Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Creon 20000 Gastro-resistant Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 300 mg pancreas powder* corresponding to
Lipase 20,000 Ph.Eur. units
Amylase 16,000 Ph. Eur. units
Protease 1,200 Ph.Eur. units

*produced from porcine pancreatic tissue
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard
Bicoloured hard gelatin capsule (size 0 elongated) with brown opaque cap and transparent body filled with brownish gastro-resistant pellets (minimicrospheres).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pancreatic enzyme replacement treatment in pancreatic excocrine insufficiency due to cystic fibrosis or other conditions (e.g. chronic pancreatitis, pancreatectomy or pancreatic cancer).

Creon gastro-resistant capsules are indicated in children, adolescents and adults.

4.2 Posology and method of administration

Posology
The posology aims at individual needs and depends on the severity of the disease and the composition of food.
Therapy should be initiated at the lowest recommended dose and gradually increased with careful monitoring of the patient's response, symptoms and nutritional status. Patients should be instructed not to increase the dosage on their own.
Changes in dosage may require an adjustment period of several days.

Dosing incystic fibrosis
Children:
The strengths of 20,000 and 35,000 Ph. Eur. lipase units may not be suitable for the initiation of therapy in patients under a certain body weight, depending on the age.
In the paediatric age group, dosing is recommended to be started with 1,000 Ph. Eur. units of lipase units per kilogram body weight per meal in children less than four years of age, and with 500 Ph.Eur. units of lipase per kilogram bodyweight per meal in children at the age of four and older.
The dose needed in this population may therefore need to be established with dosage forms containing less lipase units (e.g. 10,000 or 5,000 lipase Ph.Eur. units).

Adolescents and adults:
Weight-based enzyme dosing should begin with 500 Ph. Eur. units of lipase per kilogram bodyweight per meal.

All age groups:
Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status.
Patients should not exceed 2,500 Ph. Eur. units of lipase per kg of body weight per meal or 10,000 Ph. Eur. units of lipase per kilogram body weight per day or 4,000 Ph. Eur. units of lipase per gram fat intake. Fibrosing colonopathy has been reported in patients with cystic fibrosis taking in excess of 10,000 units of lipase per kilogram bodyweight per day (see section 4.4)

Dosing in other conditions associated with exocrine pancreatic insufficiency

Adolescents and adults:

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 25,000 to 80,000 Ph. Eur. units of lipase and half of the individual dose for snacks.

Method of administration

For oral use.

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. for small children or elderly patients), the capsules may be carefully opened and the gastro-resistant pellets added to acidic soft food [pH < 5.5] that does not require chewing, or to 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. The gastro-resistant pellets should not be mixed with water, milk or hot food.

The soft food or liquid mixture should be swallowed immediately without chewing and followed with water or juice to ensure complete ingestion. Crushing and chewing of the gastro-resistant 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.

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

Fibrosing colonopathy

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 Ph. Eur. units of lipase/per kilogram bodyweight per day.

Anaphylactic reactions

Rarely, anaphylactic reactions have been reported with pancreatic enzyme products. If this reaction occurs, patients should be advised to discontinue treatment immediately and seek urgent medical assistance.

To reduce the risk of adverse reactions due to hypersensitivity, caution is advised in patients with allergy to porcine proteins

Irritation to oral mucosa

Oral pain, irritation (stomatitis), bleeding, and ulcer formation in the mouth may occur in case the capsules are chewed and/or kept too long in the mouth. Rinsing the mouth and drinking of a glass of water may help if there are preliminary signs of mouth irritation.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of porcine pancreatic enzymes in pregnant women. There are no data from animal studies with respect to reproductive toxicity (see section 5.3), but animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected.

This medicinal product can be used during pregnancy if necessary to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency

Breastfeeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to porcine pancreatic enzymes is negligible.
Creon can be used during breast-feeding.

Fertility
No effects on fertility are anticipated, since pancreatic enzymes are not absorbed from the gastrointestinal tract.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most important serious adverse reactions observed with pancreatic enzyme medicinal products are anaphylactic reactions (see section 4.4) and fibrosing colonopathy (see section 4.4).

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 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 (cannot be estimated from the available data)**
Immune system disorders				hypersensitivity*, anaphylactic reactions*
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

* The following symptoms of hypersensitivity have been observed during post-approval use:
generalised rash, angioedema, lips swelling, oral mucosa and face swelling, burning and swelling around the eyes, asthmatic complaints. In addition, tachycardia and hypotension have been reported in the condition of an anaphylactic shock.

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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy
and as a result in some cases colonic strictures (see sections 4.2 and 4.4)
Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Digestives, incl. enzymes; Enzyme preparations; ATC code: A09A A02

Mechanism of action:
Creon contains porcine pancreas powder (pancreatin) formulated as gastro-resistant pellets (minimicrospheres) within gelatin capsules.
The capsules dissolve rapidly in the stomach releasing plenty of gastro-resistant 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.

Clinical efficacy:
Overall 33 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. Eleven 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 the placebo-controlled PEI studies, the mean CFA (%) was higher with Creon treatment (83.0%) as compared to placebo (59.1%). 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 340 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

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 repeated dose toxicity. Animal studies show no evidence for absorption of porcine pancreatic enzymes from the gastrointestinal tract after oral administration. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose phthalate
Macrogol 4000
Triethyl citrate
Dimethicone 1000
Cetyl alcohol
Capsule shell:
Gelatin
Iron oxides red, yellow and black (E 172)
Sodium laurylsulphate
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After opening do not store above 25 °C and use within 6 months. Keep the container tightly closed in order to protect from moisture.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottles with PP twist-off closure
50cps, 60cps, 100cps, 120cps, 200cps, 250cps
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/006/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st February 2019
Date of last renewal: 6th September 2023

10 DATE OF REVISION OF THE TEXT

June 2023