PRODUCT INFORMATION

CREON® MICRO ENTERIC-COATED GRANULES

NAME OF THE MEDICINE

Non-proprietary Name

Pancreatic Extract

DESCRIPTION

Creon Micro are porcine pancreatic enzyme preparations containing Pancreatic Extract encapsulated in enteric-coated granules with a pH-sensitive coating.

Each dosing unit of 100 mg of Creon Micro contains Pancreatic Extract 60,12 mg equivalent to not less than 5,000 BP units lipase, 3,600 BP units amylase and 200 Ph. Eur. units protease. Inactive ingredients include macrogol 4000, hypromellose phthalate, dimethicone 1000 triethyl citrate, cetyl alcohol. One dosage unit is measured with a measuring scoop as dosing device.

PHARMACOLOGY

Administered orally, pancreatic extract assists in the digestion of proteins, carbohydrates and fats.

Creon Micro has been specially formulated to combine the features of rapid homogeneous distribution with the chyme in the stomach, with resistance to inactivation by gastric acid and rapid dissolution in the alkaline pH of the duodenum. When the granules reach the small intestine the coating rapidly disintegrates (at pH > 5.5) to release enzymes with lipolytic, amylolytic and proteolytic activity to ensure the digestion of fats, starches and proteins. The products of pancreatic digestion are then either absorbed directly, or following further hydrolysis by intestinal enzymes. The granules are similar in size to food particles (0.7-1 mm in diameter), and mix homogeneously with the chyme while being protected from inactivation by gastric acid (pH 1) for up to 2 hours. They pass into the alkaline pH of the duodenum at least as quickly as the food they are intended to digest; here the enteric-coating rapidly dissolves releasing enzymes at the appropriate site.

Pharmacokinetics

Animal studies showed no evidence for absorption of intact enzymes and therefore classical pharmacokinetic studies have not been performed. Pancreatic enzyme supplements do not require absorption to exert their effects. On the contrary, their full therapeutic activity is exerted from within the lumen of the gastrointestinal tract. Furthermore, they are proteins, and as such undergo proteolytic digestion while passing along the gastrointestinal tract before being absorbed as peptides and amino acids.

CLINICAL TRIALS

Efficacy studies

In total, 30 studies investigating the efficacy of Creon in patients with pancreatic exocrine insufficiency have been conducted, among which 10 were placebo controlled studies performed in patients with cystic fibrosis, chronic pancreatitis or post surgical conditions.

In all randomised, placebo-controlled, efficacy studies, the pre-defined primary objective was to show superiority of Creon over placebo on the primary efficacy parameter, the coefficient of fat absorption (CFA).

The coefficient of fat absorption determines the percentage of fat that is absorbed into the body taking into account fat intake and faecal fat excretion. In the placebo-controlled PEI studies, the mean CFA (%) was higher with Creon treatment (83.0%) as compared to placebo (62.6%). The mean CFA (%) at the end of the treatment period with Creon was similar in all studies, irrespective of the trial design.

In all studies performed, irrespective of the underlying disease, marked improvement was also noted with symptomatology associated with pancreatic enzyme insufficiency (e.g., stool frequency, stool consistency, flatulence and abdominal pain).

In cystic fibrosis (CF) the efficacy of Creon was demonstrated in 43 paediatirc patients in randomised, placebo-controlled studies, and in 288 paediatric patients in all studies. The mean end-of-treatment CFA values in all studies exceeded 80% on Creon comparably in all paediatric age groups ranging from newborns to adolescents.

Two double-blind placebo-controlled studies in 74 CF patients on individualised doses of Creon showed statistically significant ($p < 0.001$) and clinically relevant results after Creon treatment of 5-7 days. The mean CFAs in the placebo groups were 52.2% and 50.9% respectively as compared to those in Creon treated patients which were 84.1% and 87.2% respectively.

The third placebo-controlled study, a cross-over study, was performed in 32 paediatric and young adult CF patients. Patients on Creon achieved a mean CFA of 88.6% compared with 49.8% for patients on placebo ($p<0.0001$). The treatment duration was 5 days on a pre-planned dose of 4000 lipase units/g fat intake.

The baseline-controlled study in 12 CF infants showed a mean CFA increase from 58.0% at baseline to 84.7 % after 8 weeks treatment with Creon on a dose of 2000 lipase units/g fat intake.

In chronic pancreatitis and pancreatic surgery three placebo-controlled studies in 161 adult patients were conducted and were each designed with a placebo run-in period followed by a double-blind parallel-group placebo or Creon treatment phase of 7 to 14 days. On average, patients in the Creon group achieved CFA values between 81.5% and 86.6% compared with CFA values between 56.3% and 68% for patients on placebo (statistically significant differences).

Studies in other diseases

Two double-blind, placebo controlled studies were performed in patients after acute pancreatitis (AP). One study in patients in a refeeding status after AP was stopped prematurely due to low recruitment. No treatment difference between Creon and placebo was found on the primary endpoint (time to normalisation of faecal elastase > 200 µg/g stool) in 56 patients. However only a subgroup of 20 patients had low faecal elastase values at baseline. The other study in 21 subjects after AP was not sufficiently powered to detect any relevant treatment differences in terms of QoL and gastrointestinal symptoms between Creon and placebo.

One double-blind, multi-center, placebo-controlled, randomised, parallel group aimed at proving superior efficacy of Creon in patients with PEI caused by total or partial gastrectomy. The study was stopped prematurely due to a too low recruitment rate with only seven patients evaluable for efficacy. No conclusion on the efficacy of Creon in gastrectomized patients could be drawn.

Two double-blind, placebo-controlled studies were performed to investigate the efficacy of Creon in 29 type 1 or 2 diabetes mellitus patients with mild PEI. Both studies were stopped prematurely because of poor recruitment. The pooled analysis of the limited data revealed no significant difference between the groups for the primary endpoint CFA. The change to baseline for stool fat reached statistical significance in favor of Creon ($p = 0.010$, -1.0 g fat/day in placebo and -6.5 g fat/day for Creon).

All studies confirmed the safe administration of Creon in the respective patient populations.

INDICATIONS

Creon Micro is indicated as pancreatic enzyme replacement in paediatric and adult patients with pancreatic exocrine insufficiency (PEI).

Pancreatic exocrine insufficiency is often associated with, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- pancreatic surgery
- gastrointestinal bypass surgery (eg. Bilroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)

CONTRAINDICATIONS

Creon Micro is contraindicated in those patients who are known to be hypersensitive to porcine protein or any of the ingredients.

PRECAUTIONS

Fibrosing Colonopathy

Fibrosing colonopathy has been reported in cystic fibrosis patients treated with some high potency enzyme supplements. The mechanism of injury is unknown. Doses in excess of 10,000 BP units lipase/kg/day should be used with caution. Patients who use doses in excess of 10,000 BP units lipase/kg/day and who develop new symptoms or have a medical history of gastrointestinal complications should be reviewed regularly (e.g. by ultrasound).

Use in Pregnancy

For pancreatic enzymes no clinical data on exposed pregnancies are available.

Animal studies show no evidence for any absorption of porcine pancreatic enzymes.

Although no reproductive or developmental toxicity would be expected, caution should be exercised when prescribing to pregnant women. If required during pregnancy, Creon should be used in doses sufficient to provide adequate nutritional status.

Use in Lactation

Animal studies suggest no systemic exposure of the breastfeeding women to porcine pancreatic enzymes, and no effects on the suckling child are anticipated. If required during lactation, Creon should be used in doses sufficient to provide adequate nutritional status.

Effects on ability to drive and use machines

Creon Micro has no influence on the ability to drive and use machinery.

Interactions with other Medicines

Antacids should not be taken concomitantly with Creon Micro as the alkaline pH may break down the enteric-coating. Should antacid administration be considered necessary, it is recommended that at least one hour elapse between the intake of antacids and any Creon Micro.

No interaction studies have been performed.

ADVERSE EFFECTS

In clinical trials nearly 900 patients with pancreatic exocrine insufficiency due to cystic fibrosis, chronic pancreatitis, and pancreatic surgery were exposed to Creon. The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity.

The following adverse reactions have been observed during clinical trials with the below indicated frequencies.

Organ system	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Frequency not known[#]
Gastrointestinal disorders	Abdominal pain*	Nausea, vomiting, constipation, abdominal distention, diarrhoea*		Strictures of the ileo-caecum and large bowel (fibrosing colonopathy)
Skin and subcutaneous tissue disorders			rash	Pruritus, urticaria
Immune system disorders				Hypersensitivity (anaphylactic reactions)

[#] Frequency cannot be estimated from the available data.

* Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for abdominal pain and diarrhoea.

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations (see Precautions section).

Postmarketing

Allergic reactions mainly but not exclusively limited to the skin have been observed and identified as adverse reactions during post approval use.

Pruritus and urticaria have been additionally identified as adverse reactions during postapproval use. Because these reactions were reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency.

Other patient populations

Multiple clinical trials were conducted in other patient populations: HIV, acute pancreatitis, diabetes mellitus. No additional adverse drug reactions were identified compared to the above 3 patient groups.

Paediatric population

No specific adverse reactions were identified in the paediatric population. Frequency, type and severity of adverse reactions were similar in children with cystic fibrosis as compared to adults.

DOSAGE AND ADMINISTRATION

The granules can be added to small amounts of acidic soft food [pH < 5.5] that do not require chewing, such as apple sauce, mashed bananas or yoghurt, or be taken with liquid such as fruit juice with a pH less than 5.5 for example apple, orange or pineapple juice. The small measuring scoop that is provided with the bottle is designed to contain a dose of 100 mg of granules. This amount provides 5,000 units of lipase.

The mixture of Creon Micro and soft food should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Crushing and chewing of the minimicrospheres or mixing with food or fluid with a pH greater than 5.5 can disrupt the protective enteric coating. This can result in early release of enzymes in the oral cavity and may lead to reduced efficacy and irritation of the mucous membranes. Care should be taken to ensure that no drug is retained in the mouth.

Any mixture of the granules with food or liquids should be used immediately and should not be stored.

Based upon Australasian Clinical Practice Guidelines for nutrition in Cystic Fibrosis 2006, the key goal of pancreatic enzyme replacement therapy is to improve the patient's nutritional status and growth as well as controlling the symptoms of maldigestion (eg. steatorrhoea). This is achieved through optimal dietary intake using a diet without restriction of fat content (>100 g fat per day if over five years of age), unless the patient is overweight. The dose of Creon required is adjusted according to the fat content of the meal and the severity of the disease.

Weight Based Dosing Recommendations for the Treatment of Paediatric and Adult Patients with Cystic Fibrosis (CF) using Creon

Patient Age	Starting Dose	Titration Considerations	Maximum Dose
Children < 4 years	1,000 units lipase/kg bodyweight per meal	Adjust dose according to: • disease severity • control of steatorrhoea • maintenance of good nutritional status	4,000 units lipase/g dietary fat intake OR 10,000 units lipase/kg bodyweight per day
Patients ≥ 4 years	500 units lipase/kg bodyweight per meal		

Dosing Recommendations for the Treatment of Pancreatic Exocrine Insufficiency (PEI) in Adult Patients using Creon

	Starting Dose	Titration Considerations	If required, increase to:
Meal	25,000 to 40,000 units lipase	Assess patient for clinical response and compliance to therapy.	80,000 units lipase
Snack	Half of **meal** dose		Half of **meal** dose

- Maximum dose 10,000 units lipase per kg bodyweight per day

Agents which increase gastric pH, such as H2-antagonists and proton pump inhibitors, have been reported to increase the activity of administered pancreatic lipase and may be helpful in patients who do not achieve adequate response to pancreatic enzyme therapy. This is not an approved indication for these agents. Prescribers should decide, on the basis of published evidence, whether or not to use them in this way.

It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation.

OVERDOSAGE

Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia.

In case of overdose, contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Creon Micro: Round, light brown enteric-coated granules in glass bottles with LDPE closure (AUST R166118). Measuring scoop supplied.

Store below 25°C. In warmer climates it may be necessary to store the product in the refrigerator. Keep the container tightly closed in order to protect from moisture. After opening use within 3 months. Keep out of reach of children.

NAME AND ADDRESS OF THE SPONSOR

BGP Products Pty Ltd
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Australia

POISON SCHEDULE OF THE MEDICINE

Not scheduled

DATE OF FIRST INCLUSION IN THE ARTG

Date of TGA approval:	28 September 2010
Date of most recent amendment:	27 May 2016