NAME OF THE MEDICINE

Non-proprietary Name
Pancreatic Extract

DESCRIPTION
Creon 10,000, 25,000 and 40,000 are porcine pancreatic enzyme preparations containing Pancreatic Extract encapsulated in minimicrospheres with a pH-sensitive coating.

Each Creon 10,000 capsule contains Pancreatic Extract 150 mg equivalent to not less than 10,000 BP units lipase, 8,000 BP units amylase and 600 Ph. Eur. units protease. Inactive ingredients include macrogol 4000, hypromellose phthalate, dimethicone 1000, cetyl alcohol, triethyl citrate, gelatin, iron oxide red CI 77491, iron oxide black CI 77499, iron oxide yellow CI 77492, titanium dioxide and sodium lauryl sulfate.

Each Creon 25,000 capsule contains Pancreatic Extract 300 mg equivalent to not less than 25,000 BP units lipase, 18,000 BP units amylase and 1,000 Ph. Eur. units protease. Inactive ingredients include macrogol 4000, hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone 1000, gelatin, iron oxide red CI 77491, iron oxide yellow CI 77492, titanium dioxide and sodium lauryl sulfate.

Each Creon 40,000 capsule contains Pancreatic Extract 400 mg equivalent to not less than 40,000 BP units lipase, 25,000 BP units amylase and 1,600 Ph. Eur. units protease. Inactive ingredients include macrogol 4000, hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone 1000, gelatin, iron oxide, titanium dioxide and sodium lauryl sulfate.

<table>
<thead>
<tr>
<th>Lipase activity (BP units)</th>
<th>Creon 10,000</th>
<th>Creon 25,000</th>
<th>Creon 40,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase activity (BP units)</td>
<td>10,000</td>
<td>25,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Protease activity (Ph.Eur.units)</td>
<td>8,000</td>
<td>18,000</td>
<td>25,000</td>
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<tr>
<td></td>
<td>600</td>
<td>1,000</td>
<td>1,600</td>
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</tbody>
</table>

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

Creon 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. This is achieved by enteric-coated minimicrospheres which are released in the stomach following dissolution of the gelatin capsule. The minimicrospheres are similar in size to food particles (0.7-1.6 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, 23 studies investigating the efficacy of Creon in patients with pancreatic exocrine insufficiency have been conducted, among which 7 were either placebo or baseline controlled studies performed in patients with cystic fibrosis, chronic pancreatitis or post surgical conditions.

In all randomized, 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).

In cystic fibrosis (CF) the efficacy of Creon over placebo was demonstrated in three placebo-controlled studies, performed in paediatric and young adult CF patients and in one baseline-controlled study in infants of 1 – 24 months. In all, 118 patients were investigated in these trials.

Two double-blind placebo-controlled studies in 74 CF patients on individualized 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 % to 68% for patients on placebo (statistically significant differences).

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).

**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 normalization 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, randomized, 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 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 (e.g. Bilroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)

**CONTRAINDICATIONS**

Creon capsules are contraindicated in 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).

**Other**

The presence of porcine parvovirus cannot be totally excluded in medicines containing extracts of pancreatic powder of porcine origin. However, there is no evidence of transmission of this virus to humans or of causing illness in humans. The presence of other porcine viruses also cannot be definitively excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic powder extracts have been reported.

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

Interactions with other medicines

Antacids should not be taken concomitantly with Creon 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. No interaction studies have been performed.

ADVERSE EFFECTS

In clinical trials over 600 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.

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Very common ≥ 1/10</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1000 to &lt; 1/100</th>
<th>Frequency not known#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain*</td>
<td>Nausea, vomiting, constipation, abdominal distention, diarrhoea*</td>
<td>Strictures of the ilo-caecum and large bowel (fibrosing colonopathy)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash</td>
<td>Pruritus, urticaria</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity (anaphylactic reactions)</td>
<td></td>
</tr>
</tbody>
</table>

* 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 ilo-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 capsules should be swallowed without crushing or chewing, with enough fluid during or after each meal or snack. When swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be carefully opened and the minimicrospheres added to acidic soft food such as apple sauce, mashed bananas, or yoghurt or fruit juice with a pH less than 5.5 that does not require chewing, or the minimicrospheres will be taken with liquid such as fruit juice with a pH less than 5.5 for example apple, orange or pineapple juice. Any mixture of the minimicrospheres with food or liquids should be used immediately and should not be stored.

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 no product is retained in the mouth.

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.

Dosing in paediatric and adult patients with cystic fibrosis
Based upon a recommendation of the Cystic Fibrosis (CF) Consensus Conference, the US CF Foundation case-control study, and the UK case-control study, the following general dosage recommendation for pancreatic enzyme replacement therapy can be proposed:

- Weight-based enzyme dosing should begin with 1,000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four.
- Dosage should be adjusted according to the severity of the disease, control of steatorrhoea and maintenance of good nutritional status.
- Most patients should remain below or should not exceed 10,000 lipase units/kg body weight per day or 4,000 lipase units/gram fat intake

Dosing in adult patients with pancreatic exocrine insufficiency associated with other conditions:
- Initiate dose at 25,000 to 40,000 BP units of lipase per meal and half of that dose for snacks.
- Assess patient for clinical response and compliance to therapy
- If required, adjust dose up to 80,000 BP units of lipase per meal and half of that dose for snacks.

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 10,000: Opaque dark brown/colourless-transparent capsule containing brownish minimicrospheres in bottles of 100 (AUST R 158453)
Creon 25,000: Opaque light brown/colourless-transparent capsule containing brownish minimicrospheres in bottles of 100 (AUST R 158452)
Creon 40,000: Opaque brown/colourless-transparent capsule containing brownish minimicrospheres in bottles of 20*, 50* or 100 capsules (AUST R 158451)
* not currently distributed in Australia
Store below 25°C. In warmer climates it may be necessary to store the product in the refrigerator. After opening use within 6 months. Keep out of reach of children.

NAME AND ADDRESS OF THE SPONSOR
Abbott Australasia Pty Ltd
32-34 Lord Street
Botany NSW 2019
Australia

POISON SCHEDULE OF THE MEDICINE
Creon 25,000 and Creon 40,000: Schedule 4,
Creon 10,000: Not Scheduled

DATE OF APPROVAL
Date of TGA approval: 28 September 2010
Date of most recent amendment: 3 October 2012