Summary of Product Characteristics

CREON® 10,000

1. Name of the medicinal product

Creon® 10,000, Capsules

2. Qualitative and quantitative composition

Each capsule contains:
150 mg pancreatin (pancreas powder) corresponding to

Amylase	8,000	Ph.Eur. units
Lipase	10,000	Ph.Eur. units
Protease	600	Ph.Eur. units

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Brown/clear capsules containing gastro-resistant granules.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of Pancreatic exocrine insufficiency.

Enzyme replacement therapy in patients with deficient exocrine pancreatic secretions, cystic fibrosis, chronic pancreatitis, postpancreatectomy, ductal obstructions caused by cancer of the pancreas, pancreatic insufficiency and for steatorrhea of malabsorption syndrome and postgastrectomy (Billroth II and Total).
Presumptive test for pancreatic function, especially in pancreatic insufficiency due to chronic pancreatitis.

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 each meal or snack.

Adults (including the elderly) and children:
Initially one to two capsules with each meal.
Dose increases, if required, should be added slowly, with careful monitoring of response and symptomatology.
The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with acidic fluid or soft food, but without chewing.

This could be apple sauce or yoghurt or any fruit juice with a pH less than 5.5, e.g. apple, orange or pineapple juice. If the granules are mixed with fluid or food it is important that they are taken immediately and the mixture not stored, otherwise dissolution of the enteric coating may result. In order to protect the enteric coating, it is important that the granules are not crushed or chewed

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 that no product is retained in the mouth.
It is important to ensure adequate hydration of patients at all times whilst dosing CreonDosing in paediatric and adult patients with cystic fibrosis

Based upon a recommendation of the Cystic Fibrosis 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:

- 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 U/kg body weight per day or 4000 lipase units/gram fat intake.

Fibrosing colonopathy has been reported in patients with cystic fibrosis taking in excess of 10,000 units of lipase/kg/day (see section 4.4).

Dosing in other conditions associated with exocrine pancreatic insufficiency

Dosage should be individualized by patient according to the degree of maldigestion and the fat content of the meal. The required dose for a main meal (breakfast, lunch or dinner) ranges from about 25000 to 80000 Ph. Eur. U of lipase and half of the individual dose for snacks.

4.3 Contraindications

Hypersensitivity to pancreatin of porcine origin 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 10,000 units of lipase/kg/day.

Creon is essentially 'sodium free' as it contains less than 1 mmol sodium (23 mg) per dose (2 mg).

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 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 breast-feeding woman to pancreatic enzymes. Pancreatic enzymes can be used during breast-feeding.
If required during pregnancy or lactation Creon should be used in doses sufficient to provide adequate nutritional status.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In clinical trials, more than 900 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, 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).

*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.
Allergic reactions mainly but not exclusively limited to the skin have been observed and 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.

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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia.
Supportive measures including stopping enzyme therapy and ensuring adequate rehydration are recommended.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Multienzymes (amylase, lipase, protease), ATC code: A09A A02
Creon contains porcine pancreatin formulated as enteric-coated (acid-resistant) minimicrospheres within gelatine capsules.
The capsules dissolve rapidly in the stomach releasing plenty of minimicrospheres, a multidose 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:
Overall 30 studies investigating the efficacy of Creon (Creon capsules with 10000, 25000 or 40000 Ph. Eur units of lipase and Creon 5000) 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 CFA (%, mean ± SD) was higher with Creon treatment (83.0 ± 12.6%) as compared to placebo (62.6 ± 21.8%). The median treatment duration was 7 days on both treatments. 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.

In placebo-controlled studies in which symptoms have been collected on diaries, the percentage of subjects with 'no abdominal pain' as most frequently reported rating was higher (73%) during Creon treatment than during placebo treatment (52%). The most frequently reported stool consistency was 'formed/normal' in 63% of the subjects during Creon treatment and in 17% of the subjects during placebo treatment. During Creon treatment, the percentage of subjects with 'no flatulence' as most frequently reported rating was higher (30%) than during placebo treatment (19%). The average number of daily stools was lower during Creon treatment than during placebo treatment (mean±SD: 1.89±0.87 vs 3.16±1.51).
In subjects with PEI due to CF in these studies, the percentage of subjects with 'no abdominal pain' as most frequently reported rating was 94% during Creon treatment and 60% during placebo treatment. The most frequently reported stool consistency was 'formed/normal' in 73% of the subjects during Creon treatment and in 18% of the subjects during placebo treatment. The percentage of subjects with 'no flatulence' as most frequently reported rating was 37% during Creon treatment and 26% during placebo treatment. The average number of daily stools (mean±SD) was 1.78±0.78 during Creon treatment and 3.24±1.49 during placebo treatment.
In subjects with PEI due to CP in these studies, the percentage of subjects with 'no abdominal pain' as most frequently reported rating was 55% during Creon treatment and 46% during placebo treatment. The most frequently reported stool consistency was 'formed/normal' in 45% of the subjects during Creon treatment and in 18% of the subjects during placebo treatment. The percentage of subjects with 'no flatulence' as most frequently reported rating was 26% during Creon treatment and 13% during placebo treatment. The average number of daily stools (mean±SD) was 2.07±1.08 during Creon treatment and 2.89±1.55 during placebo treatment.

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.

5.2 Pharmacokinetic properties

Pharmacokinetic data are not available as the enzymes act locally in the gastro-intestinal tract. After exerting their action, the enzymes are digested themselves in the intestine.

5.3 Preclinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

Granules core:	Macrogol 4000
Granules coating:	Hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone 1000
Capsule shell:	Gelatine, iron oxides (red, yellow, black) (E172), titanium dioxide (E171), sodium lauryl sulphate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 25°C, keep the container tightly closed in order to protect from moisture.

Shelf life after first opening of multidose containers**:** 3 months or expiry date whichever comes first.

6.5 Nature and contents of container

-100 or 200 capsules HDPE container with tamper-evident child resistant PP cap.
-20 capsules in aluminium-aluminium blister packs.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special instructions.

7. MANUFACTURER:

Abbott Laboratories GmbH, Hannover, Germany.

8. REGISTRATION HOLDER:

Abbott Medical Laboratories Ltd., Kiryat Atidim, POB 58099, Tel – Aviv

9. REGISTRATION NUMBER:

103-48-28837-00

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