

## New Zealand Datasheet

### Name of Medicine

**CREON<sup>®</sup> 10,000**

**CREON<sup>®</sup> FORTE**

***Pancreatin***

### Presentation

CREON 10,000 is a size 2 gelatine capsule with a brown opaque cap and a colourless opaque body. Inside each capsule are 248.5mg of brownish coloured, enteric-coated pellets containing 150mg pancreatin which consists of not less than 8,000 Ph.Eur units amylase; 10,000 Ph.Eur units lipase; 600 Ph.Eur units protease.

CREON FORTE is a size 0 gelatine capsule with a swedish orange opaque cap and a colourless opaque body. Inside each capsule are 497 mg of brownish coloured, enteric-coated pellets containing not less than 18,000 Ph.Eur units amylase; 25,000 Ph.Eur units lipase; 1000 Ph.Eur units protease.

### Uses

#### Actions

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

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.

#### 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.

#### 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).

### Dosage and Administration

At least one capsule should be taken whole with a drink (of approximately 100ml) with meals or snacks. Medication should not be taken whilst patient is in a recumbent position. The dose can be increased as necessary, depending on individual requirements. Dose increases, if required, should be added slowly, with careful monitoring of response and symptomatology.

It is important to ensure adequate hydration of patients at all times whilst dosing CREON. Inadequate hydration may aggravate constipation. Any mixture of the minimicrospheres with food or liquids should be used immediately and should not be stored.

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 soft food [pH < 5.5] that does not require chewing, or the minimicrospheres will be taken with liquid [pH < 5.5].

## **Contraindications**

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

## **Warnings and Precautions**

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations. Case control studies did not reveal evidence for an association between CREON and the appearance of fibrosing colonopathy. 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 10000 units of lipase/kg/day

As with all currently marketed porcine pancreatin products, CREON is sourced from pancreatic tissue from swine used for food consumption. Although the risk that CREON will transmit an infectious agent to humans has been reduced by the testing and inactivation of certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. The presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported, whereas they have been used for a long time.

## **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.

## **Use in Lactation**

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.

## **Effects on ability to drive and use machinery**

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

## **Adverse Effects**

In clinical trials, more than 600 patients with pancreatic exocrine insufficiency, due to cystic fibrosis, chronic pancreatitis or 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

### Gastrointestinal disorders

Common ( $\geq 1/100$ ,  $< 1/10$ ): nausea, vomiting, constipation and abdominal distention.

Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for diarrhea (common,  $\geq 1/100$ ,  $< 1/10$ ) and for abdominal pain (very common,  $\geq 1/10$ ).

### Skin and subcutaneous tissue disorders

Uncommon ( $\geq 1,000$ ,  $\leq 1/100$ ): rash

Frequency not known: pruritis, urticaria

### Immune System Disorders

Frequency not known: Hypersensitivity (anaphylactic reactions).

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.

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 pediatric population. Frequency, type and severity of adverse reactions were similar in children with cystic fibrosis as compared to adults.

## **Interactions**

No interaction studies have been performed.

## **Overdosage**

### **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.

## **Pharmaceutical Precautions**

Store in a safe place out of the reach of children.

Creon 10,000: Store below 25°C in cool dry conditions.

Creon Forte: Store below 25°C in cool dry conditions.

Keep the container tightly closed.

## **Medicine Classification**

CREON FORTE is a Prescription Medicine

CREON 10000 is a General Sale Medicine

## **Package Quantities**

Plastic (HDPE) bottles of 100 capsules.

## **Further Information**

### **List of excipients**

Macrogol 4000, hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone, iron oxide (E 172), titanium dioxide (E 171), gelatine, sodium lauryl sulphate.

### **Clinical efficacy**

Overall 23 studies investigating the efficacy of CREON in patients with pancreatic exocrine insufficiency have been conducted. Seven of these 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 all performed studies, irrespective of etiology, marked improvement was also shown in disease specific symptomatology (e.g., stool frequency, stool consistency, flatulence and abdominal pain).

### **Paediatric population**

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. Overall, 118 patients were investigated in these trials. The data indicate that there is no difference in effect as measured by CFA due to the age of subjects.

### **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.

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