Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Creon 10000 Gastro-Resistant Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg Pancreatin equivalent to:
Lipase 10,000 Ph. Eur. units
Amylase 8,000 Ph. Eur. units
Protease 600 Ph. Eur. units
Produced from porcine pancreatic tissue.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant capsules, hard.

Product imported from the UK:
Gastro-resistant capsule, hard.
Size 2 hard gelatin capsules with brown caps and colourless bodies filled with gastro-resistant brown granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pancreatic exocrine deficiency.

4.2 Posology and method of administration

Adults (including the elderly) and children:

Initially one to two capsules with meals. Dose increases, if required, should be added slowly, with careful monitoring of response and symptomatology. The daily dose of pancreatic enzymes for most patients should remain below 2500 units of lipase per kilogram per meal (10,000 units per kilogram per day), and that higher doses should be used with caution and only if quantitative measures demonstrate substantially improved absorption with such treatment. This applies particularly to young children.

It is important to ensure adequate hydration of patients at all times whilst dosing Creon.

The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with acidic fluid [pH<5.5] or acidic soft food [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.. If the granules are mixed with food, it is important that they are taken immediately and the mixture should not be 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 (see 4.8 Undesirable Effects). 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.

Colonic damage has been reported in patients with cystic fibrosis taking high doses of pancreatic enzyme supplements (see 4.8 Undesirable effects).

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.
As with all currently marketed porcine pancreatin products, Creon is sourced from pancreatic tissue from swine used for food consumption. Although the risk that Creon will transmit an infectious agent to humans has been reduced by the testing and inactivation of certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. The presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported, where they have been used for a long time.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of Creon in pregnant women. Animal studies are insufficient with respect to effects on pregnancy and embryonal/foetal development, parturition/ and postnatal development. The potential risk for humans is unknown. Creon should not be used during pregnancy or lactation unless clearly necessary but if required should be used in doses providing adequate nutritional status (see warnings about high dose sections 4.2 and 4.8.).

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 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 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 preferably via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin2; 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: A 09A A02

Creon contains porcine pancreatin formulated as enteric-coated (acid-resistant) minimicrospheres within gelatin capsules.
The capsules dissolve rapidly in the stomach releasing plenty of 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 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 either placebo or baseline 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. In all performed studies, irrespective of etiology, an improvement was also shown in disease specific symptomatology (stool frequency, stool consistency, flatulence).

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 gastrointestinal 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
Macrogol 4000
Hypromellose phthalate
Dimeticone
Triethyl citrate
Cetyl alcohol

Capsule Shell
Gelatin
Red, yellow and black iron oxides (E172)
Titanium dioxide (E171)
Sodium lauril sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C and keep in the original container. Keep the container tightly closed.

6.5 Nature and contents of container

HDPE container with polypropylene cap. Containers hold 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

LTT Pharma Limited
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B98 0RE
UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1562/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th September 2009

Date of Last Renewal: 18th September 2014

10 DATE OF REVISION OF THE TEXT

November 2014