Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Creon 40000 Gastro-resistant Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 mg pancreatin equivalent to:

Lipase 40,000 Ph.Eur. units
Amylase 25,000 Ph. Eur. units
Protease 1,600 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
Brown/clear size 00 hard gelatin capsule containing light brown, gastro-resistant granules

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of pancreatic exocrine insufficiency.

4.2 Posology and method of administration

Adults (including the elderly) and children:
Creon 40000 should only be used if the patient requires equal to or more than 40,000 lipase units per meal or snack.
Initially one or two capsules during or immediately after meals. The capsules should be swallowed whole, without crushing or chewing, with enough fluid during or after each meal or snack. Dose adjustments, if required, should be done slowly, with careful monitoring of response and symptomatology.

When swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be carefully opened and the minimicrospheres added to acidic soft food [pH < 5.5] that does not require chewing, or the minimicrospheres will be taken with acidic liquid [pH < 5.5].
This could be apple sauce or yoghurt 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 minimicrospheres or mixing with food or fluid with a pH greater than 5.5 can disrupt the protective enteric coating. This can result in the 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 Creon 40000.

Colonic damage has been reported in patients with cystic fibrosis taking in excess of 10,000 units of lipase/kg/day (see section 4.8).

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 interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

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.

Lactation
No effects on the breast-fed new-borns/infants 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 and 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 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

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 gelatin capsules.

The capsules dissolve rapidly in the stomach releasing plentyof 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.

Clinical efficacy:
Overall 30studies 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. Tenof 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 (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 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.

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

Preclinical data show no relevant acute, subchronic or chronic toxicity. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granules: Macrogol 4000
Cetyl alcohol
Triethyl citrate
Hypromellose phthalate
Dimethicone

Capsule: Gelatin
Iron oxide (E172)
Titanium dioxide (E171)
Sodium lauryl sulphate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.

After first opening: 6 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

HDPE tablet container with polypropylene closure, containing 50 or 100 Gastro-resistant capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/008/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th September 2006
Date of last renewal: 8th September 2011

10 DATE OF REVISION OF THE TEXT

July 2019