SCHEDULING STATUS S1

1. NAME OF THE MEDICINE

CREON 25 000 hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pancreatic enzyme preparation.

Each hard capsule with enteric-coated CREON Minimicrospheres® pellets contains 300 mg pancreatin, produced from porcine pancreatic tissue, equivalent to

	(Activities in European Pharmacopoeia units)
Lipase	25 000 Ph. Eur. units
Amylase	18 000 Ph. Eur. units
Protease	1 000 Ph. Eur. units.

Sugar free.

Excipients with known effect:

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Bi-coloured hard gelatine capsules size 0 with Swedish orange opaque cap and colourless transparent body filled with brownish pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supplement for pancreatic exocrine insufficiency in paediatric and adult patients, which may be caused by:

- chronic pancreatitis
- cystic fibrosis
- partial pancreatectomy.

4.2 Posology and method of administration

Posology

The dose of pancreatin must be adjusted according to the needs of the individual patient.

Dosing in paediatric and adult patients with cystic fibrosis:

Based upon a recommendation of the Cystic Fibrosis (CF) 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 1 000 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 steatorrhoea and maintenance of good nutritional status.
- Most patients should remain below or should not exceed 10 000 lipase units/kg body weight per day or 4 000 lipase units/gram fat intake.

Dosing in other conditions associated with exocrine pancreatic insufficiency:

Dosage should be individualised 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. If necessary, the dosage can be increased. The capsule should be taken, with liquid, during or immediately after meals.
The capsule should be swallowed whole, without crushing or chewing. Alternatively, the capsule may be opened and the pellets administered without the shell from a spoon. The pellets should not be chewed.

When swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be carefully opened and the pellets added to soft food [pH < 5.5] that does not require chewing, or the pellets can be taken with liquid [pH < 5.5]. Any mixture of the pellets with food or liquids should be used immediately and should not be stored.

It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation.

Children with cystic fibrosis who are taking or have been given in excess of 10 000 units of lipase/kg/day are at risk of developing colon damage.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to pancreatin of porcine origin or to any of the excipients listed in section 6.1.
- Early stages of acute pancreatitis (due to the fact that patients are not allowed to eat for the first two to three days).

4.4 Special warnings and precautions for use

Cases of strictures of the ileo-caecum and large bowel (fibrosing colonopathy) and colitis have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations. Unusual abdominal signs or changes in abdominal symptoms should be reviewed to exclude the possibility of colonic damage especially if the patient is taking in excess of 10 000 units of lipase/kg/day.

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, whereas they have been used for a long time.

Traceability

In order to improve the traceability of a biological medicine, the name of the medicine and the batch number of the medicine used must be clearly documented.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, i.e. it is virtually "sodium-free".

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of CREON in pregnancy has not been established.

Only insufficient data from animal studies are available regarding the effects on pregnancy, embryonal/fetal development, childbirth or postnatal development. The potential risk to humans is therefore not known.

CREON should not be used during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

CREON has no effect or a negligible effect on the ability to drive a vehicle and use machines.

4.8 Undesirable effects

Adverse reactions reported as more than an isolated case is listed below, by system organ class and by frequency.

Frequencies are defined as: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1 000, < 1/100), rare (< 1/1 000).

Immune system disorders

Frequency unknown:	Hypersensitivity (anaphylactic reactions)

Gastrointestinal disorders

Very common:	Abdominal pain.
Common:	Nausea, vomiting, diarrhoea, constipation, satiety and abdominal distention
Uncommon:	Abnormal stool and peri-anal soreness
Frequency unknown:	Stricture of the ileocaecal region and ascending colon (fibrosing colonopathy).

Skin and subcutaneous tissue disorders

Uncommon:	Allergic or hypersensitivity reactions of the skin to pancreatin which includes symptoms like sneezing, lachrymation or skin rashes.
Frequency unknown:	Pruritus and urticaria.

Metabolism and nutrition disorders

Uncommon:	Hyperuricosuria and hyperuricaemia with high doses.

Strictures in the ileocaecal region and the ascending colon (fibrosing colonopathy) have been reported in cystic fibrosis patients receiving high doses of pancreatin preparations (see section 4.4).

Paediatric population

No specific adverse reactions have been observed in the paediatric population. The frequency, nature and severity of the adverse reactions in children with cystic fibrosis were similar to those documented in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of CREON is important. It allows continued monitoring of the benefit/risk balance of CREON. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 11.1 Digestants.

Pharmacotherapeutic group: Digestion products, multi-enzymes.

ATC code: A09AA02.

Pharmacodynamic properties

CREON contains pancreatin produced from porcine pancreas tissue in the form of gastro-resistant pellets in hard gelatine capsules. Pancreatin contains the excretory pancreatic enzymes lipase, alpha-amylase, trypsin, chymotrypsin and other enzymes. Pancreatin also contains additional excipients devoid of enzymatic activity. The non-absorbed portion is broken down and denatured by gastric juices or bacteria. Gastrointestinal availability is determined by enzyme activity and the pharmaceutical form. Lipase enzyme activity and trypsin content are crucial whereas amylolytic activity is significant only in the treatment of cystic fibrosis since food polysaccharides continue to be broken down undisturbed even in cases of chronic pancreatitis.

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.

However, their full therapeutic activity is apparent in the intestinal lumen. As proteins, pancreatic enzymes are mainly digested in the intestine by autolysis or proteolysis as they pass through the gastrointestinal tract and are absorbed as peptides and amino acids.

5.3 Preclinical safety data

There is no evidence of relevant acute, subchronic or chronic toxicity in the preclinical data. No genotoxicity, carcinogenicity or reproduction toxicity studies have been conducted. Pancreatin is not expected to have systemic toxic effects following oral administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gastro-resistant pellets

Cetyl alcohol

Triethyl citrate

Dimethicone 1 000

Macrogol 4 000

Hypromellose phthalate.

Capsule shell

Gelatine

Sodium laurilsulfate

Titanium dioxide (E171)

Iron (III) oxide (E172)

Iron (III) oxide-hydroxide x H_2O (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C, protected from light.

Keep in original packaging until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

White high-density polyethylene (HDPE) containers with tamper evident polypropylene (PP) screw caps, packed in carton boxes in packs of 100, 150 or 300 capsules or Aluminium-aluminium blister strips, packed in carton boxes in packs 20, 50 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

A28/11.1/0645

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIOSATION

Registered: 21 June 1996

10. DATE OF REVISION OF THE TEXT

06 November 2022

NAME AND ADDRESS OF MANUFACTURER

Abbott Laboratories GmbH

Justus-von-Liebig-Str.33

31535 Neustadt

Germany

Country	**Product**	**Pack size**	**Registration number**	**Scheduling status**
Ghana	Creon	100	FDA/SD.173-11951	POM
Malawi	Creon	100	PMPB/PL147/34	POM
Mozambique	Creon	20	A5407	Hospital only
Namibia	Creon 25000	100	04/11.1/1016	NS1
Nigeria	Creon	20	C4-1548	POM
Zimbabwe	Creon	100	2018/16.8.1/5660	PP