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
Initial U.S. Approval: 2009

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

Indications and Usage, Chronic Pancreatitis, Pancreatectomy (1) 4/2010
Dosage and Administration, Chronic Pancreatitis or Pancreatectomy (2.1) 4/2010

----------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----------

Dosage

CREON is not interchangeable with any other pancrelipase product.

Infants (up to 12 months)

- Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. (2.1)
- Do not mix CREON capsule contents directly into formula or breast milk prior to administration. (2.2)

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.(2.1)

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. (2.1)

Adults with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis or Pancreatectomy

- 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. 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. Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet. (2.1)

Limitations on Dosing

- Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines. (2.1)

Administration

- CREON should be swallowed whole. For infants or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food, e.g., applesauce. (2.2)

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

- Capsules: 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase capsules have an orange opaque cap with imprint “CREON 1206” and a blue opaque body. (3)
- Capsules: 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase capsules have a brown opaque cap with imprint “CREON 1212” and a colorless transparent body. (3)
- Capsules: 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase capsules have an orange opaque cap with imprint “CREON 1224” and a colorless transparent body. (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----------

- Treatment-emergent adverse events occurring in at least 2 cystic fibrosis patients (greater than or equal to 6%) receiving CREON or placebo are abdominal pain, abdominal pain upper, abnormal feces, cough, dizziness, flatulence, headache, and weight decreased. (6.1)
- Treatment-emergent adverse events that occurred in at least 1 chronic pancreatitis or pancreatectomy patient (greater than or equal to 4%) receiving CREON were abdominal pain, abnormal feces, diabetes mellitus inadequate control, flatulence, frequent bowel movements, hyperglycemia, hypoglycemia, 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.

----------USE IN SPECIFIC POPULATIONS----------

Pediatric Patients

- The safety and effectiveness of CREON were assessed in pediatric cystic fibrosis patients, aged 12 to 17 years old. (8.4)
- The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase in pediatric patients have been described in the medical literature and through clinical experience. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: April 2010

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

2.1 Dosage

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 *[see Limitations on Dosing below and see Warnings and Precautions (5.1)]*.

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 Conferences provided in the following paragraphs. 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)

Infants may be given 2,000 to 4,000 lipase units 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 Dosage and Administration (2.2)]*.

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

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] 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.

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.

2.2 Administration

CREON should always be taken as prescribed by a healthcare professional.

Infants (up to 12 months)

CREON should be administered to infants immediately prior to each feeding, using a dosage of 2,000 to 4,000 lipase units per 120 mL of formula or per 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 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.

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 capsule strength contains the specified amounts of lipase, protease, and amylase as follows:

- 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase 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 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 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. 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 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) 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 two clinical trials conducted in 86 patients with exocrine pancreatic insufficiency (EPI). Study 1 was conducted in 32 patients with EPI due to cystic fibrosis (CF); Study 2 was conducted in 54 patients with EPI due to chronic pancreatitis or pancreatectomy.

Cystic Fibrosis

Study 1 was a randomized, double-blind, placebo-controlled, crossover study of 32 patients, ages 12 to 43 years, with EPI due to CF. In this 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. The mean exposure to CREON during this study was 5 days.

One patient experienced duodenitis and gastritis of moderate severity reported as a serious adverse event 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.

The incidence of adverse events (regardless of causality) was higher during placebo treatment (71%) than during CREON treatment (50%). Adverse events reported during the study were predominantly gastrointestinal complaints, and the type and incidence of adverse events were similar in adolescents (12 to 18 years) and adults (greater than 18 years).

Because clinical trials are conducted under controlled conditions, the observed adverse event rates may not reflect the rates observed in clinical practice.

Table 1 enumerates treatment-emergent adverse events that occurred in at least 2 patients (greater than or equal to 6%) treated with either CREON or placebo in Study 1.

Table 1: Treatment-Emergent Adverse Events Occurring in at least 2 Patients (greater than or equal to 6%) in Either Treatment Group of the Placebo-Controlled, Crossover Clinical Study of CREON in Cystic Fibrosis (Study 1)

MedDRA Primary System Organ Class Preferred Term	CREON Capsules n = 32 (%)	Placebo n = 31 (%)
Gastrointestinal Disorders		
Abnormal Feces	1 (3)	6 (19)
Flatulence	3 (9)	8 (26)
Abdominal Pain	3 (9)	8 (26)
Abdominal Pain Upper	0	3 (10)
Investigations		
Weight Decreased	1 (3)	2 (6)
Nervous System Disorders		
Headache	2 (6)	8 (26)
Dizziness	2 (6)	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2 (6)	0

Chronic Pancreatitis or Pancreatectomy

Study 2 was a randomized, double-blind, placebo-controlled, parallel group study of 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.

The incidence of treatment-emergent adverse events (regardless of causality) was 20% with CREON treatment and 21% with placebo treatment. The most common adverse events reported during the study were related to glycemic control and were reported more commonly during CREON treatment (12%) than during placebo treatment (7%).

Because clinical trials are conducted under controlled conditions, the observed adverse event rates may not reflect the rates observed in clinical practice.

Table 2 enumerates treatment-emergent adverse events that occurred in at least 1 patient (greater than or equal to 4%) in the CREON group.

Table 2: Treatment-Emergent Adverse Events Reported During the Randomized Period in at least 1 Patient (greater than or equal to 4%) in the CREON Group in Chronic Pancreatitis or Pancreatectomy (Study 2)

MedDRA Primary System Organ Class Preferred Term	CREON Capsules n = 25 (%)	Placebo n = 29 (%)
Gastrointestinal Disorders		
Abdominal Pain	1 (4)	1 (3)
Abnormal Feces	1 (4)	0
Flatulence	1 (4)	0
Frequent Bowel Movements	1 (4)	0
Infections and Infestations		
Nasopharyngitis	1 (4)	0
Metabolism and Nutritional Disorders		
Diabetes Mellitus Inadequate Control	1 (4)	0
Hyperglycemia	1 (4)	2 (7)
Hypoglycemia	1 (4)	1 (3)

6.2 Postmarketing Experience

Postmarketing data from this formulation of CREON has been available since 2009. The following adverse events have been reported with this formulation of CREON in spontaneous postmarketing reports: 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.

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 events included fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-

existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives, and pruritus. In general, these products have a well defined and favorable risk-benefit profile in exocrine pancreatic insufficiency.

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.

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. 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. Patients should notify their healthcare professional if they are pregnant or are thinking of becoming pregnant during treatment with CREON.

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 efficacy of CREON were assessed in a single, randomized, double-blind, placebo-controlled, crossover study of 32 patients with exocrine pancreatic insufficiency due to cystic fibrosis, including 12 patients between 12 and 18 years of age. The safety and efficacy in 12 to 18 year old patients in this study were similar to adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

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)]*.

10 OVERDOSAGE

There have been no reports of overdose in clinical trials with CREON, or in clinical trials or postmarketing surveillance with other pancreatic enzyme products. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Dosage and Administration (2.1) 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. The imprinting ink on the capsule contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.

6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase 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 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 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 expected to release most of the enzymes in vivo at a pH greater than 5.5. 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.

14 CLINICAL STUDIES

The short-term safety and efficacy of CREON were evaluated in two studies conducted in 86 patients with exocrine pancreatic insufficiency (EPI). Study 1 was conducted in 32 patients with EPI due to cystic fibrosis (CF); Study 2 was conducted in 54 patients with EPI due to chronic pancreatitis or pancreatectomy.

14.1 Cystic Fibrosis

Study 1 was a randomized, double-blind, placebo-controlled, crossover study in 32 patients, ages 12 to 43 years, with exocrine pancreatic insufficiency due to cystic fibrosis. The final analysis population was limited to 29 patients; 3 patients were excluded due to protocol deviations. 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 100 grams of fat per day) during the treatment periods.

The primary efficacy endpoint was the mean difference in the coefficient of fat absorption (CFA) between CREON and placebo treatment. The 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.

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 $p<0.001$.

Subgroup analyses of the CFA results 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.

14.2 Chronic Pancreatitis or Pancreatectomy

Study 2 was a randomized, double-blind, placebo-controlled, parallel group study of 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 primary efficacy endpoint was the mean change in CFA from the run-in period to the end of the double-blind 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 (Table 3).

Table 3: Percent Change in CFA in Study 2 (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

The mean percent change in CFA from the run-in period to the end of the double-blind period was 32% for CREON and 9% for placebo (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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16 HOW SUPPLIED/STORAGE AND HANDLING

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.

Keep out of reach of children.
DO NOT CRUSH CREON delayed-release capsules or the capsule contents.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

CREON is available in capsule strengths of:

- 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase
- 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase
- 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase

Healthcare professionals should inform patients of the following important information about CREON.

17.1 Dosing and Administration

- Instruct patients and caregivers that CREON should only be taken as directed by their healthcare professional *[see Dosage and Administration (2)]*.
- Instruct patients and caregivers that CREON should always be taken with food *[see Dosage and Administration (2)]*.
- Instruct patients who are unable to swallow intact capsules to sprinkle the contents of CREON on a small amount of acidic soft food, such as applesauce, at room temperature. Instruct these patients to swallow the CREON-soft food mixture immediately without crushing or chewing, and follow with water or juice to ensure complete ingestion and to avoid irritation of the oral mucosa *[see Dosage and Administration (2)]*.
- Tell patients that CREON or their contents should not be crushed or chewed as doing so could cause early release of enzymes and/or loss of enzymatic activity *[see Dosage and Administration (2)]*.
- 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)]*.

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)]*.

Manufactured by:
Abbott Products GmbH
Hannover, Germany

Marketed By:
Abbott Laboratories
North Chicago, IL 60064, U.S.A.

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MEDICATION GUIDE

CREON® (krē ′ŏn)
(pancrelipase)
Delayed-Release Capsules

Read this Medication Guide before you or your child start taking CREON and each time you or your child get a prescription refilled. There may be new information. This information does not take the place of talking with your healthcare professional about your medical condition or your treatment.

What is the most important information I should know about CREON?

- CREON may increase your chance of having a rare bowel disorder called fibrosing colonopathy. This condition is serious and may require surgery. The risk of having this condition may be reduced by following the dosing instructions that your healthcare professional gave you. Call your healthcare professional right away if you have any unusual or severe stomach area (abdominal) pain.
- **Take CREON exactly as prescribed. Do not take more or less CREON than directed by your healthcare professional.**

What is CREON?

CREON is a prescription pancreatic enzyme medicine used to improve food digestion in people who cannot digest food properly because they have exocrine pancreatic insufficiency. CREON contains a mixture of digestive enzymes (including lipases, proteases, and amylases) from pig pancreas.

CREON is safe and effective in children.

What should I tell my healthcare professional before taking CREON?

Tell your healthcare professional if you:

- are allergic to pork (pig) products.
- have a history of intestinal blockage or a condition called fibrosing colonopathy.
- have gout, kidney disease, or a condition called high blood uric acid (hyperuricemia).
- have trouble swallowing capsules.
- are pregnant or planning to become pregnant. It is not known if CREON will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if CREON passes into your breast milk. **Tell your healthcare professional about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and dietary or herbal supplements.

Know the medicines you take. Keep a list of them and show it to your healthcare professional and pharmacist when you get a new medicine.

How should I take CREON?

- **Take CREON exactly as instructed by your healthcare professional.**

Infants (up to 12 months)

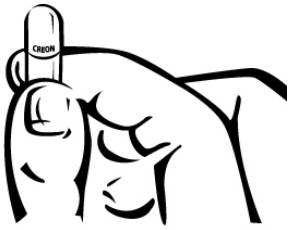
Contents of the capsule may be put directly in the infant's mouth or in a small amount of applesauce and administered (or given) just prior to feeding the infant breast milk or formula. Do not mix CREON capsule contents directly into formula or breast milk prior to administration. Care should be taken to ensure that the entire administered dose is swallowed and not retained in the mouth, to avoid irritation of the mouth.

Children and Adults

- Always take CREON during a meal or a snack and follow it with sufficient fluid.
- If you forget to take CREON, call your healthcare professional or wait until your next meal and take your usual number of capsules. **Do not make up for missed doses.** Take your next dose at the usual time.
- If you or your child takes more CREON than directed, call your healthcare professional right away.
- Swallow CREON whole. Do not crush or chew the contents of the capsules.

If you have trouble swallowing capsules, you can add the contents of an open capsule directly onto your food. To do so, carefully open the capsules and sprinkle the contents on a small amount of applesauce at room temperature as described below. Swallow the soft food right away without chewing and follow with water or juice.

A. Hold the capsule upright so that you can read the word CREON on the capsule.



B. Carefully twist off the top portion of the capsule over the food you plan to eat.

C. Sprinkle the contents of the capsule onto the soft food. Do not crush the contents of the capsules.

D. Swallow the CREON-soft food right away without chewing and follow with water or juice to make sure the contents of the capsules are swallowed completely.

What are the possible side effects of CREON?

CREON may cause serious side effects, including:

- CREON may increase your chance of having a rare bowel disorder called fibrosing colonopathy. See "What is the most important information I should know about CREON?"
- increase in blood uric acid levels, for example, worsening of gout, or painful, swollen joints. Call your healthcare professional right away if you have any of these symptoms.
- allergic reactions. For example, symptoms of an allergic reaction include: trouble with breathing, skin rashes, or swollen lips. Call your healthcare professional right away if you have any of these symptoms.

The most common side effects include:

- gassiness (flatulence)
- stomach area (abdominal) pain
- headache
- dizziness

Tell your healthcare professional if you have any side effect that bothers you or that does not go away.

These are not all the side effects of CREON. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch. You may also report side effects to Solvay Pharmaceuticals, Inc. at 1-800-241-1643.

How should I store CREON?

- Store CREON at room temperature (up to 25°C or 77°F) for up to 12 weeks after the bottle is opened.
- If you store CREON at temperatures greater than room temperature (up to 40°C or 104°F), throw away after 30 days.
- Store CREON in the container you were given by the pharmacy.
- Keep the bottle closed tightly.
- Protect the bottle from moisture.
- **Keep CREON and all medicines out of reach of children.**

General information about the safe and effective use of CREON

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CREON for a condition for which it was not prescribed. Do not give CREON to other people to take, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about CREON. If you would like more information, talk to your healthcare professional. You can ask your healthcare professional or pharmacist for information about CREON that is written for healthcare professionals. For more information, go to www.creon-us.com or call toll-free [1-800-241-1643].

What are the ingredients in CREON?

Active Ingredient: pancrelipase

Inactive Ingredients: cetyl alcohol, dimethicone, gelatin, hypromellose phthalate, polyethylene glycol, red iron oxide, sodium lauryl sulfate, titanium dioxide, triethyl citrate, and yellow iron oxide. In addition, the 6,000 strength contains FD&C Blue No. 2 and the 12,000 strength contains black iron oxide. The imprinting ink on the capsule contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.

Additional information about pancreatic enzymes

CREON and other pancreatic enzyme products are made from pancreatic organs of pigs used for food. There is a theoretical risk of contracting a viral infection from pig-derived medicines, but no human illness has been reported.

The risk of fibrosing colonopathy, increased blood uric acid levels, and the theoretical risk of viral transmission is present with all pancreatic enzyme products including CREON.

You should report any change in condition or illness to your healthcare professional.

Manufactured for Solvay Pharmaceuticals, Inc., Marietta, GA 30062, U.S.A.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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