

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kreon® 10000

Kreon® 25000

Kreon® 40000

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule Kreon® 10000 contains 150 mg Pancreatin in Kreon Minimicrospheres® granules, gastro-resistant corresponding to
Amylase 8000 Ph.Eur. units
Lipase 10000 Ph.Eur. units
Protease 600 Ph.Eur. units

1 capsule Kreon® 25000 contains 300 mg Pancreatin in Kreon Minimicrospheres® granules, gastro-resistant corresponding to
Amylase 18000 Ph.Eur. units
Lipase 25000 Ph.Eur. units
Protease 1000 Ph.Eur. units

1 capsule Kreon® 40000 contains 400 mg Pancreatin in Kreon Minimicrospheres® granules, gastro-resistant corresponding to
Amylase 25000 Ph.Eur. units
Lipase 40000 Ph.Eur. units
Protease 1600 Ph.Eur. units

Produced from porcine pancreatic tissue.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard
(Hard Gelatin Capsules filled with Gastro-Resistant Pellets (Kreon Minimicrospheres®))

DBP / DBP free formulation

Kreon® 10000 and Kreon® 40000: Bicoloured capsule with brown opaque cap and transparent body
Kreon® 25000: Bicoloured capsule with Swedish orange opaque cap and transparent body

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Violations of exocrine pancreas, accompanied by indigestion. In cystic fibrosis to compensate for the lack of exocrine pancreatic function.

4.2 Posology 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.

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 added to acidic soft food [pH < 5.5] that does not require chewing, or the pellets will 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. Crushing and chewing of Kreon 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 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.

- Weight-based enzyme dosing should begin with 1000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four.
- 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 10000 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 a meal ranges from about 25000 to 80000 Ph. Eur.units of lipase and half of the individual dose for snacks.

4.3 Contraindications

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

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 10000 units of lipase/kg/day.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No interaction studies have been performed.

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4.6 Fertility, Pregnancy and Lactation

There are no adequate data from the use of Kreon® in pregnant women. Data from animal studies are insufficient with respect to the effects on pregnancy, embryonal/foetal development, parturition and postnatal development. Hence, the potential risk for humans is unknown. Kreon® should not be used during pregnancy or lactation unless absolutely necessary.

4.7 Effects on Ability to Drive and Use Machines

Kreon® 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 Kreon®.

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.

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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.

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Pediatric 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.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Kreon[®] contains porcine pancreatin formulated as enteric-coated (acid-resistant) Kreon Minimicrospheres[®] within gelatine capsules.

The pancreatin contains the excretory pancreatic enzymes lipase, alpha-amylase, trypsin and chymotrypsin, along with other enzymes. The pancreatin also contains attendant substances that have no enzymatic activity. The portion that is not absorbed is metabolised and denatured by the digestive juices or bacteria. The digestive availability is determined by the activity of the enzymes and the galenic presentation. A decisive factor is the enzymatic activity of the lipase as well as the proportion of trypsin. The amylolytic activity is only of relevance in the treatment of cystic fibrosis, since the breakdown of nutritional polysaccharides is still unimpeded even in the presence of chronic pancreatitis.

Trypsin is converted from trypsinogen autocatalytically or through enterokinase in the small intestine, and as an endopeptidase cleaves the peptide compounds which comprise lysine and arginine.

According to more recent studies, trypsin is assumed to be a feedback inhibitor of stimulated pancreatic secretion, caused by active trypsin in the upper small intestine. In certain studies, the analgesic effect of pancreatin products is attributed to this activity.

Alpha-amylase is an endoamylase that very rapidly cleaves glucose-containing polysaccharides, meaning that its activity is still sufficient if the secretory activity of the pancreas is severely reduced as a result of disease.

Pancreatic lipase removes the fatty acids from the triacylglycerol molecule at positions 1 and 3. The free fatty acids and 2-monoglycerides that result are rapidly absorbed, mostly from the upper small intestine with the aid of bile acid. Animal pancreatic lipase, like human lipase, is unstable in an acidic environment. Hence, its lipolytic activity is increasingly inactivated at a pH of < 4, a situation that is irreversible.

The galenic principle of Kreon[®] guarantees optimal utilisation of the enzymatic activities of pancreatin for the purposes of food digestion. The gastro-resistant Kreon Minimicrospheres[®], containing a mixture of all pancreatic enzymes, are enclosed in readily soluble, hard gelatine capsules. Irrespective of the pH, the capsules take only 2 to 3 minutes to dissolve in the stomach, releasing a large number of microspheres. This multi-dosing principle was developed so as to enable the microspheres to mix thoroughly with the chyme. Consequently, Kreon Minimicrospheres[®] are guaranteed to be expelled from the stomach into the duodenum with the chyme, and the enzymes in the chyme will be readily dispersed once released. As Kreon Minimicrospheres[®] reach the small intestine, the protective film rapidly dissolves (at pH > 5.5),

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releasing the enzymes. The chyme can then begin to decompose in exactly the same way as in the physiological process of digestion, since the metabolism and absorption of the nutrients is restricted as regards time and location. The metabolites are either absorbed directly or further hydrolysed by intestinal enzymes.

Given the galenic formulation, any loss of activity in Kreon® is prevented by a highly acidic pH in the stomach. The availability of the enzymes depends on the pH.

Clinical efficacy

A total of 30 studies have been conducted to investigate the efficacy of Kreon® in patients with pancreatic exocrine insufficiency (PEI). Ten of these were placebo-controlled studies performed in patients with cystic fibrosis, chronic pancreatitis or postoperative conditions.

In all randomised, placebo-controlled efficacy studies, the primary endpoint was to demonstrate the superiority of the effect of Kreon® over placebo on the primary efficacy parameter, the coefficient of fat absorption (CFA). The CFA is the percentage of fat absorbed by the body relative to total fat intake.

In the placebo-controlled PEI studies, the mean CFA was higher under Kreon® treatment (83%) than under placebo (62.6%). In all studies, irrespective of the design, the mean CFA at the end of the treatment period with Kreon® was comparable to the mean CFA values reported in the placebo-controlled studies.

Treatment with Kreon® 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, the efficacy of Kreon® was demonstrated in 288 paediatric patients ranging in age from newborns to adults. In all studies, the mean CFA values at the end of treatment with Kreon® exceeded 80%, regardless of the age group.

5.2 Pharmacokinetic Properties

Animal studies revealed no evidence of absorption of intact enzymes. Classical pharmacokinetic studies therefore have not been performed. To exert their effect, pancreatic enzymes do not need to be absorbed. In fact, their full therapeutic activity is exerted within the intestinal lumen. They are also proteins, and as such undergo autolytic or proteolytic digestion during gastrointestinal transit before being absorbed as peptides and amino acids.

5.3 Preclinical Safety Data

Preclinical data have not revealed any relevant acute, subchronic or chronic toxicity. Studies of genotoxicity, carcinogenicity and reproductive toxicity have not been performed. No systemic toxic effects are to be expected from oral pancreatin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Kreon® 10000, 25000, 40000

Core pellet: macrogol 4000

Coating: hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone 1000.

Capsule: gelatin, iron oxide red (E 172), iron oxide yellow (E 172), iron oxide black (E 172) titanium dioxide (E 171), sodium lauryl sulphate.

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6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Kreon® 10000: 2 years

Kreon® 25000: 2 years

Kreon® 40000: 2 years

6.4 Storage conditions:

Kreon® 10000/ Kreon® 25000/ Kreon® 40000 mms in capsules in **HDPE** bottles:

“Do not store above 25°C. Keep the container tightly closed.

After opening use within 6 months”

Kreon® 10000/ Kreon® 25000/ Kreon® 40000 mms in capsules in **ALU/ALU blister**:

“Do not store above 25°C. Keep the container tightly closed”

6.5 Nature and contents of container

20 capsules in HPDE bottles. 1 bottle with leaflet in carton box.

10 capsules in ALU/ALU blister. 2 blisters with leaflet in carton box.

6.6 Distribution:

OTC

MARKETING AUTHORIZATION HOLDER

Abbott Laboratories GmbH, Germany

address:

Freundallee 9A,

30173 Hannover,

Germany

MANUFACTURER

Abbott Laboratories GmbH, Germany

address:

Justus-von-Liebig-Str. 33,

31535 Neustadt,

Germany