PRODUCT MONOGRAPH

Pr CREON MINIMICROSPHERES®

lipase/amylase/protease

Pr CREON MINIMICROSPHERES® MICRO

lipase/amylase/protease
Granules (5,000 Ph. Eur. units / 5,100 Ph. Eur. units / 320 Ph. Eur. units)

Pr CREON MINIMICROSPHERES® 10

lipase/amylase/protease
Capsules (10,000 Ph. Eur. units / 11,200 Ph. Eur. units / 730 Ph. Eur. units)

Pr CREON MINIMICROSPHERES® 20

lipase/amylase/protease
Capsules (20,000 Ph. Eur. units / 22,400 Ph. Eur. units / 1,460 Ph. Eur. units)

Pr CREON MINIMICROSPHERES® 25

lipase/amylase/protease
Capsules (25,000 Ph. Eur. units / 25,500 Ph. Eur. units / 1,600 Ph. Eur. units)

Pr CREON MINIMICROSPHERES® 35

lipase/amylase/protease
Capsules (35,000 Ph. Eur. units / 35,700 Ph. Eur. units / 2,240 Ph. Eur. units)

Pancreatic Enzymes
This product is of porcine origin

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Etobicoke, Ontario
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Submission Control No: 226040 Date of Approval: December 5, 2019

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CREON MINIMICROSPHERES®

pancreatin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Non-medicinal Ingredients
Oral	Granules / CREON MINIMICROSPHERES® MICRO	Cetyl alcohol, dimethicone 1000, hypromellose phthalate, macrogol 4000 and triethyl citrate
Oral	Capsules / CREON MINIMICROSPHERES® 10	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate
Oral	Capsules / CREON MINIMICROSPHERES® 20	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate
Oral	Capsules / CREON MINIMICROSPHERES® 25	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate
Oral	Capsules / CREON MINIMICROSPHERES® 35	Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate

INDICATIONS AND CLINICAL USE

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

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.

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 **ADVERSE REACTIONS** and **CLINICAL TRIALS**).

CONTRAINDICATIONS

- Patients who have known hypersensitivity to porcine protein, pancreatic enzymes or to any other ingredient in this product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Pancreatic enzyme products, including CREON MINIMICROSPHERES® (pancreatin) 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.**

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 **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.

Special Populations

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.

Nursing Women

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.

Pediatrics (≤ 18 years of age):

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

Geriatrics (> 65 years of age):

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

ADVERSE REACTIONS

Adverse Drug 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 **WARNINGS AND PRECAUTIONS**).

Allergic or hypersensitivity reactions have been reported.

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.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

The following adverse reactions have been observed during clinical trials with the below indicated frequencies.

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

Post-Market Adverse Drug 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 Disorders:	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 System Disorders:	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 and Subcutaneous Tissue Disorders:	Pruritus, urticaria

DRUG INTERACTIONS

Drug-Drug Interactions

No interaction studies have been performed.

DOSAGE AND ADMINISTRATION

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 **WARNINGS AND PRECAUTIONS**).

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.

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.

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 **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 **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

ACTION AND CLINICAL PHARMACOLOGY

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 dextrins 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.

Pharmacokinetics

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.

Excretion

No information is available.

STORAGE AND STABILITY

Store CREON MINIMICROSPHERES® (pancreatin) at temperatures not exceeding 25ºC in a tightly-closed container to protect from moisture.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

CREON MINIMICROSPHERES® MICRO

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.

Listing of Non-Medicinal Ingredients

CREON MINIMICROSPHERES® MICRO contains the following non-medicinal ingredients: cetyl alcohol, dimethicone 1000, hypromellose phthalate, macrogol 4000 and triethyl citrate.

CREON MINIMICROSPHERES® 10

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.

Listing of Non-Medicinal Ingredients

CREON MINIMICROSPHERES® 10 contains the following non-medicinal ingredients: cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate.

CREON MINIMICROSPHERES® 20

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.

Listing of Non-Medicinal Ingredients

CREON MINIMICROSPHERES® 20 contains the following non-medicinal ingredients: Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate.

CREON MINIMICROSPHERES® 25

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.

Listing of Non-Medicinal Ingredients

CREON MINIMICROSPHERES® 25 contains the following non-medicinal ingredients: cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate.

CREON MINIMICROSPHERES® 35

CREON MINIMICROSPHERES® 35 is available as capsules with a red brown 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.

Listing of Non-Medicinal Ingredients

CREON MINIMICROSPHERES® 35 contains the following non-medicinal ingredients: Cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate**.**

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

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.

CLINICAL TRIALS

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.

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

TOXICOLOGY

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

REFERENCES

1. Borowitz DS, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. Journal of Pediatric Gastroenterology Nutrition 2002 Sep; 35:246-259.

2. Borowitz D, Robinson KA, Rosenfeld M. et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009; 155(6, suppl):S73-S93.

3. Bruno MJ, Haverkort EB, Tijssen GP, et al. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patient with unresectable cancer of the pancreatic head region. Gut 1998; 42:92-96.

4. Carroccio A, Guarino A, Zuin G, Verghi F, Berni Canani R, Fontana M, et al. Efficacy of oral pancreatic enzyme therapy for the treatment of fat malabsorption in HIV-infected patients. Ailment Pharmacol Ther. 2001; 15:1619-1625.

5. Colombo C, Fredella C, Russo MC, et al. Efficacy and tolerability of Creon for children in infants and toddlers with PEI caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas 2009; 38(6):693-699.

6. Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Current Gastroenterology Reports 2007; 9:116-122.

7. Dominguez-Munoz JE, Garcia JI, Iglesias Rey M, Figueiras A and Vilarino-Insua M. Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomised, three-way crossover study. Aliment Pharmacol Ther 2005; 21:993-1000.

8. Graff GR, Maguiness K, McNamara J, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomised, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther 2010; 32(1):89-103.

9. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. Gut 2005; 54:(suppl VI) vi1-vi28.

10. Littlewood JM, Connett GJ, Struckmeier SS, Henniges F and the Creon® 40,000 study group. A 2-year post-authorisation safety study of high-strength pancreatic enzyme replacement therapy (pancreatin 40,000) in cystic fibrosis. Expert Opin Drug Saf 2011; 10(2):197-203.

11. Munck A, Duhamel JF, Lamireau T, et al. Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cystic Fibros 2009; 8(1):14-18.

12. Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon® 10 capsule) on steatorrhoea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas 2006; 33(2):156-162. Erratum in: Pancreas 2007; 34(1):174.

13. Sikkens ECM, Cahen DL, Kuipers KJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. Best Pract Res Clin Gastroenterol 2010; 24:337-347.

14. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. Journal of the American Dietetic Association 2008; 108:832-839.

15. Stern RC, Eisenberg JD, Wagener JS, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhoea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol 2000; 95(8):1932-1938.

16. Thorat V, Reddy N, Bhatia S, et al. Randomised clinical trial: the efficacy and safety of pancreatin enteric-coated minimicrospheres (Creon 40000 MMS) in patients with pancreatic exocrine insufficiency due to chronic pancreatitis - a double-blind, placebo-controlled study. Aliment Pharmacol Ther 2012; 36:426-436.

17. Toouli J, Biankin AV, Oliver MR, Pearce CB, Wilson JS, Wray NH. Management of pancreatic exocrine insufficiency: Australasian Pancreatic Club recommendations. Med J Aust 2010; 193(8):461-467.

18. Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of CREON 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009; 8(6):370-377.

19. Whitcomb DC, Lehman GA, Vasileva G, et al. Pancrelipase delayed-release capsules (Creon®) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol 2010 Oct; 105(10):2276-86.

PART III: CONSUMER INFORMATION

PrCREON MINIMICROSPHERES®

(pancreatin)

This leaflet is PART III of a three-part "Product Monograph" published when CREON MINIMICROSPHERES® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about CREON MINIMICROSPHERES®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is 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).

What it does:

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.

When it should not be used:

CREON MINIMICROSPHERES® should not be used:

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

What the medicinal ingredient is:

The medicinal ingredient in CREON MINIMICROSPHERES® is pancreatin. CREON MINIMICROSPHERES® is a mixture of pancreatic enzymes (lipase, amylase and protease).

What the important non-medicinal ingredients are:

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

CREON MINIMICROSPHERES® 10, 20, 25 and 35 contains cetyl alcohol, dimethicone 1000, gelatin, hypromellose phthalate, iron oxides, macrogol 4000, sodium lauryl sulphate, titanium dioxide and triethyl citrate.

What dosage forms it comes in:

CREON MINIMICROSPHERES® MICRO is available as round, light brown gastro-resistant granules (minimicrospheres), with 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 is available as brown and transparent capsules. They 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 is available as brown and transparent capsules. They 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 is available as Swedish orange and transparent capsules. They 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 is available as red brown and transparent capsules. They 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.

WARNINGS AND PRECAUTIONS

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.

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.

BEFORE you use CREON MINIMICROSPHERES® talk to your doctor or pharmacist 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

Talk to your doctor about all the drugs you are taking before taking CREON MINIMICROSPHERES®.

INTERACTIONS WITH THIS MEDICATION

No interaction studies have been performed.

PROPER USE OF THIS MEDICATION

Do not switch CREON MINIMICROSPHERES® with any other pancreatic enzyme product without first talking to your doctor.

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.

When to take CREON MINIMICROSPHERES®

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.

How to take CREON MINIMICROSPHERES®

- 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.

How long to take CREON MINIMICROSPHERES® for

Take CREON MINIMICROSPHERES® until your doctor tells you to stop. Many patients will need to take CREON MINIMICROSPHERES® for the rest of their lives.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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).

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, CREON MINIMICROSPHERES® can cause side effects, although not everybody gets them. 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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown frequency	Allergic reactions (anaphylactic reactions) - trouble breathing - swollen lips		√	√
	Fibrosing colonopathy (abnormal narrowing of the gut)		√	√

This is not a complete list of side effects. For any unexpected effects while taking CREON MINIMICROSPHERES®, contact your doctor or pharmacist.

Tell your healthcare professional if you have any side effect that bothers you or does not go away.

HOW TO STORE IT

Keep out of the reach of children.

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

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:**
  www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at
http://www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The most recent version of this document plus the full Product Monograph, prepared for health professionals can be found at:

www.mylan.ca
or by contacting the sponsor, BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6 at:
1-844-596-9526

This leaflet was prepared by BGP Pharma ULC.

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