HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CREON safely and effectively. See full prescribing information for CREON.
CREON (pancrelipase) delayed-release capsules for oral use
Initial U.S. Approval: 2009

-------RECENT MAJOR CHANGES-------

Dosage and Administration, *Infants (up to 12 months)* (2.1)	6/2011
Dosage and Administration (2.2)	6/2011
Dosage and Administration, *Infants (up to 12 months)* (2.2)	6/2011

-------INDICATIONS AND USAGE -------

CREON is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions. (1)

-------DOSAGE AND ADMINISTRATION -------

CREON is not interchangeable with any other pancrelipase product. (2.1)
Do not crush or chew capsules and capsule contents. For infants or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food, e.g., applesauce. (2.1) Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines. (2.2)

Infants (up to 12 months)

- Prior to each feeding, infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. (2.1)
- Do not mix CREON capsule contents directly into formula or breast milk prior to administration. (2.1)

Children Older than 12 Months and Younger than 4 Years

- Begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.2)

Children 4 Years and Older and Adults

- Begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.2)

Adults with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis or Pancreatectomy

- Individualize dosage based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet. (2.2)

-------DOSAGE FORMS AND STRENGTHS -------

- Delayed-Release Capsules: 3,000 USP units of lipase; 9,500 USP units of protease; 15,000 USP units of amylase (3)
- Delayed-Release Capsules: 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase (3)
- Delayed-Release Capsules: 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase (3)
- Delayed-Release Capsules: 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase (3)

-------CONTRAINDICATIONS -------

None (4)

-------WARNINGS AND PRECAUTIONS -------

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement in the treatment of cystic fibrosis patients. Exercise caution when doses of CREON exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day). (5.1)
- To avoid irritation of oral mucosa, do not chew CREON or retain in the mouth. (5.2)
- Exercise caution when prescribing CREON to patients with gout, renal impairment, or hyperuricemia. (5.3)
- There is theoretical risk of viral transmission with all pancreatic enzyme products including CREON. (5.4)
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. (5.5)

-------ADVERSE REACTIONS-------

- Adverse reactions occurring in at least 2 cystic fibrosis patients (greater than or equal to 4%) receiving CREON are vomiting, dizziness, and cough. (6.1)
- Adverse reactions that occurred in at least 1 chronic pancreatitis or pancreatectomy patient (greater than or equal to 4%) receiving CREON are hyperglycemia, hypoglycemia, abdominal pain, abnormal feces, flatulence, frequent bowel movements, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-241-1643 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CREON® (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.

2 DOSAGE AND ADMINISTRATION

CREON is not interchangeable with other pancrelipase products.

CREON is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of CREON should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet as described in the Limitations on Dosing below *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

2.1 Administration

Infants (up to 12 months)

CREON should be administered to infants immediately prior to each feeding, using a dosage of 3,000 lipase units per 120 mL of formula or prior to breast-feeding. Contents of the capsule may be administered directly to the mouth or with a small amount of applesauce. Administration should be followed by breast milk or formula. Contents of the capsule should not be mixed directly into formula or breast milk as this may diminish efficacy. Care should be taken to ensure that CREON is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

Children and Adults

CREON should be taken during meals or snacks, with sufficient fluid. CREON capsules and capsule contents should not be crushed or chewed. Capsules should be swallowed whole.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. The CREON-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

2.2 Dosage

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.[1, 2, 3] CREON should be administered in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences (also known as Conferences) provided in the following paragraphs, except for infants. Although the Conferences recommend doses of 2,000 to 4,000 lipase units in infants up to 12 months, CREON is available in a 3,000 lipase unit capsule. Therefore, the recommended dose of CREON in infants up to 12 months is 3,000 lipase units per 120 mL of formula or per breast-feeding. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

Additional recommendations for pancreatic enzyme therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy are based on a clinical trial conducted in these populations.

Infants (up to 12 months)

CREON is available in the strength of 3,000 USP units of lipase thus infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Do not mix CREON capsule contents directly into formula or breast milk prior to administration *[see Administration (2.1)]*.

Children Older than 12 Months and Younger than 4 Years

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or

equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Adults

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed CREON dose for an individualized full meal should be given with each snack. The total daily dose should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

Adults with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis or Pancreatectomy

The initial starting dose and increases in the dose per meal should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.

In one clinical trial, patients received CREON at a dose of 72,000 lipase units per meal while consuming at least 100 g of fat per day *[see Clinical Studies (14.2)]*. Lower starting doses recommended in the literature are consistent with the 500 lipase units/kg of body weight per meal lowest starting dose recommended for adults in the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1, 2, 3, 4] Usually, half of the prescribed CREON dose for an individualized full meal should be given with each snack.

Limitations on Dosing

Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1, 2, 3] If symptoms and signs of steatorrhea persist,

the dosage may be increased by the healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age *[see Warnings and Precautions (5.1)]*. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

3 DOSAGE FORMS AND STRENGTHS

The active ingredient in CREON evaluated in clinical trials is lipase. CREON is dosed by lipase units.

Other active ingredients include protease and amylase. Each CREON delayed-release capsule strength contains the specified amounts of lipase, protease, and amylase as follows:

- 3,000 USP units of lipase; 9,500 USP units of protease; 15,000 USP units of amylase delayed-release capsules have a white opaque cap with imprint “CREON 1203” and a white opaque body.
- 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase delayed-release capsules have an orange opaque cap with imprint “CREON 1206” and a blue opaque body.
- 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase delayed-release capsules have a brown opaque cap with imprint “CREON 1212” and a colorless transparent body.
- 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase delayed-release capsules have an orange opaque cap with imprint “CREON 1224” and a colorless transparent body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. [5, 6] Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in children less than 12 years of age.[1] Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs.[1] It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day *[see Dosage and Administration (2.1)]*.

Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

5.2 Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth. CREON should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity *[see Dosage and Administration (2.2) and Patient Counseling Information (17.1)]*. For patients who are unable to swallow intact capsules, the capsules may be

carefully opened and the contents added to a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce, at room temperature. The CREON-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

5.3 Potential for Risk of Hyperuricemia

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

5.4 Potential Viral Exposure from the Product Source

CREON is sourced from pancreatic tissue from swine used for food consumption. Although the risk that CREON will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

5.5 Allergic Reactions

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

6 ADVERSE REACTIONS

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) that are described elsewhere in the label include fibrosing colonopathy, hyperuricemia and allergic reactions *[see Warnings and Precautions (5)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The short-term safety of CREON was assessed in clinical trials conducted in 121 patients with exocrine pancreatic insufficiency (EPI): 67 patients with EPI due to cystic fibrosis (CF) and 25 patients with EPI due to chronic pancreatitis or pancreatectomy were treated with CREON.

Cystic Fibrosis

Studies 1 and 2 were randomized, double-blind, placebo-controlled, crossover studies of 49 patients, ages 7 to 43 years, with EPI due to CF. Study 1 included 32 patients ages 12 to 43 years and Study 2 included 17 patients ages 7 to 11 years. In these studies, patients were randomized to receive CREON at a dose of 4,000 lipase units/g fat ingested per day or matching placebo for 5 to 6 days of treatment, followed by crossover to the alternate treatment for an additional 5 to 6 days. The mean exposure to CREON during these studies was 5 days.

In Study 1, one patient experienced duodenitis and gastritis of moderate severity 16 days after completing treatment with CREON. Transient neutropenia without clinical sequelae was observed as an abnormal laboratory finding in one patient receiving CREON and a macrolide antibiotic.

In Study 2, adverse reactions that occurred in at least 2 patients (greater than or equal to 12%) treated with CREON were vomiting and headache. Vomiting occurred in 2 patients treated with CREON and did not occur in patients treated with placebo; headache occurred in 2 patients treated with CREON and did not occur in patients treated with placebo.

The most common adverse reactions (greater than or equal to 4%) in Studies 1 and 2 were vomiting, dizziness, and cough. Table 1 enumerates adverse reactions that occurred in at least 2 patients (greater than or equal to 4%) treated with CREON at a higher rate than with placebo in Studies 1 and 2.

Table 1: Adverse Reactions Occurring in at Least 2 Patients (greater than or equal to 4%) in Cystic Fibrosis (Studies 1 and 2)

Adverse Reaction	CREON Capsules n = 49 (%)	Placebo n = 47 (%)
Vomiting	3 (6)	1 (2)
Dizziness	2 (4)	1 (2)
Cough	2 (4)	0

An additional open-label, single-arm study assessed the short-term safety and tolerability of CREON in 18 infants and children, ages 4 months to 6 years, with EPI due to cystic fibrosis. Patients received their usual pancreatic enzyme replacement therapy (mean dose of 7,000 lipase units/kg/day for a mean duration of 18.2 days) followed by CREON (mean dose of 7,500 lipase units/kg/day for a mean duration of 12.6 days). There were no serious adverse reactions. Adverse reactions that occurred in patients during treatment with CREON were vomiting, irritability, and decreased appetite, each occurring in 6% of patients.

Chronic Pancreatitis or Pancreatectomy

A randomized, double-blind, placebo-controlled, parallel group study was conducted in 54 adult patients, ages 32 to 75 years, with EPI due to chronic pancreatitis or pancreatectomy. Patients received single-blind placebo treatment during a 5-day run-in period followed by an intervening period of up to 16 days of investigator-directed treatment with no restrictions on pancreatic enzyme replacement therapy. Patients were then randomized to receive CREON or matching placebo for 7 days. The CREON dose was 72,000 lipase units per main meal (3 main meals) and 36,000 lipase units per snack (2 snacks). The mean exposure to CREON during this study was 6.8 days in the 25 patients that received CREON.

The most common adverse reactions reported during the study were related to glycemic control and were reported more commonly during CREON treatment than during placebo treatment.

Table 2 enumerates adverse reactions that occurred in at least 1 patient (greater than or equal to 4%) treated with CREON at a higher rate than with placebo.

Table 2: Adverse Reactions in at Least 1 Patient (greater than or equal to 4%) in the Chronic Pancreatitis or Pancreatectomy Trial

Adverse Reaction	CREON Capsules n = 25 (%)	Placebo n = 29 (%)
Hyperglycemia	2 (8)	2 (7)
Hypoglycemia	1 (4)	1 (3)
Abdominal Pain	1 (4)	1 (3)
Abnormal Feces	1 (4)	0
Flatulence	1 (4)	0
Frequent Bowel Movements	1 (4)	0
Nasopharyngitis	1 (4)	0

6.2 Postmarketing Experience

Postmarketing data from this formulation of CREON have been available since 2009. The following adverse reactions have been identified during post approval use of this formulation of CREON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders (including abdominal pain, diarrhea, flatulence, constipation and nausea), skin disorders (including pruritus, urticaria and rash), blurred vision, myalgia, muscle spasm, and asymptomatic elevations of liver enzymes have been reported with this formulation of CREON.

Delayed- and immediate-release pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase) have been used for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis and other conditions, such as chronic pancreatitis. The long-term safety profile of these products has been described in the medical literature. The most serious adverse reactions included fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives, and pruritus.

7 DRUG INTERACTIONS

No drug interactions have been identified. No formal interaction studies have been conducted.

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. CREON should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CREON is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.

8.4 Pediatric Use

The short-term safety and effectiveness of CREON were assessed in two randomized, double-blind, placebo-controlled, crossover studies of 49 patients with EPI due to cystic fibrosis, 25 of whom were pediatric patients. Study 1 included 8 adolescents between 12 and 17 years of age. Study 2 included 17 children between 7 and 11 years of age. The safety and efficacy in pediatric patients in these studies were similar to adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

An open-label, single-arm, short-term study of CREON was conducted in 18 infants and children, ages 4 months to six years of age, with EPI due to cystic fibrosis. Patients received their usual pancreatic enzyme replacement therapy (mean dose of 7,000 lipase units/kg/day for a

mean duration of 18.2 days) followed by CREON (mean dose of 7,500 lipase units/kg/day for a mean duration of 12.6 days). The mean daily fat intake was 48 grams during treatment with usual pancreatic enzyme replacement therapy and 47 grams during treatment with CREON. When patients were switched from their usual pancreatic enzyme replacement therapy to CREON, they demonstrated similar spot fecal fat testing results; the clinical relevance of spot fecal fat testing has not been demonstrated. Adverse reactions that occurred in patients during treatment with CREON were vomiting, irritability, and decreased appetite *[see Adverse Reactions (6.1))]*.

The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience.

Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences *[see Dosage and Administration (2.1)]*. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy and colonic strictures in children less than 12 years of age *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies of CREON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

There have been no reports of overdose in clinical trials or postmarketing surveillance with this formulation of CREON. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*. High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should be used with caution in patients with a history of hyperuricemia, gout, or renal impairment *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

CREON is a pancreatic enzyme preparation consisting of pancrelipase, an extract derived from porcine pancreatic glands. Pancrelipase contains multiple enzyme classes, including porcine-derived lipases, proteases, and amylases.

Pancrelipase is a beige-white amorphous powder. It is miscible in water and practically insoluble or insoluble in alcohol and ether.

Each delayed-release capsule for oral administration contains enteric-coated spheres (0.71–1.60 mm in diameter).

The active ingredient evaluated in clinical trials is lipase. CREON is dosed by lipase units.

Other active ingredients include protease and amylase.

CREON contains the following inactive ingredients: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate.

3,000 USP units of lipase; 9,500 USP units of protease; 15,000 USP units of amylase delayed-release capsules have a white opaque cap with imprint “CREON 1203” and a white opaque body. The shells contain titanium dioxide and hypromellose.

6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase delayed-release capsules have a Swedish-orange opaque cap with imprint “CREON 1206” and a blue opaque body. The shells contain FD&C Blue No. 2, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase delayed-release capsules have a brown opaque cap with imprint “CREON 1212” and a colorless transparent body. The shells contain black iron oxide, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase delayed-release capsules have a Swedish-orange opaque cap with imprint “CREON 1224” and a colorless transparent body. The shells contain gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pancreatic enzymes in CREON catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

12.3 Pharmacokinetics

The pancreatic enzymes in CREON are enteric-coated to minimize destruction or inactivation in gastric acid. CREON is designed to release most of the enzymes *in vivo* at an approximate pH of 5.5 or greater. Pancreatic enzymes are not absorbed from the gastrointestinal tract in appreciable amounts.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

The short-term efficacy of CREON was evaluated in three studies conducted in 103 patients with exocrine pancreatic insufficiency (EPI). Two studies were conducted in 49 patients with EPI due to cystic fibrosis (CF); one study was conducted in 54 patients with EPI due to chronic pancreatitis or pancreatectomy.

14.1 Cystic Fibrosis

Studies 1 and 2 were randomized, double-blind, placebo-controlled, crossover studies in 49 patients, ages 7 to 43 years, with exocrine pancreatic insufficiency due to cystic fibrosis. Study 1 included patients aged 12 to 43 years (n = 32). The final analysis population was limited to 29 patients; 3 patients were excluded due to protocol deviations. Study 2 included patients aged 7 to 11 years (n = 17). The final analysis population was limited to 16 patients; 1 patient withdrew consent prior to stool collection during treatment with CREON. In each study, patients were randomized to receive CREON at a dose of 4,000 lipase units/g fat ingested per day or matching placebo for 5 to 6 days of treatment, followed by crossover to the alternate treatment for an additional 5 to 6 days. All patients consumed a high-fat diet (greater than or equal to 90 grams of fat per day, 40% of daily calories derived from fat) during the treatment periods.

The coefficient of fat absorption (CFA) was determined by a 72-hour stool collection during both treatments, when both fat excretion and fat ingestion were measured. Each patient's CFA during placebo treatment was used as their no-treatment CFA value.

In Study 1, mean CFA was 89% with CREON treatment compared to 49% with placebo treatment. The mean difference in CFA was 41 percentage points in favor of CREON treatment with 95% CI: (34, 47) and $p<0.001$.

In Study 2, mean CFA was 83% with CREON treatment compared to 47% with placebo treatment. The mean difference in CFA was 35 percentage points in favor of CREON treatment with 95% CI: (27, 44) and $p<0.001$.

Subgroup analyses of the CFA results in Studies 1 and 2 showed that mean change in CFA with CREON treatment was greater in patients with lower no-treatment (placebo) CFA values than in patients with higher no-treatment (placebo) CFA values. There were no differences in response to CREON by age or gender, with similar responses to CREON observed in male and female patients, and in younger (under 18 years of age) and older patients.

The coefficient of nitrogen absorption (CNA) was determined by a 72-hour stool collection during both treatments, when nitrogen excretion was measured and nitrogen ingestion from a controlled diet was estimated (based on the assumption that proteins contain 16% nitrogen). Each patient's CNA during placebo treatment was used as their no-treatment CNA value.

In Study 1, mean CNA was 86% with CREON treatment compared to 49% with placebo treatment. The mean difference in CNA was 37 percentage points in favor of CREON treatment with 95% CI: (31, 42) and p<0.001.

In Study 2, mean CNA was 80% with CREON treatment compared to 45% with placebo treatment. The mean difference in CNA was 35 percentage points in favor of CREON treatment with 95% CI: (26, 45) and p<0.001.

14.2 Chronic Pancreatitis or Pancreatectomy

A randomized, double-blind, placebo-controlled, parallel group study was conducted in 54 adult patients, ages 32 to 75 years, with EPI due to chronic pancreatitis or pancreatectomy. The final analysis population was limited to 52 patients; 2 patients were excluded due to protocol violations. Ten patients had a history of pancreatectomy (7 were treated with CREON). In this study, patients received placebo for 5 days (run-in period), followed by pancreatic enzyme replacement therapy as directed by the investigator for 16 days; this was followed by randomization to CREON or matching placebo for 7 days of treatment (double-blind period). Only patients with CFA less than 80% in the run-in period were randomized to the double-blind period. The dose of CREON during the double-blind period was 72,000 lipase units per main meal (3 main meals) and 36,000 lipase units per snack (2 snacks). All patients consumed a high-fat diet (greater than or equal to 100 grams of fat per day) during the treatment period.

The CFA was determined by a 72-hour stool collection during the run-in and double-blind treatment periods, when both fat excretion and fat ingestion were measured. The mean change in CFA from the run-in period to the end of the double-blind period in the CREON and Placebo groups is shown in Table 3.

Table 3: Change in CFA in the Chronic Pancreatitis and Pancreatectomy Trial (Run-in Period to End of Double-Blind Period)

	CREON n = 24	**Placebo n = 28**
CFA [%]		
Run-in Period (Mean, SD)	54 (19)	57 (21)
End of Double-Blind Period (Mean, SD)	86 (6)	66 (20)
Change in CFA * [%]		
Run-in Period to End of Double-Blind Period (Mean, SD)	32 (18)	9 (13)
Treatment Difference (95% CI)	21 (14, 28)	

*p<0.0001

Subgroup analyses of the CFA results showed that mean change in CFA was greater in patients with lower run-in period CFA values than in patients with higher run-in period CFA values. Only 1 of the patients with a history of total pancreatectomy was treated with CREON in the study. That patient had a CFA of 26% during the run-in period and a CFA of 73% at the end of the double-blind period. The remaining 6 patients with a history of partial pancreatectomy treated with CREON on the study had a mean CFA of 42% during the run-in period and a mean CFA of 84% at the end of the double-blind period.

15 REFERENCES

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[2] Borowitz DS, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *Journal of Pediatric Gastroenterology Nutrition.* 2002 Sep; 35: 246-259.

[3] Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association*. 2008; 108: 832-839.

[4] Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Current Gastroenterology Reports.* 2007; 9: 116-122.

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[6] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *New England Journal of Medicine.* 1997; 336: 1283-1289.

16 HOW SUPPLIED/STORAGE AND HANDLING

CREON (pancrelipase) Delayed-Release Capsules

3,000 USP units of lipase; 9,500 USP units of protease; 15,000 USP units of amylase

Each CREON capsule is available as a two piece hypromellose capsule with a white opaque cap with imprint “CREON 1203” and a white opaque body that contains tan colored, delayed-release pancrelipase supplied in bottles of:

- 70 capsules (NDC 0032-1203-70)

CREON (pancrelipase) Delayed-Release Capsules

6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase

Each CREON capsule is available as a two-piece gelatin capsule with orange opaque cap with imprint “CREON 1206” and a blue opaque body that contains tan-colored, delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 0032-1206-01)
- 250 capsules (NDC 0032-1206-07)

CREON (pancrelipase) Delayed-Release Capsules

12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase

Each CREON capsule is available as a two-piece gelatin capsule with a brown opaque cap with imprint “CREON 1212” and a colorless transparent body that contains tan-colored, delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 0032-1212-01)

- 250 capsules (NDC 0032-1212-07)

CREON (pancrelipase) Delayed-Release Capsules

24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase

Each CREON capsule is available as a two-piece gelatin capsule with orange opaque cap with imprint “CREON 1224” and a colorless transparent body that contains tan-colored, delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 0032-1224-01)
- 250 capsules (NDC 0032-1224-07)

Storage and Handling

CREON must be stored at room temperature up to 25°C (77°F) and protected from moisture. Temperature excursions are permitted between 25°C to 40°C (77°F and 104°F) for up to 30 days. Product should be discarded if exposed to higher temperature and moisture conditions higher than 70%. After opening, keep bottle tightly closed between uses to protect from moisture.

Bottles of CREON 3,000 USP units of lipase must be stored and dispensed in the original container.

Do not crush CREON delayed-release capsules or the capsule contents.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide) **17.1 Dosing and Administration**

- Instruct patients and caregivers that CREON should only be taken as directed by their healthcare professional. Patients should be advised that the total daily dose should not exceed 10,000 lipase units/kg body weight/day unless clinically indicated. This needs to be especially emphasized for patients eating multiple snacks and meals per day. Patients should be informed

that if a dose is missed, the next dose should be taken with the next meal or snack as directed. Doses should not be doubled *[see Dosage and Administration (2)]*.

- Instruct patients and caregivers that CREON should always be taken with food. Patients should be advised that CREON delayed-release capsules and the capsule contents must not be crushed or chewed as doing so could cause early release of enzymes and/or loss of enzymatic activity. Patients should swallow the intact capsules with adequate amounts of liquid at mealtimes. If necessary, the capsule contents can also be sprinkled on soft acidic foods *[see Dosage and Administration (2)]*.

17.2 Fibrosing Colonopathy

Advise patients and caregivers to follow dosing instructions carefully, as doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures in children below the age of 12 years *[see Dosage and Administration (2)]*.

17.3 Allergic Reactions

Advise patients and caregivers to contact their healthcare professional immediately if allergic reactions to CREON develop *[see Warnings and Precautions (5.5)]*.

17.4 Pregnancy and Breast Feeding

- Instruct patients to notify their healthcare professional if they are pregnant or are thinking of becoming pregnant during treatment with CREON *[see Use in Specific Populations (8.1)]*.
- Instruct patients to notify their healthcare professional if they are breast feeding or are thinking of breast feeding during treatment with CREON *[see Use in Specific Populations (8.3)]*.

Manufactured by:

Abbott Products GmbH

Hannover, Germany