NEW ZEALAND DATA SHEET

CREON® 10,000
CREON® 20,000
CREON® 25,000
CREON® 35,000

1. Product Name

Creon 10,000 capsules

Creon 20,000 capsules

Creon 25,000 capsules

Creon 35,000 capsules

2. Qualitative and Quantitative Composition

Each Creon 10,000 capsule contains 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 20,000 capsule contains brownish coloured, enteric-coated pellets containing 300 mg pancreatin (pancreas powder) equivalent to not less than 16,000 Ph.Eur. units amylase, 20,000 Ph.Eur. units lipase and 1,200 Ph.Eur. units protease.

Each Creon 25,000 capsule contains 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 1,000 Ph.Eur. units protease.

Each Creon 35,000 capsule contains brownish coloured, enteric-coated pellets containing 420 mg pancreatin (pancreas powder) equivalent to not less than 25,200 Ph.Eur. units amylase, 35,000 Ph.Eur. units lipase and 1,400 Ph.Eur. units protease.

The pancreatin is produced from porcine pancreatic tissue.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

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

Creon 20,000 is a size 0 elongated hard gelatin capsule with a brown opaque cap and a colourless transparent body, filled with minimicrospheres (gastro-resistant pellets).

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

Creon 35,000 is a size 00 elongated hard gelatin capsule with a red brown cap and a colourless transparent body, filled with minimicrospheres (gastro-resistant pellets).

4. Clinical Particulars

4.1 Therapeutic indications

Creon is indicated for the treatment of pancreatic exocrine insufficiency (PEI) in paediatric and adult patients.

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

- 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

Dose

The posology aims at individual needs and depends on the severity of the disease and the composition of food. The dose of Creon required is adjusted according to the fat content of the meal and the severity of the disease.

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 (e.g. 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.

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

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 in Adult Patients using Creon for the Treatment of Pancreatic Exocrine Insufficiency (PEI) Associated with other Conditions

	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 H_2-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.

Method of administration

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.

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.

4.3 Contraindications

Hypersensitivity to pancreatin or to any of the excipients listed in section 6.1.

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

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.

Fertility

No clinical data are available.

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

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:

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)

*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 section 4.4.

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.

Special populations

Paediatric

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Digestives, incl. enzymes; Multienzymes (amylase, lipase, protease), ATC code: A09AA02

Mechanism of action

Creon contains porcine pancreatin 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

Absorption

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

Pellet core:

- macrogol 4000

Pellet coating:

- hypromellose phthalate
- cetyl alcohol
- triethyl citrate
- dimethicone

Hard gelatin capsule:

- gelatin
- iron oxide (E 172)
- titanium dioxide (E 171)
- sodium lauryl sulfate

Gelatin raw material may contain sulfur dioxide residue. Creon is gluten free and lactose free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25°C in cool, dry conditions.

Store in a safe place out of reach of children.

After opening, do not store above 25°C and use within six months.

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottle with tamper evident PP twist-off closure. Pack size of 100 capsules.

Not all strengths may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Creon 35,000 is a Prescription Medicine.

Creon 25,000 is a Prescription Medicine.

Creon 20,000 is a General Sale Medicine.

Creon 10,000 is a General Sale Medicine.

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
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AUCKLAND

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9. Date of First Approval

Creon 10,000: 16 September 1999

Creon 25,000: 22 March 1991

Creon 20,000 and 30,000: 15 October 2020

10. Date of Revision of the Text

15 October 2020

Section	Summary of change
1	20,000 and 35,000 strengths added
2	20,000 and 35,000 strengths added
3	20,000 and 35,000 strengths added
6.1	Editorial change (excipients bullet pointed)
7	20,000 and 35,000 strengths added
9	20,000 and 35,000 strengths added