NEW ZEALAND DATA SHEET

CREON® Micro

1. Product Name

Creon Micro, 60.12 mg, modified release granules.

2. Qualitative and Quantitative Composition

Each 100 mg of minimicrospheres (equivalent to one measuring spoonful) contains 60.12 mg of pancreatin, containing the following pancreatic enzymes: Lipase 5000 Ph.Eur. units, Amylase 3600 Ph.Eur. units and Protease 200 Ph.Eur. units.

Pancreatin extract derived from porcine pancreas gland.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Creon Micro is a round, light brown minimicrospheres (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 the meals.

Dose

Creon Micro is a specific dosage form with a small minimicrosphere size in particular for use in infants and children unable to swallow capsules. Creon Micro allows improved individual dosing when low lipase doses are needed for adequate treatment of young children.

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:

- In infants dosing should be initiated at a dose of 2000 to 5000 lipase units for each feeding (usually 120 ml) and adjusted up to a dose no greater than 2500 lipase units per kilogram per feeding with a maximum daily dose of 10,000 lipase units per kg per day.

- Weight-based enzyme dosing should begin with 1000 lipase units/kg/meal for children less than 4 years of age and with 500 lipase units/kg/meal for those over age 4.

- Dosage should be adjusted according to the severity of the disease, control of steatorrhea 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 4000 lipase units/gram fat intake.

Dosing in other conditions associated with exocrine pancreatic insufficiency

Dosage should be individualized by patients according to the degree of maldigestion and the fat content of the meal. The required dose for meal ranges from about 25,000 to 80,000 Ph. Eur.units of lipase and half of the individual dose for snacks.

Method of administration

The minimicrosphere can be added to small amounts of acidic soft food (pH < 5.5) that do not require chewing or be taken with acidic liquid (pH < 5.5). This could be apple sauce or yogurt or fruit juice with a pH less than 5.5, e.g. apple, orange or pineapple juice. This mixture should not be stored.

Alternatively, Creon Micro can be mixed with a small amount of milk on a (weaning) spoon and administered to the infant immediately. The minimicrospheres should not be added to the baby's bottle. Any mixture of Creon Micro with soft food or fluid 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 product is retained in the mouth.

It is important to ensure hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation. Any mixture of the minimicrospheres with food or liquid should be used immediately and should not be stored.

4.3 Contraindications

Hypersensitivity to the active substance 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 prepartions. As a precaution, unusual abdominal symptoms or changes in the 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 and fertility

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 of developmental toxicity is to be expected. Caution should be exercised when prescribing to pregnant women.

Breast-feeding

No effects on the suckling child are anticipated since 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 Micro should be used in does sufficient to provide adequate nutritional status.

4.7 Effects on ability to drive and use machines

Creon Micro has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical trials, more than 900 patients were exposed to pancreatin enzymes. 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, diarrhea*		strictures of the ileo-caecum and large bowel (fibrosing colonopathy)
Skin and subcutaneous tissue disorders			rash	pruritus, urticaria
Immune system disorders				hypersensitivity (anaphylactic reactions).

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

Stricture 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 postapproval 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.

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

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

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

Mechanism of action

Creon Micro contains porcine pancreatin formulated as enteric-coated (acid-resistant) 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 (including Creon Micro) 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 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).

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%). in all studies, irrespective of the design, the mean CFA (%) at the end of the treatment period with Creon was similar to the mean CFA values for Creon in the placebo-controlled studies.

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% of Creon comparably in all paediatric age groups.

Creon Micro has been specifically developed to offer a dosage from for infants and children. One baseline-adjusted specific study performed over 8 weeks in infants demonstrated that Creon Micro was effective regarding the improvement of CFA and stool fat excretion as well as faecal energy loss after two weeks of treatment.

The study was designed mainly to evaluate the efficacy of Creon Micro in 12 infants, aged 1-23 months. The analysis of the results showed that the primary efficacy parameter, CFA, significantly increased from a baseline mean of 58.0% to a mean of 84.7% (mean increase 26.7%, $p = 0.0013$, paired t-test). Height and weight increased, but the weight for height percentile remained nearly constant and close to 100%.

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, subchronic or chronic toxicity. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.

6. Pharmaceutical Particulars

6.1 List of excipients

Creon Micro modified release granules also contain:

- Cetyl alcohol
- Dimeticone
- Hypromellose phthalate
- Macrogol 4000
- Triethyl citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C, protect from moisture.

After opening, do not store above 25°C, protect from moisture and use within 3 months.

6.5 Nature and contents of container

Glass bottle with LDPE stopper and dosing scoop. Pack size of 200 scoop measures (equivalent to 20 grams).

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

General Sale Medicine

8. Sponsor Details

Viatris Ltd
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AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

2 August 2012

10. Date of Revision of the Text

30 August 2021

Summary table of changes

Section	Summary of new information
All	Rebranding to Viatris.
2	Editorial update.
6.1	Removed gluten and lactose free statement.
8	Updated sponsor details

Creon® is a Viatris company trade mark.