

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **CREON MINIMICROSPHERES® MICRO**

lipase/amylase/protease

Granules, 5,000 Ph. Eur. units / 5,100 Ph. Eur. units / 320 Ph. Eur. Units, Oral

Pr **CREON MINIMICROSPHERES® 10**

lipase/amylase/protease

Capsules, 10,000 Ph. Eur. units / 11,200 Ph. Eur. units / 730 Ph. Eur. units, Oral

Pr **CREON MINIMICROSPHERES® 20**

lipase/amylase/protease

Capsules, 20,000 Ph. Eur. units / 22,400 Ph. Eur. units / 1,460 Ph. Eur. units, Oral

Pr **CREON MINIMICROSPHERES® 25**

lipase/amylase/protease

Capsules, 25,000 Ph. Eur. units / 25,500 Ph. Eur. units / 1,600 Ph. Eur. units, Oral

Pr **CREON MINIMICROSPHERES® 35**

lipase/amylase/protease

Capsules, 35,000 Ph. Eur. units / 35,700 Ph. Eur. units / 2,240 Ph. Eur. units, Oral

Pancreatic Enzymes

This product is of porcine origin

A09AA02 MULTIENZYMES (LIPASE, PROTEASE ETC)

BGP Pharma ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

Date of Initial Authorization:
NOV 25, 2013

Date of Revision:
July 11, 2024

® Registered trademark BGP Products Operations GmbH; Licensed use by BGP Pharma ULC, Mylan company.

Submission Control Number: 283477

RECENT MAJOR LABEL CHANGES

N/A	
-----	--

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics (\leq 18 years of age)	4
1.2 Geriatrics (\geq 65 years of age)	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	5
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations	5
4.2 Recommended Dose and Dosage Adjustment	5
4.4 Administration	6
4.5 Missed Dose	7
5 OVERDOSAGE	7
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	7
7 WARNINGS AND PRECAUTIONS	9
7.1 Special Populations	10
7.1.1 Pregnant Women	10
7.1.2 Breast-feeding.....	10
7.1.3 Pediatrics	10
7.1.4 Geriatrics	10
8 ADVERSE REACTIONS	10
8.1 Adverse Reaction Overview	10
8.2 Clinical Trial Adverse Reactions	11
8.2.1 Clinical Trial Adverse Reactions – Pediatrics.....	11
8.5 Post-Market Adverse Reactions.....	11

9	DRUG INTERACTIONS	12
	9.3 Drug-Drug Interactions	12
	9.4 Drug-Food Interactions.....	12
	9.5 Drug-Herb Interactions	12
	9.6 Drug-Laboratory Test Interactions.....	12
10	CLINICAL PHARMACOLOGY	12
	10.1 Mechanism of Action	12
11	STORAGE, STABILITY AND DISPOSAL	13
	PART II: SCIENTIFIC INFORMATION	13
13	PHARMACEUTICAL INFORMATION.....	13
14	CLINICAL TRIALS	13
	14.1 Trial Design and Study Demographics	13
	14.2 Study Results.....	14
15	MICROBIOLOGY	15
16	NON-CLINICAL TOXICOLOGY	15
	PATIENT MEDICATION INFORMATION.....	16

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CREON MINIMICROSPHERES[®] (pancreatin) is indicated in pediatric and adult patients for:

- treatment of pancreatic exocrine insufficiency (PEI) attributed to cystic fibrosis, chronic pancreatitis, or any other medically defined pancreatic disease that might require pancreatic enzyme therapy

including, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- pancreatic surgery
- gastrectomy
- pancreatic cancer
- gastrointestinal bypass surgery (e.g. Billroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)
- Shwachman-Diamond Syndrome
- status after an attack of acute pancreatitis and initiation of enteral or oral feeding

1.1 Pediatrics (≤ 18 years of age)

CREON MINIMICROSPHERES[®] was shown to be effective in pediatric populations with PEI due to cystic fibrosis, independent of age and severity of the disease. The efficacy and safety observed during CREON MINIMICROSPHERES[®] treatment in these patients was similar to that in adult patients (See [8 ADVERSE REACTIONS](#) and [14 CLINICAL TRIALS](#)).

1.2 Geriatrics (≥ 65 years of age)

CREON MINIMICROSPHERES[®] was shown to be similarly effective and safe in elderly patients with PEI as compared to the overall population.

2 CONTRAINDICATIONS

- CREON MINIMICROSPHERES[®] is contraindicated in patients who are hypersensitive to this drug (porcine protein or pancreatic enzymes) or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Pancreatic enzyme products, including CREON MINIMICROSPHERES® have been associated with fibrosing colonopathy (strictures of the ileo-caecum and large intestine) if given at high doses chronically to patients with cystic fibrosis. It is not clear whether this complication is caused by high dosages of pancreatic enzymes, or whether the underlying disease is responsible. Unusual 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 body weight/day or more than 4,000 units of lipase/gram fat intake.
- CREON MINIMICROSPHERES® cannot be substituted (unit for unit) with other pancreatic enzyme products because they are biological products and, therefore, differ in their manufacturing processes, formulations, exact composition, enzymatic activities, stability and bioactivity in the small intestine, so the response of the patient to the estimated dose must be monitored and adjusted as necessary. Special attention to the response of the patient is required during any change in treatment from one pancreatic enzyme product to another.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients with pancreatic exocrine insufficiency should consume a high-calorie, unrestricted fat diet appropriate for their age and clinical status. A nutritional assessment should be performed regularly as a component of routine care, and additionally when the dosage of pancreatic enzyme replacement is made.
- Dosage should be adjusted according to the severity of the pancreatic exocrine enzyme deficiency. The number of capsules or dosage strength given with meals and/or snacks should be estimated by assessing at which dose steatorrhea is minimized and good nutritional status is maintained.
- It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation. Any mixture of the minimicrospheres with food or liquids should be used immediately and should not be stored ([see 7 WARNINGS AND PRECAUTIONS](#)).

4.2 Recommended Dose and Dosage Adjustment

- **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.

Infants

In infants, dosing should be initiated at a dose of 2,000 to 5,000 lipase units for each feeding (usually 120 mL) and adjusted up to a dose no greater than 2,500 lipase units per kilogram per feeding with a maximum daily dose of 10,000 lipase units per kilogram per day.

Children Younger Than 4 Years of Age

In children less than 4 years of age, weight-based enzyme dosing should begin with 1,000 lipase units per kilogram body weight per meal. Usually, half the standard dose is given with snacks.

Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status.

Dosage should not exceed 10,000 lipase units per kilogram body weight per day or 4,000 lipase units/gram fat intake.

Children Older Than 4 Years of Age and Adults

In children older than age 4 years and in adults, weight-based enzyme dosing should begin with 500 lipase units per kilogram body weight per meal. Usually, half the standard dose is given with snacks.

Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status.

Dosage should not exceed 10,000 lipase units per kilogram body weight per day or 4,000 lipase units/gram fat intake.

- **Other Conditions Associated With Pancreatic Exocrine Insufficiency**

Adults

The required dose for a meal ranges from about 25,000 to 80,000 units of lipase and half of the required dose for snacks. Dosage should be individualized according to the degree of maldigestion and the fat content of the meal.

In certain conditions, such as with acute pancreatitis, CREON MINIMICROSPHERES® should be taken when food intake has started again.

4.4 Administration

CREON MINIMICROSPHERES® MICRO is available as gastro-resistant granules (minimicrospheres) dosed with a spoon. It is a specific dosage form with a small minimicrosphere size in particular for use in infants and children unable to swallow capsules. CREON MINIMICROSPHERES® MICRO allows improved individual dosing when low lipase doses are needed for adequate treatment of young children.

CREON MINIMICROSPHERES® 10, 20, 25 and 35 are available as capsules filled with gastro-resistant granules (minimicrospheres). The capsules should be swallowed intact, without

crushing or chewing, with enough fluid during or after each meal or snack.

It is recommended to take the enzymes during or immediately after the meals.

When swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be opened.

The minimicrospheres can be added to small amounts of acidic soft food (pH < 5.5) that do not require chewing such as apple sauce or yogurt, or be taken with acidic liquid (pH < 5.5) such as apple, orange or pineapple juice (see [7 WARNINGS AND PRECAUTIONS](#)). This mixture should not be stored. Alternatively, the minimicrospheres can be mixed with a small amount of milk on a (weaning) spoon and administered to the infant immediately. The minimicrospheres should not be added to a baby's bottle.

The CREON MINIMICROSPHERES®- soft food or fluid mixture should be swallowed immediately without crushing, chewing or holding in the mouth, and followed with water or juice to ensure complete ingestion. Mixtures with food or liquids should be used immediately and not stored, otherwise the protective enteric coating may dissolve.

Care should be taken to ensure that no product is retained in the mouth. 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 (see [7 WARNINGS AND PRECAUTIONS](#)). See [11 STORAGE, STABILITY AND DISPOSAL](#) for further information.

4.5 Missed Dose

If a dose is missed, the patient should take their next dose as usual with their next meal. The patient should not double the dose.

5 OVERDOSAGE

Extremely high doses of pancreatic enzymes have been reported to cause hyperuricosuria and hyperuricaemia. Most cases responded to supportive measures, including discontinuation of the enzyme therapy and ensuring adequate hydration.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Granules, 5,000 / 5,100 / 320 Ph. Eur. units, CREON MINIMICROSPHERES® MICRO	Cetyl alcohol, dimethicone 1000, hypromellose phthalate, macrogol 4000 and triethyl citrate
Oral	Capsules, 10,000 / 11,200 / 730 Ph. Eur. units, CREON MINIMICROSPHERES® 10	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate
Oral	Capsules, 20,000 / 22,400 / 1,460 Ph. Eur. units, CREON MINIMICROSPHERES® 20	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate
Oral	Capsules, 25,000 / 25,500 / 1,600 Ph. Eur. units, CREON MINIMICROSPHERES® 25	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, and triethyl citrate
Oral	Capsules, 35,000 / 35,700 / 2,240 Ph. Eur. units, CREON MINIMICROSPHERES® 35	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, and triethyl citrate

CREON MINIMICROSPHERES® MICRO is available as round, light brown gastro-resistant granules (minimicrospheres). It is available in glass bottles of 20 grams. The bottle comes in a carton box with a polystyrene dosing spoon.

One spoonful (100 mg) contains minimicrospheres corresponding to (Ph.Eur. units): 5,000 units of lipase, 5,100 units of amylase, and 320 units of protease.

CREON MINIMICROSPHERES® 10 is available as capsules with a brown opaque cap and a transparent body, filled with brownish granules. It is available in HDPE bottles of 100 capsules. One capsule contains minimicrospheres corresponding to (Ph. Eur. units) 10,000 units of lipase, 11,200 units of amylase, and 730 units of protease.

CREON MINIMICROSPHERES® 20 is available as capsules with a brown opaque cap and a transparent body, filled with brownish granules. It is available in HDPE bottles of 100 capsules. One capsule contains minimicrospheres corresponding to (Ph. Eur. units) 20,000 units of lipase, 22,400 units of amylase, and 1,460 units of protease.

CREON MINIMICROSPHERES® 25 is available as capsules with a Swedish orange opaque cap and a transparent body, filled with brownish granules. It is available in HDPE bottles of 100 capsules. One capsule contains minimicrospheres corresponding to (Ph. Eur. units) 25,000 units of lipase, 25,500 units of amylase, and 1,600 units of protease.

CREON MINIMICROSPHERES® 35 is available as capsules with a burnt orange cap and a transparent body, filled with brownish granules. It is available in HDPE bottles of 100 capsules. One capsule contains minimicrospheres corresponding to (Ph. Eur. units) 35,000 units of lipase, 35,700 units of amylase, and 2,240 units of protease.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

Should hypersensitivity develop, discontinue medication and treat the patient symptomatically.

It is important to ensure adequate hydration in patients at all times during therapy with pancreatic enzymes.

Capsules should be swallowed whole without crushing or chewing, with enough fluid during or after each meal or snack.

Where swallowing the capsules is difficult, they may be opened. The minimicrospheres can be added to small amounts of acidic soft food (pH < 5.5) that do not require chewing such as apple sauce or yogurt or be taken with acidic liquid (pH < 5.5) such as apple, orange, or pineapple juice (see **4 DOSAGE AND ADMINISTRATION**).

Mixtures with foods or liquids should be used immediately and not stored, otherwise the protective enteric coating may dissolve. 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 to ensure that no product is retained in the mouth.

Any change in pancreatic enzyme replacement therapy (e.g. dose or brand of medication) should be made cautiously and only under medical supervision.

Potential Viral Exposure from the Product Source

As with all currently marketed porcine pancreatin products, CREON MINIMICROSPHERES® is sourced from pancreatic tissue from swine used for food consumption. Although the risk that CREON MINIMICROSPHERES® 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.

Hepatic/Biliary/Pancreatic

CREON MINIMICROSPHERES® may cause hyperuricosuria and hyperuricemia with extremely high doses.

7.1 Special Populations

7.1.1 Pregnant Women

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. CREON MINIMICROSPHERES® should only be used during pregnancy if, in the opinion of the healthcare practitioner, the potential benefits outweigh the potential risks.

If required during pregnancy CREON MINIMICROSPHERES® should be used in doses sufficient to provide adequate nutritional status.

7.1.2 Breast-feeding

There is insufficient data to assess the risks however animal studies suggest no systemic exposure of the breastfeeding woman to pancreatic enzymes. CREON MINIMICROSPHERES® should only be used, in the opinion of the healthcare practitioner, the potential benefits outweigh the potential risks.

If required during breastfeeding CREON MINIMICROSPHERES® should be used in doses sufficient to provide adequate nutritional status.

7.1.3 Pediatrics

There are no special warnings or precautions for use in pediatrics.

7.1.4 Geriatrics

There are no special warnings or precautions for use in elderly patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity.

At extremely high doses, hyperuricosuria and hyperuricaemia have been reported. Fibrosing colonopathy have been reported in cystic fibrosis patients (see **7 WARNINGS AND PRECAUTIONS**).

Allergic or hypersensitivity reactions have been reported.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In clinical trials, more than 900 patients were exposed to CREON MINIMICROSPHERES® (pancreatin).

Table 1 Adverse Reactions Observed During Clinical Trials (with indicated frequencies).

	Frequency
Gastrointestinal	
abdominal pain*	Very common ($\geq 1/10$)
abdominal distention, constipation, diarrhea*, nausea, vomiting.	Common ($\geq 1/100$ to $< 1/10$)
Skin	
rash	Uncommon ($\geq 1/1,000$ to $< 1/100$)
* Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for diarrhea and for abdominal pain.	

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

No specific adverse reactions have been identified in the pediatric population. Frequency, type and severity of adverse reactions were similar in children with cystic fibrosis as compared to adults.

8.5 Post-Market Adverse Reactions

The following adverse events have been reported during post-marketing use. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency.

Gastrointestinal	Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations.
Immune	Hypersensitivity (anaphylactic reactions) Allergic reactions mainly but not exclusively limited to the skin have been observed and additionally identified as adverse reactions during post-approval use.
Skin:	Pruritus, urticaria

9 DRUG INTERACTIONS

9.3 Drug-Drug Interactions

No interaction studies have been performed.

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

When the minimicrospheres reach the small intestine the coating rapidly disintegrates (at pH > 5.5) to release pancreatic enzymes. These enzymes catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrans and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

Absorption

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. Pancreatic enzymes are proteins, as such they undergo proteolytic digestion while passing along the gastrointestinal tract before being absorbed as peptides and amino acids.

Distribution:

No information is available.

Metabolism:

No information is available.

Elimination

No information is available.

11 STORAGE, STABILITY AND DISPOSAL

Store CREON MINIMICROSPHERES® at temperatures not exceeding 25°C in a tightly-closed container to protect from moisture.

Once opened, store at temperatures not exceeding 25°C, keep the container tightly-closed to protect from moisture and use within 6 months.

]

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Pancreatin (synonyms include pancrelipase or pancreatic enzymes)

Chemical name: Not applicable

Molecular formula and molecular mass: Not applicable

Structural formula: Not applicable

Physicochemical properties: The active pharmaceutical ingredient of CREON MINIMICROSPHERES® is pancreatin (also referred to as pancrelipase), an extract from porcine pancreas glands containing enzymes with lipolytic, amylolytic and proteolytic activity.

Pancreatin is a slightly brown amorphous powder, with a faint characteristic odour, partly soluble in water and practically insoluble in alcohol and ether.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Pancreatic Exocrine Insufficiency

Overall 30 studies investigating the efficacy of CREON MINIMICROSPHERES® capsules 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.

Pediatric Population

In cystic fibrosis (CF) the efficacy of CREON MINIMICROSPHERES[®] was demonstrated in 288 pediatric patients covering an age range from newborns to adolescents.

14.2 Study Results

Pancreatic Exocrine Insufficiency

In all randomized, placebo-controlled, efficacy studies, the pre-defined primary objective was to show superiority of CREON MINIMICROSPHERES[®] over placebo on the primary efficacy parameter, the coefficient of fat absorption (CFA).

The CFA determines the percentage of fat that is absorbed into the body taking into account fat intake and fecal fat excretion. In the placebo-controlled pancreatic exocrine insufficiency studies, the mean CFA (%) was higher with CREON MINIMICROSPHERES[®] 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 MINIMICROSPHERES[®] was similar to the mean CFA values for CREON MINIMICROSPHERES[®] in the placebo-controlled studies.

In the placebo-controlled studies, the mean percentage of days without the clinical symptoms of abdominal pain and flatulence was highest in the CREON MINIMICROSPHERES[®] group as compared to placebo. Vice versa, the mean percentage of days with abdominal pain or flatulence of most different intensities (mild, moderate, severe) was lowest with CREON MINIMICROSPHERES[®] compared to placebo. The mean percentage of days with hard and formed/normal stools was highest with CREON MINIMICROSPHERES[®] treatment (6.6% and 59.8%, respectively) compared with placebo (4.8% and 38.1%, respectively). The percentage of days with soft and watery stools was always lowest with CREON MINIMICROSPHERES[®] treatment compared to placebo. In all performed studies, irrespective of etiology, an improvement was also shown in disease specific symptomatology (stool frequency, stool consistency, flatulence).

Pediatric Population

In all studies, the mean end-of-treatment CFA values exceeded 80% on CREON MINIMICROSPHERES[®] comparably in all pediatric age groups.

Additional Data in Pediatric Population for CREON MINIMICROSPHERES[®] MICRO

CREON MINIMICROSPHERES[®] MICRO has been specifically developed to offer a dosage form for infants and children. One baseline-adjusted specific study performed over 8 weeks in 12 infants, aged 1 to 23 months, demonstrated that CREON MINIMICROSPHERES[®] MICRO was effective regarding the improvement of CFA and stool fat excretion as well as fecal energy loss after two weeks of treatment. The analysis of the results showed that the primary efficacy parameter, CFA, significantly increased from a baseline mean of 58.0% to a mean of 84.7% (mean increase 26.7%, $p = 0.0013$, paired t-test). Height and weight increased, but the weight

for height percentile remained nearly constant and close to 100%.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Non-clinical data show no relevant acute, subchronic or chronic toxicity. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **CREON MINIMICROSPHERES**[®]

pancreatin

Read this carefully before you start taking **CREON MINIMICROSPHERES**[®] and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CREON MINIMICROSPHERES**[®].

Serious Warnings and Precautions

- A rare bowel condition called “fibrosing colonopathy”, where your gut is narrowed, has been reported in patients with cystic fibrosis taking high doses of pancreatic enzymes. As a precaution, consult your doctor if you experience any unusual abdominal symptoms or any change in abdominal symptoms, especially if you are taking more than 10,000 units of lipase/kg body weight/day or more than 4,000 units of lipase/gram fat intake.

What is **CREON MINIMICROSPHERES**[®] used for?

- **CREON MINIMICROSPHERES**[®] is used by children and adults for the treatment of pancreatic exocrine insufficiency attributed to cystic fibrosis, chronic pancreatitis, or any other medically defined pancreatic disease that might require pancreatic enzyme therapy, as determined by the doctor, including but not limited to cystic fibrosis (a rare inherited disorder), acute pancreatitis (an attack of acute inflammation of the pancreas) or chronic pancreatitis (chronic inflammation of the pancreas), pancreatic surgery/pancreatectomy, gastrectomy (surgical removal of all or part of the stomach), pancreatic cancer, gastrointestinal bypass surgery (e.g. Billroth II gastroenterostomy) (surgical opening between the stomach wall and intestine), ductal obstruction of the pancreas or common bile duct (e.g. from tumor) and Shwachman-Diamond Syndrome (genetic disorder).]

How does **CREON MINIMICROSPHERES**[®] work?

CREON MINIMICROSPHERES[®] is intended as replacement therapy when your pancreas, which produces enzymes necessary to digest fat, protein and sugars, has stopped functioning or is not functioning as it should be. The medical term for this condition is pancreatic exocrine insufficiency. Symptoms of pancreatic exocrine insufficiency include steatorrhea (excess of fat in stools).

CREON MINIMICROSPHERES[®] contains an enzyme mixture that helps you digest food. The enzymes are taken from pig pancreas glands.

CREON MINIMICROSPHERES[®] contains small granules which slowly release the pancreatic enzymes in your gut (gastro-resistant granules, called minimicrospheres).

The enzymes in **CREON MINIMICROSPHERES**[®] work by digesting food as it passes through the gut. You should take **CREON MINIMICROSPHERES**[®] during or after a meal or snack. This will allow the enzymes to mix thoroughly with the food.

What are the ingredients in CREON MINIMICROSPHERES®?

Medicinal ingredients: Pancreatin [a mixture of pancreatic enzymes (lipase, amylase and protease)].

Non-medicinal ingredients:

CREON MINIMICROSPHERES® MICRO: cetyl alcohol, dimethicone 1000, hypromellose phthalate, macrogol 4000 and triethyl citrate.

CREON MINIMICROSPHERES® 10 and 20: cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate.

CREON MINIMICROSPHERES® 25 and 35: cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate and triethyl citrate.

CREON MINIMICROSPHERES® comes in the following dosage forms:

CREON MINIMICROSPHERES® MICRO: round, light brown gastro-resistant granules (minimicrospheres), 5,000 Ph. Eur. units of lipase, 5,100 Ph. Eur. units of amylase, and 320 Ph. Eur. units of protease per spoonful (100 mg).

CREON MINIMICROSPHERES® 10: brown and transparent capsules, contain gastro-resistant granules (minimicrospheres) with 10,000 Ph. Eur. units of lipase, 11,200 Ph. Eur. units of amylase, and 730 Ph. Eur. units of protease per capsule.

CREON MINIMICROSPHERES® 20: brown and transparent capsules contain gastro-resistant granules (minimicrospheres) with 20,000 Ph. Eur. units of lipase, 22,400 Ph. Eur. units of amylase, and 1,460 Ph. Eur. units of protease per capsule.

CREON MINIMICROSPHERES® 25: Swedish orange and transparent capsules contain gastro-resistant granules (minimicrospheres) with 25,000 Ph. Eur. units of lipase, 25,500 Ph. Eur. units of amylase, and 1,600 Ph. Eur. units of protease per capsule.

CREON MINIMICROSPHERES® 35: burnt orange and transparent capsules contain gastro-resistant granules (minimicrospheres) with 35,000 Ph. Eur. units of lipase, 35,700 Ph. Eur. units of amylase, and 2,240 Ph. Eur. units of protease per capsule.

Do not use CREON MINIMICROSPHERES® if:

- you have known hypersensitivity or allergy to porcine protein, pancreatic enzymes or to any other ingredient in this product.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CREON MINIMICROSPHERES®. Talk about any health conditions or problems you may have, including if you:

- are allergic to pork (pig) products
- have a history of intestinal blockage of your intestines or scarring or thickening of your bowel wall (fibrosing colonopathy)
- have any other medical condition

- are pregnant or might become pregnant
- are breast-feeding or plan to breast-feed
- have trouble swallowing capsules

Other warnings you should know about:

CREON MINIMICROSPHERES[®] and other pancreatic enzyme products are made from the pancreas of pigs, the same pigs used for food. These pigs may carry viruses. Although it has never been reported, it may be possible for a person to get a viral infection from taking pancreatic enzyme products that come from pigs.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

No interaction studies have been performed with CREON MINIMICROSPHERES[®].

How to take CREON MINIMICROSPHERES[®]:

- Do not switch CREON MINIMICROSPHERES[®] with any other pancreatic enzyme product without first talking to your doctor.
- Always take CREON MINIMICROSPHERES[®] during or after a meal or a snack. This will allow the enzymes to mix thoroughly with the food and digest it as it passes through the gut.
- Swallow the capsules whole.
- Do not crush or chew the capsules.
- If it is difficult to swallow the capsules, open them carefully and add the granules to a small amount of soft acidic food or mix them with acidic liquids. Acidic soft foods could for example be apple sauce or yogurt. Acidic liquids could be apple, orange or pineapple juice. Alternatively the minimicrospheres can be mixed with a small amount of milk on a (weaning) spoon and given to the infant immediately. The minimicrospheres should not be added to a baby's bottle.
- Swallow the mixture immediately, without crushing or chewing and drink some water or juice. Mixing with non-acidic foods, or crushing or chewing of the granules may cause irritation in your mouth or change the way CREON MINIMICROSPHERES[®] works in your body.
- Do not hold CREON MINIMICROSPHERES[®] capsules or its content in your mouth.
- Do not store the mixture.
- As a general rule, drink plenty of liquid every day.

Usual dose:

Your dose is measured in 'lipase units'. Lipase is one of the enzymes in CREON MINIMICROSPHERES[®].

Different strengths of pancreatic enzymes may contain different amounts of lipase.

Always follow your doctor's advice on how much CREON MINIMICROSPHERES[®] to take.

Your doctor will adjust your dose to suit you. It will depend on:

- your illness
- your weight
- your diet
- how much fat is in your stools.

If you still have fatty stools or other stomach or gut problems (gastrointestinal symptoms), talk to your doctor as your dose may need to be adjusted.

Cystic fibrosis

- The usual starting dose for infants is 2,000 to 5,000 lipase units for each feeding (usually 120 mL). CREON MINIMICROSPHERES® MICRO can be given to infants.
- The usual starting dose for children under 4 years of age is 1,000 lipase units per kilogram body weight per meal. Usually, half the standard dose is given with snacks.
- The usual starting dose for children 4 years of age and over, adolescents and adults is 500 lipase units per kilogram body weight per meal. Usually, half the standard dose is given with snacks.

Other problems with your pancreas

- The usual dose for a meal is between 25,000 and 80,000 lipase units.
- The usual dose for a snack is half the dose for a meal.
- In certain conditions, such as with acute pancreatitis, Creon Minimicrospheres should be taken when food intake has started again.

Overdose:

If you know or suspect that you have taken more of this product than you normally do, or notice any unusual symptoms, contact your doctor or nearest hospital emergency department immediately. Ensure that you are adequately hydrated during this time by drinking plenty of fluids.

Extremely high doses of pancreatic enzymes have sometimes caused too much uric acid in the urine (hyperuricosuria) and in the blood (hyperuricaemia).

If you think you, or a person you are caring for, have taken too much CREON MINIMICROSPHERES®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of this medication has been missed, take your next dose at the usual time, with your next meal. Do not try to make up for the dose that you have missed.

What are possible side effects from using CREON MINIMICROSPHERES®?

These are not all the possible side effects you may have when taking CREON MINIMICROSPHERES®. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects were seen during studies in patients taking CREON MINIMICROSPHERES®.

- | | |
|--------------|--|
| Very common: | Pain in stomach (abdomen) |
| Common: | Bloating (abdominal distention), constipation, diarrhea*, nausea, vomiting |
| Uncommon: | Rash |

Frequency unknown: Severe itching (pruritus) and hives (urticaria)

* These may be due to the condition you are taking CREON MINIMICROSPHERES® for. During studies, the number of patients taking CREON MINIMICROSPHERES® who had pain in their stomach or diarrhea was similar or lower than in patients not taking CREON MINIMICROSPHERES®.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN FREQUENCY			
Allergic reactions (anaphylactic reactions)			
- trouble breathing		√	√
- swollen lips			
Fibrosing colonopathy (abnormal narrowing of the gut)		√	√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at temperatures not exceeding 25°C in a tightly-closed container to protect from moisture.

Once opened, store at temperatures not exceeding 25°C, keep the container tightly-closed to protect from moisture and use within 6 months.

Keep out of reach and sight of children.

If you want more information about CREON MINIMICROSPHERES®:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.mylan.ca], or by calling 1-844-596-9526.

This leaflet was prepared by BGP Pharma ULC.

Last Revised: July 11, 2024