.
The light mineral oil that is used as an excipient in the Sponsor’s drug product is described as “medical white mineral oil”, or “paraffinum perliquidum”. White mineral oil may be safely used in foods provided that it is a mixture of liquid hydrocarbons (essentially parafinic and naphthenic in nature), meets the test requirements of the USP (United States Pharmacopeia) XX (1980, pg. 532) for readily carbonizable substances, meets the test requirements of USP XVII (pg. 400) for sulfur compounds, and meets the specifications prescribed in the “Journal of the Association of Official Analytical Chemists” (Vol. 45, pg. 66, 1962) for added antioxidants (21 CFR 172.878).

Given that an adequate dose regimen for the Sponsor’s drug product may require the daily ingestion of a large number of capsules, the potential toxicity due to the excipients as well as the drug substance should be considered in the overall safety assessment of this product. The incidence of fibrosing colonopathy associated with high dose levels of PEPs (pancreatic enzyme preparations) in cystic fibrosis patients supports this viewpoint. It is noteworthy that an excipient present in certain delayed-release PEPs is suspected of being involved in the pathogenesis of fibrosing colonopathy, based on evidence from animal studies. This excipient, Eudragit® L30D55 (methacrylic acid copolymer), is not present in Creon® Minimicrospheres®.

The maximum daily dose of the major excipients in Creon® Minimicrospheres® can be estimated based on a maximum recommended daily dose of 20,000 lipase units/kg, which would result in the ingestion of 60 Creon® 20 capsules/day in a 60-kg adult and 20 capsules/day in a 20-kg child. The maximum dose levels of the major excipients for both adults and children are estimated to be the following: [mg/kg/day] PEG 4000, [mg/kg/day] light mineral oil, [mg/kg/day] hydroxypropylmethylcellulose phthalate, [mg/kg/day] dimethicone 1000, and [mg/kg/day] dibutyl phthalate. The submitted toxicity studies of PEG 4000, light mineral oil, hydroxypropylmethylcellulose phthalate, dimethicone 1000, and dibutyl phthalate were deficient in the methods used (e.g. incomplete histopathology). However, there is no indication from these studies that these excipients are likely to produce toxicity in patients treated with Creon® Minimicrospheres®, even at the highest recommended dose levels. The observed no effect doses in the chronic toxicity studies of the excipients exceeded the potential maximum human dose by greater than 10-fold. PEG 4000 and light mineral oil (white mineral oil) are approved as direct food additives (21 CFR 172.820 and 21 CFR 172.878, respectively). Dimethicone 1000 is a form of dimethylpolysiloxane, which is approved as a secondary direct food additive for use as a defoaming agent (21 CFR 173.340). Furthermore, there is extensive human experience with Creon® Minimicrospheres®, which was initially marketed in Germany starting in 1990. This product has been marketed in the United States since 1993 as an over-the-counter product. The Sponsor claims that fibrosing colonopathy is not associated with the use of Creon® Minimicrospheres®.

Gelatin is defined as a food (21 CFR 170.3(n)(22)). Thus, the ingestion of gelatin capsules, even in the large numbers needed for Creon® Minimicrospheres®, is considered to be safe. The drug product also contains low quantities of the following excipients: FD&C Blue No. 2, titanium dioxide, iron oxide, shellac, soya lecithin, and 2-ethoxyethanol.
FD&C Blue No. 2 is an approved color additive for drugs (21 CFR 74.1102), and is present only in Creon® 5 capsules. This color additive is considered to be safe when used in amounts consistent with current good manufacturing practice. The ADI (acceptable daily intake) is 0-17.0 mg/kg, as recommended by the Joint Expert Committee on Food Additives of the World Health Organization. The maximum potential dose of FD&C Blue No. 2 associated with use of the drug product is estimated by the Sponsor to be 0.04 mg/kg/day, based on the ingestion 60 Creon® 5 capsules in a 60-kg adult or 20 Creon® 5 capsules in a 20-kg child. Thus, the estimated maximum dose level is well within the limits of the ADI.

Titanium dioxide is an approved color additive for drugs (21 CFR 73.1575). The quantities present in the drug product are consistent with current good manufacturing practice. The estimated maximum dose level is estimated to be 0.4 mg/kg/day (based on the ingestion of 60 Creon® 5 capsules/day in a 60-kg adult and 20 capsules/day in a 20-kg child).

Iron oxide is approved as a color additive for drugs in an amount not to exceed 5 mg/day of elemental iron (21 CFR 73.1200). The maximum daily intake of iron oxide (and elemental iron) associated with the clinical use of Creon® Minimicrospheres® can be estimated by assuming a maximum daily ingestion of 60 capsules for a given dosage form. The maximum daily dose of iron oxide in Creon® 5, Creon® 10, and Creon® 20 will be 0 mg, respectively. These dose levels are approximately equal to the following daily doses of elemental iron: 0 mg for Creon® 5, Creon® 10, and Creon® 20, respectively. Thus, the maximum daily intake of iron oxide associated with the administration of Creon® Minimicrospheres® will exceed the approved maximum daily intake (5 mg elemental iron/day).

Chronic exposure to excess iron causes increased iron absorption from the gastrointestinal tract and elevated levels of transferrin. Chronic iron overload can lead to an increased synthesis of ferritin in hepatocytes. When the rate of ferritin synthesis in liver exceeds the rate at which lysosomes can process iron for excretion, the lysosomes can convert ferritin into hemosiderin, which remains within cells as a stored form of iron. Iron accumulation in liver, pancreas, endocrine organs, and heart are characteristic of chronic iron overload. Thus, disturbances in liver function, development of diabetes mellitus, and abnormalities in endocrine and cardiovascular function are symptomatic of iron overload. At the cellular level, iron overload produces lipid peroxidation and consequent damage to mitochondria, microsomes, and other cellular organelles. The maximum daily intake of elemental iron associated with the use of Creon® Minimicrospheres® is estimated to be 0 mg, whereas the Recommended Daily Allowance in adult males and females is 10 mg and 15 mg, respectively.

Shellac and 2-ethoxyethanol (ethylene glycol monoethyl ether) are used as ingredients in the imprinting ink for the drug product. Both of these ingredients are approved for use in inks for marking food supplements in tablet form, gum, or confectionery (21 CFR 73.1(b)). Soya lecithin is also an ingredient in the imprinting ink. Lecithin is approved for use as a food ingredient with no limitation other than good manufacturing practice, and is categorized as GRAS (21 CFR 184.1400).
RECOMMENDATIONS:

From a preclinical viewpoint, the application is recommended for approval, with a provision that the labeling will be changed as described in the Labeling section.

David B. Joseph, Ph.D.
Pharmacologist, HFD-180

Comment:

Jasti B. Choudary, B.V.Sc., Ph.D.
Supervisory Pharmacologist, HFD-180

cc:
Orig NDA 20-725
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Joseph
HFD-048/Dr. Viswanathan

R/D Init.: J. Choudary 8/26/03

DJ/dbj: 9/4/03
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/s/

David Joseph
9/4/03 11:26:32 AM
PHARMACOLOGIST

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PHARMACOLOGIST