1. **CREON® 10,000 Capsules**
   **CREON® 25,000 Capsules**

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Pancreatin, produced from porcine pancreatic tissue

   For a full list of excipients, see Section 6.1

   CREON 10,000 and 25,000 are porcine pancreatic enzyme preparations containing Pancreatic Extract encapsulated in mininmicrospheres with a pH-sensitive coating.

   Each CREON 10,000 capsule contains 248.5 mg of brownish coloured, enteric-coated pellets containing 150 mg Pancreatin (Pancreas Powder) equivalent to not less than 8,000 Ph. Eur. units amylase, 10,000 Ph. Eur. units lipase and 600 Ph. Eur. units protease.

   Each CREON 25,000 capsule contains 497 mg of brownish coloured, enteric-coated pellets containing 300 mg Pancreatin (Pancreas Powder) equivalent to not less than 18,000 Ph. Eur. units amylase, 25,000 Ph. Eur. units lipase and 1000 Ph. Eur. units protease.

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

3. **PHARMACEUTICAL FORM**

   CREON 10,000 is a size 2 gastro-resistant hard gelatin capsule with a brown opaque cap and a colourless transparent body, filled with mininmicrospheres (gastro-resistant pellets).

   CREON 25,000 is a size 0 gastro-resistant hard gelatin capsule with a Swedish orange opaque cap and a colourless transparent body, filled with mininmicrospheres (gastro-resistant pellets).

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

   For treatment of conditions associated with pancreatic exocrine insufficiency, such as:

   - cystic fibrosis
   - chronic pancreatitis
   - post-pancreatectomy
   - post-gastrointestinal bypass surgery (e.g. Billroth II, gastroenterostomy)
   - ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)
4.2 Dose and Method of Administration

The posology aims at individual needs and depends on the severity of the disease and the composition of food. It is recommended to take the enzymes during or immediately after meals.

The capsules should be swallowed intact, 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, 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 that 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 on 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 Dosing Recommendations for the Treatment of Paediatric and Adult Patients with Cystic Fibrosis (CF) using CREON**

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Starting Dose</th>
<th>Titration Considerations</th>
<th>Maximum Dose</th>
</tr>
</thead>
</table>
| 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 in Adult Patients using CREON for the Treatment of Pancreatic Exocrine Insufficiency (PEI) Associated with other Conditions**

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Titration Considerations</th>
<th>If required, increase to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meal</td>
<td>25,000 to 40,000 units lipase</td>
<td>Assess patient for clinical response and compliance to therapy.</td>
<td>80,000 units lipase</td>
</tr>
<tr>
<td>Snack</td>
<td>Half of meal dose</td>
<td></td>
<td>Half of meal dose</td>
</tr>
</tbody>
</table>

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 of patients at all times whilst dosing CREON, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation. Any mixture of the minimicrospheres with food or liquids should be used immediately and should not be stored.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warnings and Precautions for Use

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy, especially if the patient is taking in excess of 10,000 units of lipase/kg/day

4.5 Interaction with other Medicines and other Forms of Interaction

No interaction studies have been performed.

4.6 Fertility, Pregnancy and Lactation

Fertility and Pregnancy

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

Animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected.

Caution should be exercised when prescribing to pregnant women.

Breast-feeding

No effects on the child are anticipated as animal studies suggest no systemic exposure of the breastfeeding woman to pancreatic enzymes. Pancreatic enzymes can be used during breastfeeding.

If required during pregnancy and lactation CREON should be used in doses sufficient to provide adequate nutritional status.

4.7 Effects on ability to drive and use machines

There is no evidence that CREON has any effect on the ability to drive or operate machines.
4.8 Undesirable effects

Adverse reactions from clinical trials

In clinical trials, more than 900 patients 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 ileo-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>

*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 Special Warnings and Precautions for Use.

Allergic reactions mainly but not exclusively limited to the skin have been observed and identified as adverse reactions during post approval use. Because these reactions were reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency.

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.

4.9 Overdose

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

Treatment
Most cases respond to supportive measures including stopping enzyme therapy and ensuring adequate hydration.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).
5. **PHARMACOLOGICAL PROPERTIES**

5.1 Pharmacodynamic properties

Multienzymes (amylase, lipase, protease), ATC code: A09A A02

**Mechanism of action**

CREON contains porcine pancreatic formulated as enteric-coated (acid-resistant) minimicrospheres within gelatin capsules. The capsules dissolve rapidly in the stomach releasing hundreds of minimicrospheres, a multi-dose principle which is designed to achieve good mixing with the chyme, emptying from the stomach together with the chyme and after release, good distribution of enzymes within the chyme. When the minimicrospheres 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.

**Clinical efficacy and safety**

Overall 30 studies investigating the efficacy of CREON in patients with pancreatic exocrine insufficiency have been conducted. Ten of these 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%). Treatment with CREON markedly improves the symptoms of pancreatic exocrine insufficiency including stool consistency, abdominal pain, flatulence and stool frequency, independent of the underlying disease.

Treatment with CREON markedly improves the symptoms of pancreatic exocrine insufficiency including stool consistency, abdominal pain, flatulence and stool frequency, independent of the underlying disease.

**Paediatric population**

In cystic fibrosis (CF) the efficacy of CREON was demonstrated in 288 paediatric patients covering an age range from newborns to adolescents. In all studies, the mean end-of-treatment CFA values exceeded 80% on CREON comparably in all paediatric age groups.

5.2 **Pharmacokinetic properties**

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.

5.3 **Preclinical safety data**

Preclinical data show no relevant acute, sub chronic or chronic toxicity. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Macrogol 4000, hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone, iron oxide (E 172), titanium dioxide (E 171), gelatin, sodium lauryl sulphate.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months from the date of manufacture

6.4 Special precautions for storage
Store in a safe place out of the reach of children.
Creon 10,000: Store below 25°C in cool dry conditions.
Creon 25,000: Store below 25°C in cool dry conditions.
Keep the container tightly closed in order to protect from moisture.
After opening do not store above 25°C and use within 3 months.

6.5 Nature and contents of container
Plastic (HDPE) bottles of 100 capsules.

6.6 Special precautions for disposal
No special precautions.

7. MEDICINE SCHEDULE
CREON 25,000 is a Prescription Medicine
CREON 10,000 is a General Sale Medicine

8. SPONSOR
BGP Products
4 Pacific Rise
Mount Wellington
Auckland
Telephone: 0800 737 271

9. DATE OF FIRST APPROVAL
16 September 1999

10. DATE OF REVISION OF THE TEXT
17 May 2016