

**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 (2.2) 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**

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, give 2,000 to 4,000 lipase units per 120 mL of formula or 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**

- Capsules: 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase (3)
- Capsules: 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase (3)
- 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: July 2010

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3 **FULL PRESCRIBING INFORMATION**

4 **1 INDICATIONS AND USAGE**

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

7 **2 DOSAGE AND ADMINISTRATION**

8 CREON is not interchangeable with other pancrelipase products.

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

13 **2.1 Administration**

14 Infants (up to 12 months)

15 CREON should be administered to infants immediately prior to each feeding, using a dosage of 2,000 to  
16 4,000 lipase units per 120 mL of formula or prior to breast-feeding. Contents of the capsule may be administered  
17 directly to the mouth or with a small amount of applesauce. Administration should be followed by breast milk or  
18 formula. Contents of the capsule should not be mixed directly into formula or breast milk as this may diminish  
19 efficacy. Care should be taken to ensure that CREON is not crushed or chewed or retained in the mouth, to avoid  
20 irritation of the oral mucosa.

21 Children and Adults

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

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

29 **2.2 Dosage**

30 Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic  
31 Fibrosis Foundation Consensus Conferences.<sup>1,2,3</sup> CREON should be administered in a manner consistent with the  
32 recommendations of the Conferences provided in the following paragraphs. Patients may be dosed on a fat  
33 ingestion-based or actual body weight-based dosing scheme.

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

36 Infants (up to 12 months)

37 Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Do not mix  
38 CREON capsule contents directly into formula or breast milk prior to administration [*see Dosage and*  
39 *Administration (2.1)*].

40 Children Older than 12 Months and Younger than 4 Years

41 Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age  
42 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  
43 units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

44 Children 4 Years and Older and Adults

45 Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age  
46 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  
47 units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

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

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

#### 52 Adults with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis or Pancreatectomy

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

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

#### 60 Limitations on Dosing

61 Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation  
62 Consensus Conferences Guidelines.<sup>1, 2, 3</sup> If symptoms and signs of steatorrhea persist, the dosage may be increased  
63 by the healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great  
64 inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may  
65 require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal,  
66 further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than  
67 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be  
68 effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses  
69 greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of  
70 fibrosing colonopathy, in children less than 12 years of age [see *Warnings and Precautions (5.1)*]. Patients currently  
71 receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either  
72 immediately decreased or titrated downward to a lower range.

### 73 **3 DOSAGE FORMS AND STRENGTHS**

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

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

- 77 ● 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase capsules have an  
78 orange opaque cap with imprint “CREON 1206” and a blue opaque body.
- 79 ● 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase capsules have a  
80 brown opaque cap with imprint “CREON 1212” and a colorless transparent body.
- 81 ● 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase capsules have  
82 an orange opaque cap with imprint “CREON 1224” and a colorless transparent body.  
83

### 84 **4 CONTRAINDICATIONS**

85 None.

### 86 **5 WARNINGS AND PRECAUTIONS**

#### 87 **5.1 Fibrosing Colonopathy**

88 Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products.<sup>5, 6</sup>  
89 Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic  
90 enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic  
91 fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme  
92 products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in  
93 children less than 12 years of age.<sup>1</sup> Patients with fibrosing colonopathy should be closely monitored because some  
94 patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing

95 colonopathy occurs.<sup>1</sup> It is generally recommended, unless clinically indicated, that enzyme doses should be less than  
96 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  
97 than 4,000 lipase units/g fat ingested per day [see *Dosage and Administration (2.1)*].

98 Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of  
99 body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat  
100 measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than  
101 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or  
102 titrated downward to a lower range.

## 103 **5.2 Potential for Irritation to Oral Mucosa**

104 Care should be taken to ensure that no drug is retained in the mouth. CREON should not be crushed or  
105 chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating  
106 resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity [see *Dosage and*  
107 *Administration (2.2) and Patient Counseling Information (17.1)*]. For patients who are unable to swallow intact  
108 capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a  
109 pH of 4.5 or less, such as applesauce, at room temperature. The CREON-soft food mixture should be swallowed  
110 immediately and followed with water or juice to ensure complete ingestion.

## 111 **5.3 Potential for Risk of Hyperuricemia**

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

## 114 **5.4 Potential Viral Exposure from the Product Source**

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

## 121 **5.5 Allergic Reactions**

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

## 127 **6 ADVERSE REACTIONS**

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

### 131 **6.1 Clinical Trials Experience**

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

135 The short-term safety of CREON was assessed in clinical trials conducted in 103 patients with exocrine  
136 pancreatic insufficiency (EPI): 49 patients with EPI due to cystic fibrosis (CF) and 25 patients with EPI due to  
137 chronic pancreatitis or pancreatectomy were treated with CREON.

#### 138 Cystic Fibrosis

139 Studies 1 and 2 were randomized, double-blind, placebo-controlled, crossover studies of 49 patients, ages 7  
140 to 43 years, with EPI due to CF. Study 1 included 32 patients ages 12 to 43 years and Study 2 included 17 patients  
141 ages 7 to 11 years. In these studies, patients were randomized to receive CREON at a dose of 4,000 lipase units/g fat

142 ingested per day or matching placebo for 5 to 6 days of treatment, followed by crossover to the alternate treatment  
143 for an additional 5 to 6 days. The mean exposure to CREON during these studies was 5 days.

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

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

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

154 **Table 1: Adverse Reactions Occurring in at Least 2 Patients (greater than or equal to 4%) in Cystic Fibrosis**  
155 **(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

156 Chronic Pancreatitis or Pancreatectomy

157 Study 3 was a randomized, double-blind, placebo-controlled, parallel group study of 54 adult patients, ages  
158 32 to 75 years, with EPI due to chronic pancreatitis or pancreatectomy. Patients received single-blind placebo  
159 treatment during a 5-day run-in period followed by an intervening period of up to 16 days of investigator-directed  
160 treatment with no restrictions on pancreatic enzyme replacement therapy. Patients were then randomized to receive  
161 CREON or matching placebo for 7 days. The CREON dose was 72,000 lipase units per main meal (3 main meals)  
162 and 36,000 lipase units per snack (2 snacks). The mean exposure to CREON during this study was 6.8 days in the 25  
163 patients that received CREON.

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

166 Table 2 enumerates adverse reactions that occurred in at least 1 patient (greater than or equal to 4%) treated  
167 with CREON at a higher rate than with placebo in Study 3.

168 **Table 2: Adverse Reactions in at least 1 Patient (greater than or equal to 4%) in Chronic Pancreatitis or**  
169 **Pancreatectomy (Study 3)**

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

170 **6.2 Postmarketing Experience**

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

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

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

## 184 **7 DRUG INTERACTIONS**

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

## 186 **8 USE IN SPECIFIC POPULATIONS**

### 187 **8.1 Pregnancy**

188 Teratogenic effects

189 Pregnancy Category C: Animal reproduction studies have not been conducted with pancrelipase. It is also not  
190 known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect  
191 reproduction capacity. CREON should be given to a pregnant woman only if clearly needed. The risk and benefit of  
192 pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant  
193 woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal  
194 maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with  
195 adverse pregnancy outcomes.

### 196 **8.3 Nursing Mothers**

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

### 201 **8.4 Pediatric Use**

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

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

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

## 214 **10 OVERDOSAGE**

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

220 **11 DESCRIPTION**

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

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

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

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

229 Other active ingredients include protease and amylase.

230 CREON contains the following inactive ingredients: cetyl alcohol, dimethicone, hypromellose phthalate,  
231 polyethylene glycol, and triethyl citrate. The imprinting ink on the capsule contains dimethicone, 2-ethoxyethanol,  
232 shellac, soya lecithin, and titanium dioxide.

233 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase capsules have a  
234 Swedish-orange opaque cap with imprint “CREON 1206” and a blue opaque body. The shells contain FD&C Blue  
235 No. 2, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

236 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase capsules have a  
237 brown opaque cap with imprint “CREON 1212” and a colorless transparent body. The shells contain black iron  
238 oxide, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

239 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase capsules have a  
240 Swedish-orange opaque cap with imprint “CREON 1224” and a colorless transparent body. The shells contain  
241 gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

242 **12 CLINICAL PHARMACOLOGY**

243 **12.1 Mechanism of Action**

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

248 **12.3 Pharmacokinetics**

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

252 **13 NONCLINICAL TOXICOLOGY**

253 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

255 **14 CLINICAL STUDIES**

256 The short-term safety and efficacy of CREON were evaluated in three studies conducted in 103 patients with  
257 exocrine pancreatic insufficiency (EPI). Studies 1 and 2 were conducted in 49 patients with EPI due to cystic  
258 fibrosis (CF); Study 3 was conducted in 54 patients with EPI due to chronic pancreatitis or pancreatectomy.

259 **14.1 Cystic Fibrosis**

260 Studies 1 and 2 were randomized, double-blind, placebo-controlled, crossover studies in 49 patients, ages 7 to  
261 43 years, with exocrine pancreatic insufficiency due to cystic fibrosis. Study 1 included patients aged 12 to 43 years  
262 (n = 32). The final analysis population was limited to 29 patients; 3 patients were excluded due to protocol  
263 deviations. Study 2 included patients aged 7 to 11 years (n = 17). The final analysis population was limited to 16  
264 patients; 1 patient withdrew consent prior to stool collection during treatment with CREON. In each study, patients

265 were randomized to receive CREON at a dose of 4,000 lipase units/g fat ingested per day or matching placebo for 5  
 266 to 6 days of treatment, followed by crossover to the alternate treatment for an additional 5 to 6 days. All patients  
 267 consumed a high-fat diet (greater than or equal to 90 grams of fat per day, 40% of daily calories derived from fat)  
 268 during the treatment periods.

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

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

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

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

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

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

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

289 **14.2 Chronic Pancreatitis or Pancreatectomy**

290 Study 3 was a randomized, double-blind, placebo-controlled, parallel group study of 54 adult patients, ages  
 291 32 to 75 years, with EPI due to chronic pancreatitis or pancreatectomy. The final analysis population was limited to  
 292 52 patients; 2 patients were excluded due to protocol violations. Ten patients had a history of pancreatectomy (7  
 293 were treated with CREON). In this study, patients received placebo for 5 days (run-in period), followed by  
 294 pancreatic enzyme replacement therapy as directed by the investigator for 16 days; this was followed by  
 295 randomization to CREON or matching placebo for 7 days of treatment (double-blind period). Only patients with  
 296 CFA less than 80% in the run-in period were randomized to the double-blind period. The dose of CREON during the  
 297 double-blind period was 72,000 lipase units per main meal (3 main meals) and 36,000 lipase units per snack (2  
 298 snacks). All patients consumed a high-fat diet (greater than or equal to 100 grams of fat per day) during the  
 299 treatment period.

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

303 **Table 3: Change in CFA in Study 3 (Run-in Period to End of Double-Blind Period)**

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

\* $p < 0.0001$

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

## 310 **15 REFERENCES**

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## 324 **16 HOW SUPPLIED/STORAGE AND HANDLING**

### 325 CREON (pancrelipase) Delayed-Release Capsules

326 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase

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

- 330 • 100 capsules (NDC 0032-1206-01)
- 331 • 250 capsules (NDC 0032-1206-07)

### 332 CREON (pancrelipase) Delayed-Release Capsules

333 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase

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

- 337 • 100 capsules (NDC 0032-1212-01)
- 338 • 250 capsules (NDC 0032-1212-07)

### 339 CREON (pancrelipase) Delayed-Release Capsules

340 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase

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

- 344 • 100 capsules (NDC 0032-1224-01)
- 345 • 250 capsules (NDC 0032-1224-07)

### 346 Storage and Handling

347 CREON must be stored at room temperature up to 25°C (77°F) and protected from moisture. Temperature  
348 excursions are permitted between 25°C to 40°C (77°F and 104°F) for up to 30 days. Product should be discarded if

349 exposed to higher temperature and moisture conditions higher than 70%. After opening, keep bottle tightly closed  
350 between uses to protect from moisture.

351

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

## 353 **17 PATIENT COUNSELING INFORMATION**

354 [See Medication Guide]

### 355 **17.1 Dosing and Administration**

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

### 367 **17.2 Fibrosing Colonopathy**

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

### 371 **17.3 Allergic Reactions**

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

### 374 **17.4 Pregnancy and Breast Feeding**

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

379

380 Manufactured by:  
381 Abbott Products GmbH  
382 Hannover, Germany

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

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