

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) Capsules, Delayed Release for Oral Use
Initial U.S. Approval: _____

INDICATIONS AND USAGE

CREON Capsules is a pancrelipase which is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

DOSAGE AND ADMINISTRATION

Dosage (2.1)

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.
- 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.

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.

Limitations on Dosing

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

Administration (2.2)

CREON should be swallowed whole. For infants or patients unable to swallow intact capsules, the contents may be administered without crushing or chewing, followed by fluid to ensure complete ingestion.

DOSAGE FORMS AND STRENGTHS

- 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)
- 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)
- 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.

WARNINGS AND PRECAUTIONS

- Fibrosing colonopathy, a rare, serious adverse reaction has been described in association with high-dose use of pancreatic enzyme replacement in the treatment of cystic fibrosis patients. Caution should be exercised 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)
- Care should be taken to ensure that CREON is not chewed or retained in the mouth to avoid irritation of oral mucosa. (5.2)
- Caution should be exercised 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)
- Caution should be exercised 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 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)
- There is no postmarketing experience. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Solvay Pharmaceuticals, Inc. at 1-800-241-1643 or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

DRUG INTERACTIONS

None known. (7)

USE IN SPECIFIC POPULATIONS

Pediatric Patients

- The safety and effectiveness of CREON have been demonstrated in pediatric patients 12 years and older. (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 FDA-approved Medication Guide

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4
5 **FULL PRESCRIBING INFORMATION**

6 **1 INDICATIONS AND USAGE**

7 CREON[®] (pancrelipase) Delayed-Release Capsules is indicated for the treatment of exocrine pancreatic
8 insufficiency due to cystic fibrosis or other conditions.

9 **2 DOSAGE AND ADMINISTRATION**

10 **2.1 Dosage**

11 CREON is not interchangeable with any other pancrelipase product.

12 CREON is orally administered. Therapy should be initiated at the lowest recommended dose and gradually
13 increased. The dosage of CREON should be individualized based on clinical symptoms, the degree of steatorrhea
14 present, and the fat content of the diet (see Limitations on Dosing below).

15 Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic
16 Fibrosis Foundation Consensus Conferences.^{1,2,3} CREON should be administered in a manner consistent with the
17 recommendations of the Conferences provided in the following paragraphs. Patients may be dosed on a fat
18 ingestion-based or actual body weight-based dosing scheme.

19 **Infants (up to 12 months)**

20 Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Do not mix
21 CREON capsule contents directly into formula or breast milk prior to administration [*see Dosage and*
22 *Administration (2.2)*].

23 **Children Older than 12 Months and Younger than 4 Years**

24 Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4
25 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
26 of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

27 **Children 4 Years and Older and Adults**

28 Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age
29 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
30 units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

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

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

35 **Limitations on Dosing**

36 Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation
37 Consensus Conferences Guidelines.^{1,2,3} If symptoms and signs of steatorrhea persist, the dosage may be increased
38 by the healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great
39 inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may
40 require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal,
41 further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than
42 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be
43 effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses
44 greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of
45 fibrosing colonopathy, in children less than 12 years of age [*see Warnings and Precautions (5.1)*]. Patients currently
46 receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either
47 immediately decreased or titrated downward to a lower range.

48 **2.2 Administration**

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

50 **Infants (up to 12 months)**

51 CREON should be administered to infants immediately prior to each feeding, using a dosage of 2,000 to
52 4,000 lipase units per 120 mL of formula or per breast-feeding. Contents of the capsule may be administered directly
53 to the mouth or with a small amount of applesauce. Administration should be followed by breast milk or formula.
54 Contents of the capsule **should not** be mixed directly into formula or breast milk as this may diminish efficacy. Care
55 should be taken to ensure that CREON is not crushed or chewed or retained in the mouth, to avoid irritation of the
56 oral mucosa.

57 **Children and Adults**

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

60 For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the
61 contents added to a small amount of acidic soft food with a pH of 4 or less, such as applesauce, at room temperature.
62 The CREON-soft food mixture should be swallowed immediately without crushing or chewing, and followed with
63 water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

64 **3 DOSAGE FORMS AND STRENGTHS**

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

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

- 68
- 69 ● 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase capsules have an
70 orange opaque cap with imprint “CREON 1206” and a blue opaque body.
- 71 ● 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase capsules have a
72 brown opaque cap with imprint “CREON 1212” and a colorless transparent body.
- 73 ● 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase capsules have
74 an orange opaque cap with imprint “CREON 1224” and a colorless transparent body.

75 **4 CONTRAINDICATIONS**

76 None.

77 **5 WARNINGS AND PRECAUTIONS**

78 **5.1 Fibrosing Colonopathy**

79 Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products.^{4,5}
80 Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic
81 enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic
82 fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme
83 products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in
84 children less than 12 years of age.¹ Patients with fibrosing colonopathy should be closely monitored because some
85 patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing
86 colonopathy occurs.¹ It is generally recommended, unless clinically indicated, that enzyme doses should be less than
87 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
88 than 4,000 lipase units/g fat ingested per day [see *Dosage and Administration (2.1)*].

89 Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of
90 body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat
91 measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than
92 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or
93 titrated downward to a lower range.

94 **5.2 Potential for Irritation to Oral Mucosa**

95 Care should be taken to ensure that no drug is retained in the mouth. CREON should not be crushed or
96 chewed or mixed in foods having a pH greater than 4. These actions can disrupt the protective enteric coating
97 resulting in early release of enzymes, irritation of oral mucosa, and/or loss or enzyme activity [see *Dosage and*
98 *Administration (2.2) and Patient Counseling Information (17.4)*]. For patients who are unable to swallow intact
99 capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a

100 pH of 4 or less, such as applesauce, at room temperature. The CREON-soft food mixture should be swallowed
101 immediately and followed with water or juice to ensure complete ingestion.

102 **5.3 Potential for Risk of Hyperuricemia**

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

105 **5.4 Potential Viral Exposure from the Product Source**

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

112 **5.5 Allergic Reactions**

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

118 **6 ADVERSE REACTIONS**

119 The most serious adverse reactions reported with different pancreatic enzyme products of the same active
120 ingredient (pancrelipase) include fibrosing colonopathy [*see Warnings and Precautions (5.1)*], hyperuricemia [*see*
121 *Warnings and Precautions (5.3)*] and allergic reactions [*see Warnings and Precautions (5.5)*].

122 **6.1 Adverse Reactions in Clinical Trials**

123 The short-term safety of CREON was assessed in a single, randomized, double-blind, placebo-controlled,
124 crossover study of 32 patients, ages 12 to 43 years, with exocrine pancreatic insufficiency due to cystic fibrosis. In
125 this study, patients were randomized to receive CREON at a dose of 4,000 lipase units/g fat ingested per day or
126 matching placebo for 5 to 6 days of treatment, followed by crossover to the alternate treatment for an additional 5 to
127 6 days. The mean exposure to CREON during this study was 5 days.

128 One patient experienced duodenitis and gastritis of moderate severity reported as a serious adverse event 16
129 days after completing treatment with CREON.

130 Transient neutropenia without clinical sequelae was observed as an abnormal laboratory finding in one
131 patient receiving CREON and a macrolide antibiotic.

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

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

138 Table 1 enumerates treatment-emergent adverse events that occurred in at least 2 patients (greater than or
139 equal to 6%) treated with either CREON or placebo in the clinical study. Adverse events were classified by Medical
140 Dictionary for Regulatory Activities (MedDRA) terminology.

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

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

143 **6.2 Postmarketing Experience**

144 There is no postmarketing experience with this formulation of CREON.

145 Delayed- and immediate-release pancreatic enzyme products with different formulations of the same active
 146 ingredient (pancrelipase) have been used for the treatment of patients with exocrine pancreatic insufficiency due to
 147 cystic fibrosis and other conditions, such as chronic pancreatitis. The long-term safety profile of these products has
 148 been described in the medical literature. The most serious adverse events included fibrosing colonopathy, distal
 149 intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions
 150 including anaphylaxis, asthma, hives, and pruritus. The most commonly reported adverse events were
 151 gastrointestinal disorders, including abdominal pain, diarrhea, flatulence, constipation and nausea, and skin disorders
 152 including pruritus, urticaria and rash. In general, these products have a well defined and favorable risk-benefit
 153 profile in exocrine pancreatic insufficiency.

154 **7 DRUG INTERACTIONS**

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

156 **8 USE IN SPECIFIC POPULATIONS**

157 **8.1 Pregnancy**

158 Teratogenic effects

159 Pregnancy Category C: Animal reproduction studies have not been conducted with pancrelipase. It is also not
 160 known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect
 161 reproduction capacity. The risk and benefit of pancrelipase should be considered in the context of the need to
 162 provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric
 163 intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight
 164 gain and malnutrition can be associated with adverse pregnancy outcomes. Patients should notify their healthcare
 165 professional if they are pregnant or are thinking of becoming pregnant during treatment with CREON.

166 **8.3 Nursing Mothers**

167 It is not known if pancrelipase is excreted in human milk. Patients should notify their healthcare professional
 168 if they are breast-feeding.

169 **8.4 Pediatric Use**

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

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

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

181 **10 OVERDOSAGE**

182 There have been no reports of overdose in clinical trials with CREON, or in clinical trials or postmarketing
183 surveillance with other pancreatic enzyme products. Chronic high doses of pancreatic enzyme products have been
184 associated with fibrosing colonopathy [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.1)*].
185 High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should
186 be used with caution in patients with a history of hyperuricemia, gout, or renal impairment [see *Warnings and*
187 *Precautions (5.3)*].

188 **11 DESCRIPTION**

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

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

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

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

197 Other active ingredients include protease and amylase.

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

201 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase capsules have a
202 Swedish-orange opaque cap with imprint “CREON 1206” and a blue opaque body. The shells contain FD&C Blue
203 No. 2, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

204 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase capsules have a
205 brown opaque cap with imprint “CREON 1212” and a colorless transparent body. The shells contain black iron
206 oxide, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

207 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase capsules have a
208 Swedish-orange opaque cap with imprint “CREON 1224” and a colorless transparent body. The shells contain
209 gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

210 **12 CLINICAL PHARMACOLOGY**

211 **12.1 Mechanism of Action**

212 The pancreatic enzymes in CREON are enteric-coated to resist destruction or inactivation in gastric acid, and
213 to release most of the enzymes *in vivo* in the duodenum at a pH greater than 5.5. In the duodenum and proximal
214 small intestine, the enzymes catalyze the hydrolysis of fats to monoglycerol, glycerol and fatty acids, protein into
215 peptides and amino acids, and starch into dextrans and short chain sugars, thereby acting as a replacement for
216 digestive enzymes physiologically secreted by the pancreas.

217 Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount, and are not
218 systemically active.

219 **13 NONCLINICAL TOXICOLOGY**

220 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

222 **14 CLINICAL STUDIES**

223 The short-term efficacy and safety of CREON were evaluated in one double-blind, placebo-controlled,
224 crossover study in 32 patients, ages 12 to 43 years, with exocrine pancreatic insufficiency due to cystic fibrosis. The
225 final analysis population was limited to 29 patients; 3 patients were excluded due to protocol deviations. Patients

226 were randomized to receive CREON at a dose of 4,000 lipase units/g fat ingested per day or matching placebo for 5
227 to 6 days of treatment, followed by crossover to the alternate treatment for an additional 5 to 6 days. All patients
228 consumed a high-fat diet (greater than or equal to 100 grams of fat per day) during the treatment periods. The
229 primary efficacy endpoint was the mean difference in the coefficient of fat absorption (CFA) between CREON and
230 placebo treatment. The CFA was determined by a 72-hour stool collection during both treatments, when both fat
231 excretion and fat ingestion were measured. Each patient's CFA during placebo treatment was used as their
232 no-treatment CFA value.

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

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

239 **15 REFERENCES**

240 ¹ Borowitz DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in
241 the context of fibrosing colonopathy. *Journal of Pediatrics*. 1995; 127: 681-684.

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

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

247 ⁴ Smyth RL, Ashby D, O'Hea U, et al. Fibrosing colonopathy in cystic fibrosis: results of a case-control study.
248 *Lancet*. 1995; 346: 1247-1251.

249 ⁵ FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing
250 colonopathy in children with cystic fibrosis. *New England Journal of Medicine*. 1997; 336: 1283-1289.

251 **16 HOW SUPPLIED/STORAGE AND HANDLING**

252 **CREON (pancrelipase) Delayed-Release Capsules**

253 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase

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

- 257 • 100 capsules (NDC 0032-1206-01)
- 258 • 250 capsules (NDC 0032-1206-07)

259 **CREON (pancrelipase) Delayed-Release Capsules**

260 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase

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

- 264 • 100 capsules (NDC 0032-1212-01)
- 265 • 250 capsules (NDC 0032-1212-07)

266 **CREON (pancrelipase) Delayed-Release Capsules**

267 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase

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

- 271 • 100 capsules (NDC 0032-1224-01)
- 272 • 250 capsules (NDC 0032-1224-07)

273 **Storage**

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

276 exposed to higher temperature and moisture conditions higher than 70%. AFTER OPENING, KEEP BOTTLE
277 TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE.

278
279 Keep out of reach of children.

280

For further information, please call Solvay Pharmaceuticals, Inc.'s
Medical Information Department toll-free at 1-800-241-1643.



281 **17 PATIENT COUNSELING INFORMATION**

282 *See Medication Guide (17.4).*

283 CREON is available in capsule strengths of:

- 284 • 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP units of amylase
- 285 • 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP units of amylase
- 286 • 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP units of amylase

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

288 **17.1 Dosing and Administration**

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

298 **17.2 Fibrosing Colonopathy**

299 Advise patients and caregivers to follow dosing instructions carefully, as doses of pancreatic enzyme
300 products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures in
301 children below the age of 12 years.

302 **17.3 Allergic Reactions**

303 Advise patients and caregivers to contact their healthcare professional immediately if allergic reactions to
304 CREON develop.

305 **Manufactured by:**

306 Solvay Pharmaceuticals GmbH
307 Hannover, Germany

308 **Marketed By:**

309 Solvay Pharmaceuticals, Inc.
310 Marietta, GA 30062

311

312 1055216 1E Rev Apr 2009

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314 **17.4 FDA-Approved Medication Guide**

315

316

MEDICATION GUIDE

317

CREON® (krē 'ōn)

318

(pancrelipase)

319

Delayed-Release Capsules

320

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

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

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

331 **What is CREON?**

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

335 CREON is safe and effective in children.

336 **What should I tell my healthcare professional before taking CREON?**

337 Tell your healthcare professional if you:

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

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

348 **How should I take CREON?**

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

350 **Infants (up to 12 months)**

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

355 **Children and Adults**

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

360 ● Swallow CREON whole. Do not crush or chew the contents of the capsules.

361 If you have trouble swallowing capsules, you can add the contents of an open capsule directly onto your food.
362 To do so, carefully open the capsules and sprinkle the contents on a small amount of applesauce at room temperature
363 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.



364 **What are the possible side effects of CREON?**

365 **CREON may cause serious side effects, including:**

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

372 The most common side effects include:

- 373 ● gassiness (flatulence)
- 374 ● stomach area (abdominal) pain
- 375 ● headache
- 376 ● dizziness

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

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

381 **How should I store CREON?**

- 382 ● Store CREON at room temperature (up to 25°C or 77°F) for up to 12 weeks after the bottle is opened.
- 383 ● If you store CREON at temperatures greater than room temperature (up to 40°C or 104°F), throw away after
384 30 days.
- 385 ● Store CREON in the container you were given by the pharmacy.
- 386 ● Keep the bottle closed tightly.
- 387 ● Protect the bottle from moisture.

388 • **Keep CREON and all medicines out of reach of children.**

389 **General information about the safe and effective use of CREON**

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

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

397 **What are the ingredients in CREON?**

398 **Active Ingredient:** pancrelipase

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

403 **Additional information about pancreatic enzymes**

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

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

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

410

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

413 1055216 1E Rev Apr 2009

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

415 Issued April 2009

416

Appendix A

Risk Evaluation and Mitigation Strategy (REMS)

NDA 20-725

CREON (pancrelipase) Delayed-Release Capsules

Drug Class: Pancreatic Enzyme Products

Solvay Pharmaceuticals Inc.
901 Sawyer Road
Marietta, GA 30062

For further information, please call Solvay Pharmaceuticals Inc.'s Medical Information Department at 1-800-241-1643

1 Goals

To ensure that the following serious risks are communicated to patients and caregivers:

- The risk of fibrosing colonopathy which may be mitigated by properly dosing CREON;
- The theoretical risk of transmission of viral disease to patients treated with a porcine-derived pancreatic enzyme product.

2 REMS Elements

A. Medication Guide

A Medication Guide (see attachment) will be a required element of the REMS for CREON. To comply with 21 CFR 208.24, sufficient numbers of the Medication Guide will be provided to ensure that a copy can be provided with each CREON prescription. CREON container or package labels will include an instruction alerting the pharmacist to provide a Medication Guide to each patient to whom the product is dispensed, and stating how the Medication Guide is provided.

One copy of the Full Prescribing Information that includes a Medication Guide will be provided with each bottle of CREON. One additional copy of the Medication Guide will be supplied with the 12 count bottle, two additional Medication Guides will be supplied with the 100 count bottle and the 250 count bottle. The Full Prescribing Information, including the Medication Guide, will be available to download on the Internet at www.CREON-US.com.

B. Communication Plan

The REMS for CREON does not include a Communication Plan.

C. Elements to Assure Safe Use

The REMS for CREON does not include Elements to Assure Safe Use.

D. Implementation System

Because this REMS for CREON does not include Elements to Assure Safe Use, an Implementation System is not required.

3 Assessment of the REMS for CREON

A. Timetable for Submission of Assessments

The assessment interval period will close no earlier than 60 days prior to the date the respective assessment is due as noted below:

- 1st Assessment: [October 30, 2010] 18 months after NDA approval
- 2nd Assessment: [April 30, 2012] 3 years after NDA approval
- 3rd Assessment: [April 30, 2016] 7 years after NDA approval

The assessments will include an evaluation of the effectiveness of the Medication Guide in communicating the risks of CREON.

MEDICATION GUIDE

CREON® (krē 'ōn) (pancrelipase) Delayed-Release Capsules

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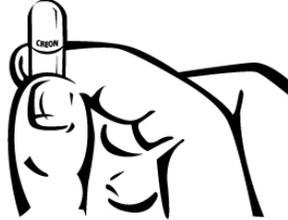
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