CREON (Pancrelipase Delayed-Release Capsules) for the Treatment of Exocrine Pancreatic Insufficiency

Robert J. Kuhn · Andres Gelrud · Anne Munck · Steven Caras

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ABSTRACT

Exocrine pancreatic insufficiency (EPI) is associated with conditions including cystic fibrosis (CF), chronic pancreatitis (CP), and pancreatic surgery (PS). The symptoms include maldigestion, malnutrition, weight loss, flatulence, and steatorrhea. Pancreatic enzyme replacement therapy (PERT) is the standard treatment for EPI; it is regulated in many countries and most recently in the USA following a US FDA mandate for all PERT manufacturers to submit new drug applications. Pancrelipase delayed-release capsules (CREON®, Abbott, Marietta, GA, USA) have been available

in Europe since 1984 and in the USA since 1987; a new formulation was the first PERT to gain approval in the USA in 2009. The efficacy and safety of CREON have been demonstrated in double-blind, randomized, placebo-controlled trials in patients with CF aged ≥ 7 years and in patients with CP or post-PS. The data consistently demonstrate significantly better fat and nitrogen absorption with CREON versus placebo, and improvements in clinical symptoms, stool frequency, and body weight. Additionally, efficacy and safety of CREON have been shown in open-label studies in young children with CF (aged 1 month to 6 years), with control of fat malabsorption and control of clinical symptoms. The most commonly reported adverse events (AEs) with PERT are gastrointestinal disorders and allergic skin reactions. In clinical studies, CREON was well tolerated with very few withdrawals due to AEs and a low frequency of AEs judged treatment related, regardless of patient age. To further support the known safety profile of PERT, all manufacturers are required to investigate risk factors for fibrosing colonopathy, a rare gastrointestinal complication of CF, and the theoretical risk of viral transmission from porcine-derived PERT products. Together, the clinical study data and wealth of clinical

Robert J. Kuhn (✉)
Division of Pharmacy, Practice and Science, University
of Kentucky, Lexington, Kentucky 40536-0596, USA.
Email: rjkuhn1@email.uky.edu

Andres Gelrud
Division of Gastroenterology, Hepatology, and
Nutrition, UPMC, Pittsburgh, Pennsylvania, USA

Anne Munck
Paediatric Gastroenterology, Nutrition and Cystic
Fibrosis Department, Hospital Robert Debre, AP-HP,
Paris, France

Steven Caras
Abbott, Marietta, Georgia, USA

experience suggest that CREON is effective and safe in patients with EPI regardless of etiology, with a very favorable risk-benefit profile.

Keywords: chronic pancreatitis; CREON®; cystic fibrosis; delayed-release; exocrine pancreatic insufficiency; pancreatin; pancreatic enzyme replacement therapy; pancrelipase

INTRODUCTION

Pancreatic enzyme replacement therapy (PERT) products are prescribed for the treatment of exocrine pancreatic insufficiency (EPI), which is often associated with cystic fibrosis (CF), chronic pancreatitis (CP), malignant ductal obstruction of the pancreas, or pancreatic surgical procedures.¹ The pancreas secretes digestive enzymes (lipase, protease, and amylase) into the duodenal lumen, where they facilitate the breakdown of macronutrients. Thus, patients with untreated EPI typically have difficulty digesting fat and suffer symptoms of both maldigestion and malnutrition, with deficiencies of essential fatty acids and fat-soluble vitamins, weight loss, cramping, flatulence, bloating, and greasy, foul-smelling, loose stools (steatorrhea). The overt clinical symptoms of EPI are mainly a consequence of fat maldigestion. However, protein and carbohydrate maldigestion also contribute to EPI-associated malnutrition, affecting nutritional status and overall health. Protein maldigestion results in excess protein in the stool (creatorrhea) and chronic protein malabsorption may result in hypoalbuminemia, which can lead to generalized edema or ascites. Symptoms of carbohydrate malabsorption include diarrhea, flatulence, and abdominal pain/distension. For patients with CF, inadequate treatment of EPI may have serious consequences for nutritional status, which has been directly correlated with lung function^{2,3} and survival.^{4,5}

By convention, PERT products are labeled according to the amount of lipase they contain; all PERT products also contain protease and amylase, but the labeled and actual amounts of these two enzymes may differ from product to product even when labeled lipase amounts are the same. Older pancreatic enzyme formulations were based on pancreatin, a substance obtained from the pancreas of the hog or ox. Current PERT formulations are based on pancrelipase, a more potent extract from the hog pancreas, which the US Pharmacopeia (USP)⁶ defines as containing not less than 24 USP units of lipase activity, 100 USP units of amylase activity, and 100 USP units of protease activity per mg. International application of these definitions is somewhat confusing, because outside the USA pancrelipase is typically referred to as “pancreatin” even though it is the same active substance with similar potency and activity.

For exogenous PERT to be effective, it is crucial that as much as possible of the dose reaches the proximal small intestine at the same time as the partially digested food (chyme). Lipase is the most sensitive of the pancreatic enzymes to the effects of both pepsin and acid, and is irreversibly inactivated at pH 4.0 or lower.⁷ Early PERT preparations consisting of tablets or encapsulated powder were not protected against such inactivation in the stomach, and perhaps only as little as 8% of ingested lipase was bioavailable in the small intestine. Therefore, it was necessary to administer orally up to five to 10 times as much lipase as was required for intraluminal digestion; bicarbonate or H₂ receptor antagonists were often administered concomitantly to attempt to reduce degradation by stomach acid. The development of enteric coatings and microsphere and microtablet formulations in the 1970s made it possible to protect pancreatic enzymes for passage through the stomach, enabling enzyme delivery to the

duodenum simultaneously with the chyme, and thus allowing enzyme release when the intestinal pH is most conducive for enzyme activity. This allowed patients with CF to shift from the previously recommended low-fat, high-protein program to a diet high in fat as well as protein, making it possible for them to meet their high energy needs. Subsequent refinements in microencapsulation technology have facilitated increases in lipase content and more efficient dosing.^{8,9}

Previous studies have suggested that PERT products vary in terms of actual enzyme content and in-vitro response to simulated gastric and duodenal conditions.^{10–12} As pancreatic enzymes are sensitive proteins and liable to inactivation, capsules were routinely overfilled to ensure that potency would not drop below label claims before the end of shelf-life.¹³ Over the past decade, the USP standard has evolved in recognition of these circumstances and actually states upper and lower limits of labeled amounts of enzymes. Currently, the US Food and Drug Administration (FDA) labeling requirements mandate that approved pancreatic enzymes in the USA have no stability overfill and hence new preparations are labeled accordingly.

PERT products are approved around the world; however, because PERT products were available before the passage of the 1938 Federal Food, Drug, and Cosmetic Act, they have historically been, in the absence of any specific concerns, marketed in the USA without any requirements for safety and efficacy testing. These prescribed products have been documented with in-vitro performance studies and in-vivo clinical efficacy data.^{12–18} Citing concerns about the significant differences in bioavailability among PERT products and consequent instances of serious under- and over-dosing, the FDA formally announced in 2004 the New Drug Application requirement for EPI drug products,¹⁹ with the stipulation that

because the drugs are “medically necessary,” manufacturers could continue to market their products without an approved application for the next 4 years, which was extended until May 2010. To date, three pancreatic enzyme preparations are on the market in the USA that have received FDA approval: CREON® (pancrelipase delayed-release capsules; Abbott, Marietta, GA, USA) in April 2009, Zenpep® ([pancrelipase] Delayed Release Capsules; Eurand Pharmaceuticals Ltd, Yardley, PA, USA) in August 2009, and Pancreaze™ ([pancrelipase] delayed-release capsules; McNeil Pharmaceuticals, Ruritan, NJ, USA) in April 2010. These products represent the first enteric-coated pancrelipase preparations approved in the USA since the introduction of crude extracts over 50 years ago to treat infants with CF, and all are of porcine origin. As new dosage forms are approved, some manufacturers have taken the opportunity to modify their formulations with regards to excipients, improved packaging, and stability to allow for a more consistent delivery of pancreatic enzymes.

CREON INDICATIONS AND PRESCRIBING INFORMATION

CREON is indicated for the treatment of EPI due to CF, CP, pancreatectomy, and other conditions in which EPI is present.²⁰ Dosages are individually titrated based on clinical symptoms and the degree of steatorrhea, and are adjusted for the amount of dietary fat consumed. For patients with CF, guidelines from the CF Consensus Conferences^{21–24} are used for initiating PERT and are summarized in Table 1. Dosing in patients with CF and CP will also be discussed in later sections. CREON capsules should be swallowed whole and not crushed or chewed. Capsules can be opened and the contents given on a spoon mixed with soft acidic food, such as applesauce, until children are able to swallow

Table 1. Cystic Fibrosis Consensus Conference dosing guidelines for pancreatic enzyme replacement therapy.²¹⁻²⁵

Infants up to 12 months	2000-4000 IU lipase/120 mL of formula or per breast feeding
Children 12 months to 4 years	1000 IU lipase/kg body weight/meal to a maximum of 2500 IU/kg body weight/meal (daily maximum of 10,000 IU/kg/day or 4000 IU/g dietary fat/day)
Children 4 years and older and adults	500 IU lipase/kg body weight/meal to a maximum of 2500 IU/kg body weight/meal (daily maximum of 10,000 IU/kg/day or 4000 IU/g dietary fat/day)

IU=international unit.

capsules whole; this mixture should be given during meals, immediately after mixing.²⁰ If capsules are opened, care should be taken to mix the contents only with foods of pH ≤ 4.5 to avoid disruption of the protective enteric coating and thus early release of enzymes and/or loss of enzyme activity before ingestion.²⁰ As CREON is an enteric-coated formulation and therefore protected against gastric acid inactivation, routine administration of a concomitant proton pump inhibitor or H₂ receptor antagonist is not required.

The active pharmaceutical ingredient of CREON is pancrelipase, a porcine pancreatic extract containing multiple enzyme classes. Each delayed-release gelatin capsule for oral administration contains enteric-coated spheres approximately 1 mm in diameter.²⁰ The following inactive ingredients are also present in the current FDA-approved formulation: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate.²⁰ The inactive ingredients differ from previous formulations in that light mineral oil has been removed from the spheres and dibutyl phthalate has been removed from the enteric coating in response to general FDA and European Union directives, respectively.

By convention, PERT preparations listed with a numerical value refer to the thousands of units of lipase per dosage form contained in the product. In the USA, USP standards are used for pancrelipase, while in Europe other standards

are used including European Pharmacopoeia (Ph. Eur.)/Fédération Internationale Pharmaceutique (FIP) units. Standardization of lipase units has occurred (1 USP=1 Ph. Eur.=1 FIP unit) but there are differences with regards to amylase and protease unit standards. As PERT is traditionally dosed based on lipase units, we can use them interchangeably and no conversion is needed.^{26,27}

Enteric-coated (delayed-release) CREON formulations have been available in Europe since 1984 and in the USA since 1987. Currently, in the USA, CREON is available in three strengths, containing 6000, 12,000, and 24,000 USP units of lipase per capsule.²⁰ In addition, protease and amylase are included in these preparations in the amounts shown in Table 2.

Other formulations of CREON (with the same active ingredient) are available outside the US (Creon 10000 Ph. Eur., Creon 25000 Ph. Eur., Creon 40000 Ph. Eur. and a special formulation

Table 2. CREON dosage forms and strengths currently available in the USA.²⁰

	USP units		
	Lipase	Protease	Amylase
CREON 6,000	6000	19,000	30,000
CREON 12,000	12,000	38,000	60,000
CREON 24,000	24,000	76,000	120,000

USP=United States Pharmacopoeia.

The 6000, 12,000, and 24,000 strengths are equivalent in lipase activity to previously available Creon 5, 10, and 20, respectively.

for children, Creon micro [5000 Ph. Eur. lipase units per dosing scoop]).

CYSTIC FIBROSIS

Overview of Exocrine Pancreatic Insufficiency in Cystic Fibrosis and Long-term Consequences

EPI is present in approximately 85% of patients with CF overall and in up to 99% of patients who are F508del homozygotes, most often from birth.^{28–30} The clinical triad of increased appetite, steatorrhea, and malnutrition is highly suggestive of CF with EPI. Nowadays, with increasing worldwide implementation of newborn screening programs,³¹ CF is usually diagnosed in very early life. Nevertheless, at initial consultation, half of all infants with CF are symptomatic for EPI and the majority present with impaired growth, low body weight, and digestive symptoms.³² In addition to malnutrition and steatorrhea, other frequent symptoms include abdominal pain, bloating, flatulence, and rectal prolapse.^{27,33} EPI can also lead to edema caused by hypoalbuminemia, deficiencies in fat-soluble vitamins, and hemolytic anemia related to vitamin E deficiency. Even in the context of symptoms, a laboratory test to define pancreatic function status or confirm fat excretion levels is recommended.^{21,27} The fecal elastase-1 test is highly sensitive (using a monoclonal rather than polyclonal antibody) and involves an enzyme-linked immunosorbent assay to determine levels of this human pancreas-specific enzyme in a small specimen of well-formed feces; thus it is simply a diagnostic tool of pancreatic function.^{34,35} Assessment of the coefficient of fat absorption (CFA) involves 72-hour stool collection, recording of dietary fat during the stool collection period, and calculation of the percentage CFA.^{36,37} This test, which is very

cumbersome for the patient, is the most valuable tool for assessing fat maldigestion in PERT-supplemented patients with poor nutritional status or inadequately controlled gastrointestinal symptoms, or in clinical trials to evaluate PERT efficacy.

It has been documented that newborn screening programs for CF confer nutritional advantages, as a result of earlier diagnosis, compared with traditional CF diagnosis based on clinical symptoms.³⁸ As better nutritional status and growth is strongly associated with improved pulmonary function and improved survival in CF,^{2–4,39} prompt nutritional support and PERT should be provided as soon as EPI is confirmed, whatever the patient's age and mode of feeding, in order to maintain normal growth status.

Current Recommendations and Practice for the Treatment of Exocrine Pancreatic Insufficiency in Cystic Fibrosis

The standard of care for EPI is based on oral PERT, regardless of etiology. The dosing guidelines for patients with CF are summarized in Table 1.^{21–25} The occurrence in the 1990s of fibrosing colonopathy (FC) in young children receiving very high daily doses of PERT^{40,41} had a major impact on PERT prescriptions, despite the rarity of this severe gastrointestinal complication. As a result, consensus guidelines for PERT published in 1995 and 2002 recommended that daily doses should not exceed the equivalent of 10,000 IU lipase/kg/day or 4000 IU lipase/g dietary fat/day.^{21–23} However, it should be noted that these dosing recommendations were based on older PERT formulations, which were overfilled in terms of lipase units.^{11–13,18} Therefore, some patients may have been receiving actual doses that exceeded the recommended upper limit. In the current era of better controlled manufacturing processes, and the US FDA

requirements for PERT labeling to state actual lipase content, these dosing recommendations and limits may need to be revisited.

Studies have shown that standard- and high-strength PERT preparations provide similar efficacy in terms of fat absorption, as summarized by Littlewood et al.;²⁷ standard-strength enzyme preparations are recommended for infants and children. Many factors may affect enzyme efficacy; dose requirements therefore remain approximate and doses should be individualized. Adequate PERT should enable the patient to eat a normal or high-fat diet without unpleasant gastrointestinal symptoms and to achieve a satisfactory nutritional and growth status.²⁷ PERT should be given with all fat- and protein-containing foods, according to the dosing guidelines, with pancreatic enzyme dosage gradually increased on a dietitian's or physician's advice if needed until symptom relief and adequate weight gain are achieved. Individualization of doses is supported by a recent report of evidence-based practice recommendations from the Cystic Fibrosis Foundation (CFF) Growth and Nutrition Subcommittee,²⁵ which concluded that there was insufficient evidence for making recommendations regarding specific PERT doses and CFA values or growth status; there was also insufficient evidence to support the efficacy of generic PERT formulations.

Efficacy of CREON in Cystic Fibrosis

The efficacy of the various formulations of CREON (with the same active ingredient) has been confirmed through extensive clinical experience and in a number of clinical studies in patients with CF.^{17,42-47} A summary of published efficacy data from six clinical studies investigating formulations that are currently available in either the USA or Europe is provided

in Table 3. A seventh study reporting use of a pre-FDA mandate US formulation (Creon 20¹⁷) has also been included as this formulation has equivalent lipase content per capsule to current CREON 24,000 USP, with similar pharmaceutical characteristics and sphere size, and therefore provides valid efficacy and safety information. Four studies had an open-label design without placebo control as they included infants and young children.⁴⁴⁻⁴⁷ The target lipase doses in these studies were selected according to the CFF and EU consensus guidelines²¹⁻²⁴ relevant to the age group under investigation. The three recent studies carried out in the USA used the new formulation of CREON that is now currently available.⁴²⁻⁴⁴

The data summarized in Table 3 provide substantial evidence for the efficacy of the different CREON formulations in significantly improving fat absorption (as measured by the CFA) versus placebo or baseline (no treatment). On-treatment efficacy appears to be consistent regardless of study design, patient age, and CREON formulation, with CREON demonstrating efficacy in improving malabsorption in preschool-age children⁴⁴⁻⁴⁶ as well as older children and adults. Improvements were also seen with CREON in secondary outcome measures such as the coefficient of nitrogen absorption (CNA), clinical symptoms, stool frequency, and body weight (Table 3). The CNA is measured in the same way as the CFA but with assessment of nitrogen as a marker for protein absorption. Comparison of data from two randomized, double-blind, placebo-controlled studies with the FDA-approved formulation of CREON indicates consistent on-treatment efficacy in patients aged 7-11 years and patients aged ≥ 12 years: mean CFA 82.8% and 88.6% and mean CNA 80.3% and 85.1%, respectively.^{42,43} Significant improvements in these parameters versus placebo were seen with CREON in both

Table 3. Summary of CREON efficacy in clinical studies enrolling patients with exocrine pancreatic insufficiency due to cystic fibrosis.

Study	n	Age group	Study design	Treatment	Mean CFA on CREON	Mean CFA on placebo/ at baseline	P-value	Other relevant outcomes
Formulations currently available in the USA (FDA-approved)								
Trapnell et al., 2009 ⁴²	32	≥12 years	Multicenter, double-blind, randomized, placebo-controlled, crossover	CREON 24,000 or placebo for 5 days each	88.6%*	49.6%*	<0.001	Mean* CNA 85.1% on CREON vs. 49.9% placebo ($P<0.001$) Mean* daily stool frequency 1.8 on CREON vs. 2.8 placebo ($P<0.001$) Abdominal pain and flatulence less severe and stool consistency less watery on CREON vs. placebo
Graff et al., 2010 ⁴³	17	7-11 years	Multicenter, randomized, double-blind, placebo-controlled, crossover	CREON 12,000 or placebo for 5 days each	82.8%*	47.4%*	<0.001	Mean* CNA 80.3% on CREON vs. 45.0% placebo ($P<0.001$) Stool frequency/day 1.9 on CREON vs. 3.4 placebo ($P<0.001$) Abdominal pain, flatulence, and stool consistency better on CREON
Graff et al., 2010 ⁴⁴	18	<7 years	Multicenter, open-label, single arm	CREON 3,000, 6,000, and 12,000 for 10-14 days after standard therapy	Spot stool fat 28.1%	Spot stool fat 27.9%†	NT	Abdominal pain, stool consistency, and flatulence similar for CREON and standard therapy Slightly more day-to-day variability in mean daily stool frequency on standard therapy vs. CREON
Formulations currently available in Europe								
Colombo et al., 2009 ⁴⁵	12	1-24 months	Multicenter, open-label, single arm	Creon for Children (Creon micro#) for 8 weeks (CFA measured after 2 weeks)	84.7%	58.0%§	0.0013§	Patients with steatorrhea decreased from 100% to 58% over 2 weeks Mean weight change +1.0 kg over 8 weeks Mean stool frequency change -0.7/day Days with normal stool +11% Days with no gastrointestinal symptoms +13%

(continued on next page)

Table 3. Summary of CREON efficacy in clinical studies enrolling patients with exocrine pancreatic insufficiency due to cystic fibrosis. (Continued)

Study	n	Age group	Study design	Treatment	Mean CFA on CREON	Mean CFA on placebo/ at baseline	P-value	Other relevant outcomes
Formulations currently available in Europe (Continued)								
Munck et al., 2009 ⁴⁶	40	6-36 months	Multicenter, open-label, randomized, crossover	Creon for Children (Creon micro [†]) and Creon 10000 for 2 weeks each	77.8% [¶] 78.7% [¶]	NA	NA	Stools formed/normal on 47.8% and 42.6% days [§] Free from abdominal pain on 91% days (both groups) Mild flatulence on 23.1% and 34.9% of days [§]
Parchell et al., 2002 ⁴⁷	59	3-17 years	Multicenter, randomized, open-label, crossover	Creon 10000 MMS for 28 days ^{**}	91.3%	NA	NA	Median stool frequency 2/day Majority of stools formed in consistency Flatulence and abdominal pain mainly absent or mild
Other formulations								
Stern et al., 2000 ¹⁷	47	7-18 years	Multicenter, randomized, double-blind, placebo-controlled	Creon 20 or placebo for 5-7 days after open-label run-in on CREON	84.1%	52.2%	<0.001	Stool frequency 8/72 h on CREON vs. 12/72 h placebo Formed stools 83% patients on CREON vs. 5% placebo
	50	18-40 years			87.2%	50.9%	<0.001	Stool frequency 7/72 h on CREON vs. 14/72 h placebo Formed stools 67% patients on CREON vs. 22% placebo

CFA=coefficient of fat absorption; CNA=coefficient of nitrogen absorption; FDA=US Food and Drug Administration; MMS=minimicrospheres; NA=not applicable; NT=not tested.

*Least squares mean reported.

[†]Value on standard therapy before CREON treatment phase.

[‡]5000 Ph. Eur. lipase units per dosing spoon.

[§]Baseline-controlled study (without treatment).

[¶]Values for Creon for Children (Creon micro) and CREON 10000, respectively.

^{**}Reference control was Creon 8000 MS (formulation no longer available).

trials and improvements in clinical symptoms were also consistent (Table 3). The outcomes in the CREON clinical trials compare favorably with normal CFA and CNA values; a study of 16 healthy individuals indicated a mean CFA value of 94% and a mean CNA value of 88%.⁴⁸

Combining individual patient data for on-treatment CFA values and changes in CFA versus placebo from the two randomized, double-blind, placebo-controlled studies with the FDA-approved formulation of CREON^{42,43} indicated no apparent differences in CFA values on-treatment according to the severity of EPI (as measured by the CFA during placebo treatment). Thus, patients with more severe EPI (lower CFA on placebo) had correspondingly larger increases in their CFA on CREON treatment, and all subjects with a placebo CFA of less than 40% had an on-treatment difference from placebo of over 30% (Figure 1). No obvious differences were observed regarding efficacy of CREON for the different age groups (Figure 1). In the Trapnell et al.⁴² study, prospectively planned subanalyses showed no differences in terms of CFA, CNA, abdominal pain, stool consistency, and flatulence between subjects aged 12–18 years and those aged >18 years.

Figure 1. On-treatment coefficient of fat absorption (CFA) in the two double-blind, placebo-controlled studies with the US Food and Drug Administration-approved formulation of CREON in patients with cystic fibrosis: difference between on-treatment and placebo CFA as a function of placebo CFA (lower placebo CFA indicates more severe exocrine pancreatic insufficiency).

Safety of CREON in Cystic Fibrosis

The long-term safety profile of PERT, such as CREON, has been described in the medical literature, with the most commonly reported adverse events being gastrointestinal disorders and allergic skin reactions (rash, urticaria).²⁰ Table 4 summarizes treatment-emergent adverse events (TEAEs) occurring in six published clinical studies of CREON that report safety data on currently available formulations.^{17,42–46}

TEAEs were generally more frequent with placebo compared with CREON, reflecting the effects of untreated EPI in these patients. The majority of patients completed treatment in these studies, and there were very few withdrawals due to TEAEs, indicating that CREON was well tolerated. As expected due to the nature of the underlying disease, gastrointestinal disorders were the most frequent class of TEAEs on both CREON and placebo. There was a low frequency of TEAEs judged to be probably or possibly treatment related in patients receiving CREON. Serious TEAEs were a severe *Pseudomonas* species lung infection and bronchial obstruction in the study by Munck et al.⁴⁶ and hospitalization for pulmonary exacerbation in the study by Stern et al.¹⁷

There were no obvious trends for TEAEs in patients with CF by age group. Safety data from studies with the new FDA-approved formulation^{42–44} are consistent with those of other formulations, with low frequencies of treatment-related TEAEs and withdrawals due to TEAEs. Global post-marketing surveillance data on the various CREON formulations have been collected since January 1984; no data have been noted during this time that would suggest any safety issues associated with CREON formulations.⁴⁹

Taken together, these data indicate that CREON is safe and well tolerated in patients with

Table 4. Summary of CREON safety in clinical studies enrolling patients with exocrine pancreatic insufficiency due to cystic fibrosis.

Study	n	Age group	Most common TEAE class (>20% any group)	Overall TEAEs, n (%)		Treatment-related TEAEs, n (%)		Withdrawals due to TEAEs, n (%)		Serious TEAEs, n (%)	
				CREON	PBO	CREON	PBO	CREON	PBO	CREON	PBO
Formulations currently available in the USA (FDA-approved)											
Trapnell et al., 2009 ⁴²	32	≥12 years	GI disorders, nervous system disorders	14 (43.8)	20 (64.5)	6 (18.8)*	12 (38.7)*	1 (3.1)	0	0	0
Graff et al., 2010 ⁴³	17	7-11 years	GI disorders	5 (29.4)	9 (56.3)	0	4 (25.0) [diarrhea, flatulence, abdominal pain, frequent bowel movements, weight decrease, rash]	0	0	0	0
Graff et al., 2010 ⁴⁴	18	<7 years	Infections and infestations	9 (50.0)	NA	1 (5.6) [diaper rash]	NA	0	NA	0	NA
Formulations currently available in Europe											
Colombo et al., 2009 ⁴⁵	12	1-24 months	Fever, cough	9 (75.0)	NA	2 (16.7) [constipation]	NA	0	NA	0	NA
Munck et al., 2009 ⁴⁶	40	6-36 months	URTI, GI disorders§	CfC 17 (42.5)	NA	3 (7.5) [abdominal pain, constipation, vomiting]	NA	1 (2.5)	NA	1 (2.5)	NA
Other formulations											
Stern et al., 2000 ¹⁷	47	7-18 years	Body as a whole, GI disorders, respiratory†	11 (61.1)†	14 (70.0)†	NR	NR	0	1 (5.0)	0	0
	50	18-40 years	Body as a whole, GI disorders†	7 (38.9)†	12 (66.7)†	NR	NR	2 (11.1)‡	1 (5.6)	1 (5.6)‡	0

CfC=Creon for Children (Creon micro); FDA=US Food and Drug Administration; GI=gastrointestinal; NA=not applicable; NR=not reported; PBO=placebo; TEAE=treatment-emergent adverse event; URTI=upper respiratory tract infections.

*Individual events not reported.

†Occurring during double-blind phase only.

‡Occurred during open-label run-in phase.

§Frequency not reported.

EPI due to CF irrespective of age, highlighting its favorable risk–benefit profile in these patients.

CHRONIC PANCREATITIS AND OTHER PATIENT POPULATIONS

Overview of Exocrine Pancreatic Insufficiency in Chronic Pancreatitis and Long-term Consequences

CP is the most common cause of EPI in adults and the most common underlying etiology is alcohol abuse. In 1788, Cawley reported on a “free living young man” who had died of emaciation and diabetes whose post mortem examination revealed multiple pancreatic calculi.⁵⁰ Since that early description thousands of reports have been published. We now know that this multifactorial condition is characterized by chronic inflammation with subsequent loss of exocrine and occasionally endocrine parenchyma, with fibrotic tissue replacement, ultimately resulting in maldigestion, malnutrition, and diabetes mellitus. The exact mechanisms triggering and perpetuating the disease are not fully understood, but there is a complex interaction between noxious stimuli, the environment, and genetic predisposition that leads to an excessive inflammatory response with subsequent tissue destruction. However, our understanding of this condition has increased over the past few years and molecular and cellular events contributing to chronic inflammation with subsequent tissue destruction are better understood, particularly the important role that genes and the environment (alcohol consumption and cigarette smoking being independent risk factors) play in this complex condition.^{51,52} Other etiologies that lead to EPI include tumors that obstruct pancreatic enzyme secretion (pancreatic cancer, intraductal papillary mucinous neoplasia, ampullary tumors), genetic mutations (CF,

cationic trypsinogen, chymotrypsin C, and serine protease inhibitor Kazal type 1), extensive necrotizing pancreatitis, and different types of pancreatic surgery (PS), such as local resection, longitudinal pancreaticojejunostomy, and total pancreatectomy, with EPI severity depending on the type and extent of surgery.^{53,54}

Patients with CP usually present with chronic recurrent abdominal pain and then, over a period of many years, CP may lead to steatorrhea (defined as >7 g of fecal fat/day while consuming a 100 g fat diet, with clinical/symptomatic steatorrhea seen when >15 g/day⁵⁵), malnutrition, and occasionally endocrine pancreatic dysfunction, but this may vary based on the etiology of CP. Steatorrhea occurs in CP only after the pancreatic enzyme output has diminished by 90% of normal levels.^{56,57} The large reserve capacity of the pancreas noted in earlier studies may be due to the non-pancreatic gastric and lingual lipases.⁵⁸

The diagnosis of CP can be made on the basis of clinical symptoms in combination with structural and functional criteria, but in some patients it can be very difficult to make. Structural changes may take years to develop and functional tests can be normal or not easily accessible; chronic abdominal pain may or may not be present. It is important to recognize and treat EPI in patients with CP to prevent maldigestion of fat, proteins, and carbohydrates, malnutrition, and weight loss. In healthy individuals, fat-soluble vitamins are absorbed from the small intestine along with digested dietary fats via micelles (aggregates of monoglycerides, fatty acids, and bile salts). Deficiencies in fat-soluble vitamins A, E, and K are therefore often present in patients with EPI as a result of fat maldigestion (and therefore reduced micelle formation), and may lead to symptoms such as impaired night-time vision, cerebellar ataxia, and/or increased prothrombin time,^{59–61}

and vitamin B₁₂ deficiency may be present due to both impaired release of the B₁₂ complex and bacterial overgrowth in the intestine.⁶² Compared with healthy controls, patients with CP have lower serum levels of vitamin D and decreased bone mineral density.⁶³⁻⁶⁵

Summary of Current Practice for Pancreatic Enzyme Replacement Therapy for the Treatment of Exocrine Pancreatic Insufficiency in Chronic Pancreatitis

As previously mentioned, the standard of care for EPI regardless of underlying etiology is oral PERT. There are currently few formal dosing guidelines for PERT in CP. Approximately 90,000 USP or Ph. Eur. units of lipase must reach the duodenum at the same time as ingested food to assure maximal fat digestion and absorption in patients with EPI. As some endogenous lipase secretion is usually preserved in CP, a starting dose of PERT of 25,000-40,000 USP/Ph. Eur. units of lipase per meal is recommended for the vast majority of patients,^{26,66,67} which can then be adjusted based on individual clinical need (symptom severity, degree of steatorrhea, and fat content of diet). To date, there are no studies showing that PERT corrects fat-soluble vitamin deficiencies or B₁₂ deficiency without simultaneous vitamin supplementation.^{59,62}

Efficacy and Safety of CREON in Chronic Pancreatitis and Other Populations

Randomized and/or placebo-controlled trials of CREON in patients with EPI due to CP or PS have shown improvement of steatorrhea, as measured by increased fat absorption, reduced fecal fat excretion, decreased stool weight and frequency, improved stool consistency, and improved symptom scores.^{54,67-71} Another

prospective study has shown improvement in quality of life.⁷²

In a recent randomized, double-blind, placebo-controlled study by Whitcomb et al.,⁷¹ a new formulation of CREON 12,000 lipase unit (USP) capsules was shown to be safe and effective when patients with CP or post-PS were treated with 72,000 lipase units (USP) per main meal and 36,000 lipase units (USP) per snack compared with placebo for 7 days following a 5-day placebo run-in period ($n=54$). The change from baseline in CFA was significantly greater with CREON compared with placebo: mean $\pm$ standard deviation 32.1% $\pm$ 18.5% versus 8.8% $\pm$ 12.5% ($P<0.0001$). Greater improvements from baseline in stool frequency, stool consistency, abdominal pain, and flatulence were also observed with CREON over placebo. TEAEs were reported in five patients (20.0%) in the CREON group and in six (20.7%) in the placebo group, the most common being gastrointestinal events and metabolism/nutrition disorders. There were no treatment discontinuations due to TEAEs in this study.

A prospective, crossover, randomized, controlled trial by Domínguez-Muñoz et al.⁶⁷ in 24 patients with CP and EPI evaluated the effect of the administration schedules of CREON (the Creon 10000 formulation currently available in Europe). The dosing schedules were four capsules before meals (schedule A), four capsules after meals (schedule B), or four capsules throughout the meal (one before, two during, and one after; schedule C). Regardless of the administration schedule used, CREON improved fat digestion in all patients, with recovery rates of 54% with schedule A, 61% with schedule B, and 61% with schedule C (all $P<0.0001$ versus baseline value of 24%) using the ¹³C-mixed triglyceride breath test. There was no difference in patients' preference for the three dosing schedules in this study. Fat digestion was optimal when

the enzyme preparations were taken during or after meals, and tended to be better than that observed when capsules were administered just before meals although the differences were not significant; therefore, these results should not be used as a recommendation for CREON dosing. The US prescribing information for CREON recommends administration during meals in all patients with EPI;²⁰ however, in practice, PERT is often administered before meals as well as during meals in patients with CF, whereas in non-CF patients it is often administered after meals.

In a randomized, double-blind, multicenter, placebo-controlled trial, 27 patients with CP received four capsules of CREON (Creon 10; a pre-FDA mandate formulation with equivalent lipase content per capsule to current CREON 12,000 USP) with each meal (two capsules with snacks) for 2 weeks, following a 2-week placebo run-in period.⁷⁰ Patients receiving CREON for 2 weeks had a significantly higher mean change in CFA compared with those receiving placebo: +36.7% versus +12.1% ($P=0.0185$). Compared with placebo, CREON also decreased stool frequency (5.2 per day vs. 14.6 per day; $P=0.0015$), controlled steatorrhea (change in stool fat excretion −56.6 g/day vs. −11.4 g/day; $P=0.0181$), and improved stool consistency (stools became more firm in seven subjects vs. one subject; $P=0.0102$ for overall consistency). No major adverse effects were reported in this small study.

The efficacy of CREON in maintaining postoperative digestion and nutrition in 11 patients who underwent local resection-longitudinal pancreaticojejunostomy for CP was evaluated in a placebo-controlled trial (using Creon 8000, a previous formulation no longer available) at different doses based on initial daily fat excretion.⁵⁴ Patients who received CREON showed significant improvements in

the CFA (83.3% vs. 52.7%; $P=0.02$) and the coefficient of total energy absorption (88.3% vs. 71.9%; $P=0.02$) when compared with placebo. Of interest, the nutritional status of these patients was not significantly altered over the period of the study, although four of five patients receiving CREON gained more than 3.6 kg body weight whereas none of the six patients receiving placebo gained weight. These data suggest that postoperative PERT is necessary and effective in improving absorption in patients with CP after local resection-longitudinal pancreaticojejunostomy.

PANCREATIC ENZYME REPLACEMENT THERAPY TREATMENT FAILURES

In clinical practice, some patients do not respond adequately to PERT and they should be encouraged to discuss openly with their healthcare team any problems they have. In these cases, various other factors may be involved, such as lack of patient compliance, suboptimal PERT dosing, miscalculation of fat intake, deficiency of pancreatic bicarbonate secretion, abnormal composition of bile salts, intestinal ion transport abnormalities, intestinal inflammation, altered gut motility, bacterial overgrowth, and impaired absorption of long chain fatty acids.^{26,66,73} High-fiber diets have been associated with a small but significant increase in fecal fat excretion in patients with CP with EPI.⁷⁴ In addition, calcium- and magnesium-containing antacids are associated with the formation of soaps and the precipitation of glycine-conjugated bile salts in the intestine, which may lead to worsening of steatorrhea in patients with underlying EPI.⁷⁵ Factors related to the PERT preparation itself may have an impact, including the size of the enzyme particles, the dissolution characteristics of the preparation, the rate of emptying from

the stomach, and the timing of intake in relation to meals. Variations in the enzyme content of PERT preparations was a potential consideration in the USA before the introduction of the newly approved PERT preparations, as noted earlier in this review. With the new preparations, this is not expected to be an issue.

In compliant patients who do not respond to PERT, increasing the dose twofold and decreasing the amount of fat in meals may be an option in non-CF patients with EPI. Patients with EPI commonly have lower pancreatic bicarbonate secretion, which may become insufficient, resulting in a pH level in the duodenum and small intestine that is too low for adequate dissolution of the PERT enteric coating.^{21,66,73} While bicarbonate transport is difficult to treat, intestinal pH can be raised to optimize PERT dissolution by increasing the pH of gastric secretions flowing into the duodenum. Furthermore, increasing duodenal pH may reduce the precipitation of bile salts. Thus, if symptoms of maldigestion persist, adding an H₂ receptor antagonist or a proton pump inhibitor may be beneficial in improving PERT efficacy,⁷⁶⁻⁷⁸ as is currently prescribed in patients with CF. If all of the above fail, other digestive conditions that may interfere with intestinal absorption should be considered, such as bacterial overgrowth, giardiasis, celiac disease, or blind loop syndrome after gut surgery.^{26,66} A complete medical assessment is needed in the absence of clinical improvement.

POTENTIAL RISKS OF PANCREATIC ENZYME REPLACEMENT THERAPY

Fibrosing Colonopathy

FC is a painful condition characterized by shortening and fibrosis of the colon,⁷⁹ and is a recognized gastrointestinal complication

seen almost exclusively in patients with CF. Littlewood⁸⁰ characterized this condition as:

- “Severe submucosal thickening by mature fibrous connective tissue
- Intraluminal fusiform narrowing but with little change in the external bowel diameter, mainly in distal caecum and ascending colon
- Loss of haustral pattern sometimes with a ‘cobblestone’ appearance of the intestinal epithelium, although the epithelium is generally intact but with some localized defects. Altered architecture suggests there has been repair of previous damage
- Little or no evidence of inflammation or other lesions suggesting Crohn’s disease. Some slight inflammation and fat around blood vessels
- The small bowel is not involved
- A few patients have chylous ascites.”

FC symptoms include abdominal pain, diarrhea, hematochezia (bloody stools), and, in some cases, partial or complete abdominal obstruction where significant narrowing or stricture has occurred. Treatment of FC ranges from reduction in excessive doses of pancreatic enzymes to surgery (eg, partial or total colonic resection).

The first reported case of FC in the USA occurred in 1991⁸¹ and five cases occurring in Europe had been reported by 1993.⁸² The only apparent common factor in these cases was a switch from standard- to high-strength PERT. Before PERT dosing guidelines were established in 1995, more than 60 cases were reported worldwide.⁸³ Despite the voluntary withdrawal of high-strength formulations by manufacturers in early 1994, and the 1995 CF Consensus Conference recommendations that daily dosages should not exceed 10,000 IU lipase per kg body weight,²² 37 cases of FC had been identified in the USA alone between 1995 and 1999.⁸⁴

Early reports of FC in the USA led the CFF in collaboration with the FDA to perform a case-controlled study to investigate FC.⁴⁰ This and another case-control study showed a very strong association with the use of high doses of both standard- and high-strength PERT, usually over a prolonged period of time.^{40,41} Other possible risk factors identified for FC in one case-controlled study included previous intestinal surgery, meconium ileus, distal intestinal obstruction syndrome, and use of H₂ receptor antagonists, corticosteroids, and recombinant human DNase.⁴⁰

The underlying pathogenesis of FC remains unclear and mechanisms other than previous exposure to high doses of PERT are under discussion. According to the current literature, an association between FC and intake of methacrylic acid copolymer (Eudragit®, Evonik Röhm GmbH, Darmstadt, Germany) cannot be ruled out. This compound is sometimes a component of the enteric coating for drug products, including some PERT products and mesalazine.^{81,85} In 2002, a review of the use of PERT products stated that the continued occurrence of FC in the CF population emphasized the need for close monitoring of PERT dosing and adherence in patients with CF.⁸⁶

Although FC occurs predominantly in children, it has been reported in adults.^{87–90} FC occurred in one adult with CF long after stopping high-dose enzyme preparations⁹⁰ and, rarely, has occurred even in the absence of PERT, suggesting that it might be a complication of CF, rather than just a result of PERT use.^{91,92} In this context it should be noted that fibrosis of internal organs, particularly the pancreas, liver, and bile ducts, is inherent in the CF disease process,^{93,94} and an increased prevalence of CF transmembrane receptor mutations has been found in patients with primary sclerosing cholangitis,⁹⁵ a disease characterized by progressive inflammation and

fibrosis of the bile ducts. In a trans-abdominal ultrasound study assessing 83 patients with CF and 31 control subjects, a slight but significant gut wall thickening in both adults and children with CF was observed compared with controls.⁹⁶ There was no association of wall thickness with intake of high-strength enzymes, enzyme dosage, age, or sex. These findings are often mirrored in clinical practice in children with CF. Nevertheless, use of PERT at doses recommended by the CF consensus guidelines^{21–24} remains essential for most patients with CF.

Overall, review of cumulative data and widespread exposure to CREON in the market suggests that FC is an extremely rare event, although continued monitoring is important. In line with a FDA requirement for all US-approved PERT products, the manufacturer of CREON will conduct a 10-year observational study looking at the incidence of and risk factors associated with FC in patients with CF in the USA (this is a class requirement for all PERT manufacturers).

Potential for Viral Transmission

The active ingredient of CREON, pancrelipase, is a mixture of digestive enzymes extracted from porcine pancreas glands harvested from pigs raised and slaughtered for food production. However, as with all porcine-derived PERT products, the possibility of contamination of the starting material with swine viruses capable of infecting humans has to be considered.

During manufacture, reduction of viral pathogens starts with meticulous sourcing of the raw material, specific measures to reduce the introduction of viruses into the raw material, and steps in the manufacturing process to inactivate or remove viral contaminants. In compliance with national and international guidelines for slaughterhouses, only pancreatic glands from animals released fit for human

consumption are used. The manufacturing process is carried out according to Good Manufacturing Practices and complies with relevant guidelines.⁹⁷⁻⁹⁹ Viral safety of the medicinal product is ensured by correct sourcing of the material, the validated manufacturing process, and testing of the active pharmaceutical ingredient (pancrelipase).

The pancrelipase manufacturing process is highly effective in inactivating enveloped viruses; however, it does not reduce all non-enveloped virus loads to the same extent. For non-enveloped viruses where contamination is a possibility, each virus is assessed individually as to the potential risk to patients. Testing is carried out for potentially zoonotic porcine viruses that may not be inactivated by the manufacturing process, with the rejection of positive batches.

Currently, the swine hepatitis E virus (HEV) is the only one of four non-enveloped viruses that is known to be zoonotic and could theoretically be a risk to humans. Previously, HEV infection in humans was thought to be primarily waterborne, occurring mainly in developing countries with poor sanitation. However, it is currently recognized that zoonotic transmission of HEV from swine and other animals can occur in both the developing and industrialized world. Swine HEV can be transmitted to humans by eating raw or undercooked swine livers and intestines, and by direct contact with infected animals.¹⁰⁰ Epidemiological data from blood donors in the USA and Europe show a seroprevalence for anti-HEV of 2%-21%.^{101,102} In general, HEV causes a self-limiting disease and patients typically recover without sequelae within 2-4 weeks. Hepatitis E can present with the typical symptoms of viral hepatitis very similar to hepatitis A, but many cases are subclinical.^{101,103} It was previously thought

that HEV (mostly genotype 1) was associated with a high mortality rate in pregnant women, particularly in certain geographic areas; however, more recent studies and laboratory data suggest that this may not be the case.¹⁰⁰ In addition, humans are the natural host for genotype 1 and it does not infect swine.^{100,103}

CREON clinical and safety databases have been reviewed to look for potential HEV cases. Taken together, no clinically relevant risk could be identified in terms of CREON intake and any liver diseases. In particular, no association between CREON and potential HEV infections could be established. Database review has limitations in risk detection; however, given that HEV is not found in pancreatic cells,¹⁰⁴ together with the implementation of appropriate mitigation steps for HEV contamination in the production process, it is considered unlikely that a causal relationship between CREON intake and HEV infection exists.

In summary, the manufacturer of CREON has instituted measures to minimize the potential for zoonotic agents in the source materials, inactivate many such agents that may be present, and screen the finished product for those considered potentially resistant to inactivation. In addition, no safety concern regarding unexplained viral illness has been identified with over 20 years' exposure history of CREON products. Therefore, the risk of viral illness associated with CREON is considered theoretical at the present time. As with any products derived from animal tissues, the potential risk for infectious disease due to the transmission of an infective agent cannot be totally excluded. In this light, the manufacturer will remain vigilant and will conduct a 10-year observational study to look at viral transmission of selected viruses in the CREON product, in line with the FDA requirement for all manufacturers of US-approved PERT products to carry out such studies.

CONCLUSION

PERT is the standard treatment for EPI. It remains essential in patients with CF to maintain adequate nutrition and normal growth status, and in some patients with CP or post-PS to prevent malnutrition and excessive weight loss. PERT products are available worldwide and are regulated in many countries, most recently in the USA following a FDA mandate for all PERT manufacturers to submit new drug applications. CREON has been available in Europe since 1984 and in the USA since 1987 in various formulations for the treatment of EPI; a new FDA-approved formulation of CREON is now available in the USA. Extensive clinical experience and clinical studies have confirmed the efficacy and safety of CREON in patients with CF, CP, and post-PS, including children aged <7 years. In clinical studies, consistent improvements in fat and nitrogen absorption, stool frequency, and clinical symptoms have been shown compared with placebo or baseline. CREON appears to be well tolerated regardless of patient age, with few withdrawals due to TEAEs and a low frequency of treatment-related TEAEs in clinical studies. No safety issues have been identified with the various CREON formulations based on global post-marketing surveillance data collected since 1984. As requested by the FDA, all PERT manufacturers in the USA are now carrying out studies to investigate further the incidence and risk factors associated with the rare gastrointestinal complication, FC, in patients with CF, and also the theoretical risk of viral transmission from porcine-derived PERT products; these studies will add to the existing evidence for a good safety profile of PERT products. Together the data suggest a very favorable risk-benefit profile for CREON in the treatment of EPI.

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