AUSTRALIAN PRODUCT INFORMATION

CREON® MICRO

(pancreatic extract) enteric-coated granules

1 NAME OF THE MEDICINE

Pancreatic extract

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CREON MICRO is a porcine pancreatic enzyme preparation 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 Ph.Eur. units lipase, 3,600 Ph.Eur. units amylase and 200 Ph. Eur. units protease.

Excipients with known effect: phenylalanine.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

CREON MICRO: Round, light brown enteric-coated granules. One dosage unit is measured with a measuring scoop as dosing device.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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 (e.g. Bilroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)

4.2 DOSE AND METHOD OF 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 (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. The dose of CREON required is adjusted according to the fat content of the meal and the severity of the disease.

Table 1: 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
Patient ≥ 4 years	500 units lipase/kg bodyweight per meal		

Table 2: 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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Ph.Eur. units lipase/kg/day should be used with caution. Patients who use doses in excess of 10,000 Ph.Eur. 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 the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, more than 1000 patients with pancreatic exocrine insufficiency due to cystic fibrosis, chronic pancreatitis, and pancreatic surgery were exposed to CREON.

Adverse events reported from clinical trials

Table 3: Adverse Events reported by ≥1% of patients treated with CREON (all causalities)

		Placebo-controlled studies		All studies
System Organ Class	**Adverse Event**	**Placebo (N=350) %**	**CREON (N=424) %**	**CREON (N=1037) %**
Gastrointestinal disorders	Abdominal pain	10.9%	6.6%	9.6%
	Diarrhoea	3.4%	3.5%	5.9%
	Vomiting	2.0%	3.8%	5.0%
	Constipation	1.7%	3.3%	4.8%
	Abdominal distension	2.0%	2.4%	4.0%
	Nausea	2.6%	1.9%	3.9%
	Flatulence	6.0%	3.3%	2.6%
	Abdominal pain upper	2.6%	1.2%	2.5%
	Dyspepsia	2.3%	3.1%	2.2%
	Abdominal discomfort	1.1%	1.9%	1.7%
	Abdominal tenderness	0.3%	0.0%	1.1%
General disorders and administration site conditions	Pyrexia	1.1%	1.9%	4.9%
	Malaise	1.1%	0.9%	3.1%
	Pain	1.4%	1.4%	1.2%
	Asthenia	0.3%	0.2%	1.1%
Hepatobiliary disorders	Cholangitis	0.3%	0.5%	1.5%
Infections and infestations	Nasopharyngitis	0.9%	1.2%	5.8%
	Bronchitis	0.3%	0.0%	1.8%
	Respiratory tract infection			1.0%
Investigations	Blood glucose increased	1.4%	1.9%	2.7%
	Alanine aminotransferase increased	1.1%	2.4%	2.1%
	Aspartate aminotransferase increased	0.9%	1.7%	2.1%
	Blood glucose			2.1%
	Gamma-glutamyltransferase increased	0.3%	0.9%	2.0%
	Blood alkaline phosphatase increased	0.6%	0.9%	1.5%
	Weight decreased	1.7%	1.7%	1.4%
	Haematocrit			1.4%
	Haemoglobin			1.3%
	White blood cell count increased	0.0%	0.7%	1.2%
	Red blood cell count			1.2%
	Blood cholesterol decreased	0.6%	0.9%	1.1%
Metabolism and nutrition disorders	Hypoglycaemia	4.0%	2.8%	2.6%
	Decreased appetite	0.9%	0.5%	1.9%
	Diabetes mellitus (incl subtypes)	0.3%	0.0%	1.5%
	Diabetes mellitus	0.3%	0.0%	1.2%
	Hyperglycaemia	1.1%	1.7%	1.2%

		Placebo-controlled studies		All studies
System Organ Class	**Adverse Event**	**Placebo (N=350) %**	**CREON (N=424) %**	**CREON (N=1037) %**
Musculoskeletal and connective tissue disorders	Back pain	2.9%	1.4%	3.3%
	Arthralgia	1.1%	1.2%	1.4%
	Musculoskeletal pain	0.9%	1.7%	1.0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to specified sites	0.3%	0.0%	1.3%
	Pancreatic carcinoma recurrent			1.1%
Nervous system disorders	Headache	5.7%	5.2%	6.8%
	Dizziness	1.1%	1.2%	1.0%
Psychiatric disorders	Insomnia	0.0%	0.2%	1.6%
Respiratory, thoracic and mediastinal disorders	Cough	0.0%	1.4%	5.2%
	Oropharyngeal pain	0.0%	1.2%	1.3%
Skin and subcutaneous tissue disorders	Pruritus	0.9%	1.4%	1.4%
Vascular disorders	Hypertension	0.9%	0.5%	1.2%

Incidences of TEAEs, as they occurred at least in 10 patients, i.e. in 1% of patients, in the All studies column. N = Number of subjects in the Safety Subject Sample. Adverse Events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Adverse reactions

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 4: Adverse Reactions Observed During Clinical Trials

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post-marketing

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 post-approval 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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.

Clinical Trials

Efficacy studies

In total, 33 studies investigating the efficacy of CREON in patients with pancreatic exocrine insufficiency have been conducted, among which 11 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 (59.1%). 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 paediatric patients in randomised, placebo-controlled studies, and investigated in 340 paediatric patients in all studies combined. 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-centre, 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 favour 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.

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

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Inactive ingredients include macrogol 4000, hypromellose phthalate, dimeticone 1000, triethyl citrate, cetyl alcohol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

Use within 3 months after opening.

Keep out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Glass bottle with LDPE closure. Measuring scoop supplied.
Pack sizes: 20 g bottle
Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)
AUST R 166118 – CREON MICRO pancreatic extract 20 g enteric coated granules bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

No data available.

CAS Number

8049-47-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled.

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

28/09/2010

10 DATE OF REVISION

19/06/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Addition of Schedule 1 ingredient declaration

Creon Micro_pi\Jun24/00