Creon® 10000

hard gelatine capsules filled with gastro-resistant granules

INN 150 mg pancreas powder

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Creon 10 000 is a bicoloured hard gelatine capsule with brown opaque cap and colourless transparent body filled with brownish gastro-resistant granules for oral administration. Creon 10 000 contains 150 mg pancreas powder corresponding to
Amylase 8 000 Ph.Eur. units

Lipase 10 000 Ph.Eur. units

Protease 600 Ph.Eur. units

Produced from porcine pancreatic tissue.

Indications
Creon 10 000 is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.

Dosage and 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.
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 pellets may be added to acidic soft food [pH < 5.5] that does not require chewing, or the pellets can be taken with 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.

Crushing and chewing of the pellets 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 at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation. Any mixture of the pellets with food or liquids should be used immediately and should not be stored.

Posology in cystic fibrosis
Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences. Creon 10 000 should be administered in a manner consistent with the recommendations of the Conferences provided in the following paragraphs. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

Additional recommendations for pancreatic enzyme therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy are based on a clinical trial conducted in these populations.

Infants (up to 12 months)
Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Do not mix Creon 10 000 capsule contents directly into formula or breast milk prior to administration.

Children Older than 12 Months and Younger than 4 Years
Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Adults
Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Posology in other pancreatic exocrine insufficiency disorders
Dosage should be individualized by patient according to the degree of maldigestion and the fat content of the meal. The required dose for a meal ranges from about 25 000 to 80 000 Ph. Eur. units of lipase and half of the individual dose for snacks.

Limitations on Dosing
Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines. If symptoms and signs of steatorrhea persist, the dosage may be increased by the healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

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

Special warnings and precautions for use

Fibrosing Colonopathy
Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly

reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. 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 10 000 units of lipase/kg/day. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in children less than 12 years of age. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day.

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Potential for Irritation to Oral Mucosa
Care should be taken to ensure that no drug is retained in the mouth. Creon 10 000 should not be crushed or chewed or mixed in foods having a pH ≥ 5.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity. For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a pH < 5.5, such as applesauce, at room temperature. The Creon 10 000-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

Potential for Risk of Hyperuricemia
Caution should be exercised when prescribing Creon 10 000 to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

Allergic Reactions
Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued Creon 10 000 treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

Interactions
No interaction studies have been performed.

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.

Lactation
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 should be used in doses sufficient to provide adequate nutritional status.

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

Undesirable effects
In clinical trials, more than 1000 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, 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).

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

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

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

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

Creon 10 000 contains porcine pancreatin formulated as enteric-coated (acid-resistant) pellets within gelatine capsules. The capsules dissolve rapidly in the stomach releasing plenty of pellets, 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 pellets 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:
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 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 fecal fat excretion. In 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% on Creon comparably in all paediatric age groups.

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.

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.

List of excipients
Pellet core: Macrogol 4000
Pellet coating: Hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone 1,000
Capsule: Gelatin, iron oxide (E172), titanium dioxide (E171), sodium lauryl sulphate

Incompatibilities
Not applicable.

Shelf life
Please refer to the product carton for expiry

Storage conditions
For HDPE bottle, do not store above 25 °C.
For aluminium-aluminium blister, do not store above 30 °C.
Store in the original package. The container of the medicine should be kept tightly closed order to protect from moisture. Do not use for a period of longer than 3 months after first opening the bottle.

Do not use the medicine after the expiry date stated on the carton.

Updated 14 Mar 2022

Keep this medicine out of the reach and sight of children.

Pack sizes
20, 50, 100 or 200 capsules per pack.
Not all pack sizes may be marketed.
Container may come in the form of HDPE bottle or aluminium-aluminium blisters.

Special Precautions for Disposal and Other Handling
Administration through gastric tube (carefully test appropriateness of the selected syringe and tube).

Creon 10 000 can be administered via G-tube 16Fr and above, in most cases, if medically indicated. The pellet has a diameter of 0.7-1.6mm. It is important that the appropriateness of the selected syringe and tube is carefully tested. In order to maintain pellet integrity and to prevent clogging or sticking, the pellets should be mixed with a small amount of (thickened) acidic liquid or baby food (like apple sauce, fruit juice, sirupus simplex, full-fat yoghurt) (pH < 4.5) and the feeding tube should be flushed with water before and after administration of the mixture. Clogging was observed with certain brands of G-tube and baby food used.

1. Put a thickened acidic liquid (applesauce, baby food, sirupus simplex, full-fat yoghurt), with a ‘’nectar thick’ consistency into a small clean container. (use 15mL of thickened liquid/applesauce per capsule)
2. Open the Creon 10 000 and add the contents (pellets) to the container. Stir gently to suspend contents evenly through the thickened acidic liquid.
3. If applicable, pause tube feeds and flush the G-tube with an appropriate amount of water. (20-30ml of water)
4. Draw up the mixture from the container with an enteral syringe of appropriate size for the volume and feeding tube size.
5. Administer the mixture slowly through the feeding tube with slow-gentle pressure.
6. Flush the feeding tube with an appropriate amount of water (20-30ml) and resume tube feeds if applicable.

In case small bore G-tubes with ≤ Fr 12 are used, or in case of clogging of G-tube, the uncrushed pellets can be mixed with 20ml of 8.4% sodium bicarbonate solution and allowed to dissolve (about 30 minutes). Subsequently administer the solution slowly through the feeding tube and flush the tube with water before and after each dose. With this method, there is, despite the buffering capacity of sodium bicarbonate, a certain risk of enzyme inactivation, yet tube occlusion is avoided.

For each 10,000 international units of lipase, about 800 mg of sodium bicarbonate is used. This is the amount provided by one 10-mL vial of 8.4% sodium bicarbonate solution.

Further information
The information in this leaflet is limited. For further information, please contact your doctor or pharmacist.

Date of information
14 Mar 2022 (SIN-CRE-0322/0)
RDCCDS000192/10

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