PRODUCT MONOGRAPH

COTAZYM®

Pancrelipase Preparations

Cotazym® Capsules:
10,000 USP units (Lipase activity) / 40,000 USP units (amylase activity) / 35,000 USP units (protease activity)
Cotazym® ECS 8 Capsules:
10,800 USP units (Lipase activity) / 42,000 USP units (amylase activity) / 45,000 USP units (protease activity)
Cotazym® ECS 20 Capsules:
25,000 USP units (Lipase activity) / 100,000 USP units (amylase activity) / 100,000 USP units (protease activity)

USP

Enzymes–Digestant

Organon Canada Inc.
16766 route Transcanadienne
Kirkland QC Canada H9H 4M7
www.Organon.ca

Date of Preparation:
March 30, 2021

Submission Control No: 249338

Table of Contents

COTAZYM®

(Pancrelipase Preparations)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Cotazym® Capsule/ 10,000/40,000/35,000 USP units (lipase/amylase/protease) Cotazym® ECS 8 Enteric coated capsule/ 10,800/42,000/45,000 USP units (lipase/amylase/protease) Cotazym® ECS 20 Enteric coated capsule/ 25,000/100,000/100,000 USP units (lipase/amylase/protease)	Cornstarch, pregelatinized starch, sucrose. ***For a complete listing see Dosage Forms, Composition and Packaging section.***

DESCRIPTION
COTAZYM® is a pancreatic enzyme preparation consisting of pancrelipase, an extract derived from porcine pancreatic glands. Pancrelipase contains multiple enzyme classes, including porcine-derived lipases, proteases, and amylases.

INDICATIONS AND CLINICAL USE
COTAZYM® (pancreatic enzymes) is indicated for the treatment of pancreatic insufficiency attributed to cystic fibrosis, chronic pancreatitis, or any other medically defined pancreatic disease that might require pancreatic enzyme therapy.

Geriatrics (> 65 years of age):
Clinical studies of COTAZYM® in geriatric patients have not been conducted.

Pediatrics (<18 years of age):
Post approval, several clinical studies have been conducted supporting the safe and effective use of COTAZYM® in pediatric patients with established pancreatic insufficiency.

CONTRAINDICATIONS
- Patients who have known hypersensitivity to porcine protein, pancreatic enzymes or any excipients.

- During acute pancreatitis or the acute exacerbation of chronic pancreatitis.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Pancreatic enzyme products, including COTAZYM® 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.

COTAZYM® 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.

The capsules should not be chewed or crushed because the coating (that is formulated to deliver the enzymes to the correct place in the intestines) will be destroyed. If the capsules are opened and the contents shaken onto soft food, it should not have an alkaline pH (e.g., milk, custard, ice cream, other dairy products) because the enteric coating will dissolve prematurely and limit absorption (see **DOSAGE and ADMINISTRATION**).

To avoid irritation of the mouth, lips and tongue, opened capsules should be swallowed immediately before meals or snacks to minimize the probability of retaining some of the drug in the mouth. Proteolytic enzymes present in COTAZYM®, when retained in the mouth, may begin to digest the mucous membranes and cause ulcerations. Therefore, in the event that capsules are opened for sprinkling the powder on food or drink or for any other reason, care should be taken so that powder is not spilled on hands or inhaled since it may prove irritating to the skin or mucous membranes.

A proper balance between fat, protein and starch intake must be maintained to avoid temporary indigestion.

Any change in pancreatic enzyme replacement therapy (e.g., dose or brand of medication) should be made cautiously and only under medical supervision. Pancreatic extracts can form insoluble complexes with folic acid, resulting in folic acid deficiency.

Pancreatic enzyme replacement therapy, in patients in whom both the exocrine and endocrine pancreas are not functioning, may interact with insulin therapy of diabetes. High-dose pancreatin mini-microspheres improve but do not fully normalize fat absorption, possibly because of the residual influence of diabetes and malnutrition on absorptive function. Since control of blood glucose may be brittle in malnourished, insulin-dependent patients, enzyme adjustment should be carefully supervised in-hospital to avoid exacerbation of pancreatic dysfunction.

Potential Viral Exposure from the Product Source
As with all currently marketed porcine pancreatin products, COTAZYM® is sourced from pancreatic tissue from swine used for food consumption. Although the risk that COTAZYM® 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.

Carcinogenesis and Mutagenesis
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Hepatic/Biliary/Pancreas
COTAZYM® (or pancreatic enzyme products) may cause hyperuricosuria and hyperuricemia with very high doses. Also at very high doses, perianal irritation and inflammation may occur.

Special Populations

Pregnant Women:
There is insufficient data from the use of COTAZYM® in pregnant women. Although some animal studies have been conducted, no adequate, well controlled studies have been conducted in pregnant women. COTAZYM® should only be used during pregnancy if, in the opinion of the physician, the potential benefits outweigh the potential risks.

Nursing Women:
There is insufficient data to assess the risks. Pancreatic enzymes act locally in the gastrointestinal tract, and cannot be absorbed in their intact state systemically. Some of the constituent amino acids and nucleic acids are probably absorbed with dietary protein. However, the possibility of protein constituents being secreted into breast milk cannot be excluded. COTAZYM® should be used only if, in the opinion of the physician, the potential benefits outweigh the potential risks.

Pediatrics (<18 years of age)
Post approval, several clinical studies have been conducted supporting the safe and effective use of COTAZYM in pediatric patients with established pancreatic insufficiency.

Geriatrics (> 65 years of age):
Clinical studies of COTAZYM® in geriatric patients have not been conducted.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most common adverse reactions are abdomenal discomfort and pain. Other gastrointestinal reactions are less common and include abnormal stool and diarrhea. Nausea and vomiting have been reported, but these are not common. With high doses, perianal irritation and inflammation have been reported (see **WARNINGS and PRECAUTIONS**).

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 of the skin have been reported.

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.

The following adverse reactions have been observed for pancreatic enzyme products 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 for pancreatic enzyme products. 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

There have been no reports of interactions with other drugs or other forms of interaction.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients with pancreatic 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 exocrine pancreatic 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.

The capsules should be taken orally with each meal or snack. They can either be swallowed whole, preferably with some fluid, or can be opened and the contents sprinkled on food or drink. If the capsules are opened and the contents shaken onto soft food, it should not have an alkaline pH (e.g., milk, custard, ice cream, other dairy products) because the enteric coating will dissolve prematurely and limit absorption (see **WARNINGS and PRECAUTIONS**).

Take the medication immediately. Do not store it to be taken later.

Recommended Dose and Dosage Adjustment

Average dose: 1 to 3 capsules with each meal and 1 capsule with each snack as directed by physician.

OVERDOSAGE

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

Extremely high dosages 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

COTAZYM® delivers predictable biologically active pancreatic enzymes (lipase, amylase and protease) into the duodenum. The enzymes catalyze the breakdown of fats into glycerol and fatty acids, proteins into proteases and derivatives, and starch into dextrins and sugars.

STORAGE AND STABILITY

Store in a tightly closed container at a temperature not exceeding 25ºC. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Not applicable for COTAZYM®

DOSAGE FORMS, COMPOSITION AND PACKAGING

COTAZYM®: Each clear capsule contains: lipase activity of 10,000 USP units, amylase activity of 40,000 USP units and protease activity of 35,000 USP units. Nonmedicinal ingredients: gelatin, magnesium stearate, opacode S-1-4126 (print ink), precipitated calcium carbonate, pregelatinized starch, silicon dioxide, sodium lauryl sulphate and talc. Tartrazine-free. Bottles of 100 and 1,000.

COTAZYM® ECS 8: Each clear capsule with enteric coated microspheres contains: lipase activity of 10,800 USP units, amylase activity of 42,000 USP units and protease activity of 45,000 USP units. Nonmedicinal ingredients: cellulose acetate phthalate, colloidal silicon dioxide, cornstarch, diethyl phthalate, gelatin, opacode S-1-4126 (print ink), propylene glycol, propylene glycol monostearate, povidone, silicon dioxide, sodium lauryl sulphate, sucrose and talc. Tartrazine-free. Bottles of 100 and 500.

COTAZYM® ECS 20: Each clear orange capsule with enteric coated microspheres contains: lipase activity of 25,000 USP units, amylase activity of 100,000 USP units and protease activity of 100,000 USP units. Nonmedicinal ingredients: cellulose acetate phthalate, colloidal silicon dioxide, cornstarch, D&C Yellow No. 10, diethyl phthalate, FD&C Red No. 40, gelatin, opacode

S-1-4126 (print ink), propylene glycol, propylene glycol monostearate, povidone, silicon dioxide, sodium lauryl sulphate, sucrose and talc. Tartrazine-free. Bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Pancrelipase

Chemical name: Not Applicable

Molecular formula and molecular mass: Not Applicable

Structural formula: Not Applicable

Physicochemical properties:

COTAZYM® is a pancreatic enzyme preparation consisting of pancrelipase, an extract derived from porcine pancreatic glands. Pancrelipase contains multiple enzyme classes, including porcine-derived lipases, proteases, and amylases. Pancreatin is a cream colored granular powder with a faint, characteristic meaty odor.

CLINICAL TRIALS
Information not available for COTAZYM®.

DETAILED PHARMACOLOGY
Information not available for COTAZYM®.

MICROBIOLOGY
Information not available for COTAZYM®.

TOXICOLOGY
Information not available for COTAZYM®.

REFERENCES

PART III: CONSUMER INFORMATION

COTAZYM®

(Pancrelipase Preparations)

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

ABOUT THIS MEDICATION

What the medication is used for:

COTAZYM® is used for the treatment of pancreatic 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.

What it does:

COTAZYM® is a prescription medicine used to treat people who cannot digest food normally because their pancreas does not make enough enzymes due to cystic fibrosis, swelling of the pancreas that lasts a long time (chronic pancreatitis), removal of some or all of the pancreas (pancreatectomy), or other conditions.

COTAZYM® may help your body use fats, proteins, and sugars from food. It contains a mixture of digestive enzymes including lipases, proteases, and amylases from pig pancreas.

When it should not be used:

COTAZYM® should not be used if you:

● have known hypersensitivity to porcine protein, pancreatic enzymes or any excipients; and/or during acute pancreatitis or the acute exacerbation of chronic pancreatitis

What the medicinal ingredient is:

Lipase, amylase, protease, mixed conjugated bile salts and cellulose.

What the important nonmedicinal ingredients are:

Capsule print ink, cellulose acetate phthalate, colloidal silicon dioxide, cornstarch, diethyl phthalate, gelatin, magnesium stearate, povidone, precipitated calcium carbonate, pregelatinized starch, propylene glycol, silicon dioxide, sodium lauryl sulphate, sucrose, talc, titanium dioxide, red food dye (FD&C Red No. 40), yellow food dye (D&C Yellow No. 10).

What dosage forms it comes in:

Capsules containing 10,000 units of lipase, 40,000 units of amylase and 35,000 units of protease (Cotazym®).

Enteric coated capsules containing 10,800 units of lipase, 42,000 units of amylase and 45,000 units of protease (Cotazym® ECS 8).

Enteric coated capsules containing 25,000 units of lipase, 100,000 units of amylase and 100,000 units of protease (Cotazym® ECS 20).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

COTAZYM® may increase your chance of having a rare bowel disorder called fibrosing colonopathy. This condition is serious and may require surgery. The risk of having this condition may be reduced by following the dosing instructions that your doctor gave you.

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

BEFORE you use COTAZYM® talk to your doctor or pharmacist if you:

- Are allergic to pork (pig) products
- Have a history of intestinal blockage or scarring or thickening of your bowel wall (fibrosing colonopathy)
- Have gout, kidney disease, or high blood uric acid (hyperuricemia or hyperuricosuria)
- Have trouble swallowing capsules
- Have any other medical condition
- Are pregnant, plan to become pregnant, are breast-feeding or plan to breast-feed. It is not known if COTAZYM® will harm your unborn baby or if COTAZYM® passes into your breast milk. Enzymes such as COTAZYM® are broken down in your gastrointestinal tract, and thus are not absorbed into the body as intact enzymes.

Tell your doctor all the medications that you take, including prescription and nonprescription drugs, natural health products, vitamins and herbs.

Talk to your doctor if the following occurs while taking COTAZYM®:

- stomach area (abdominal) pain
- bloating
- trouble passing stool (having bowel movements)
- nausea, vomiting, or diarrhea

Take COTAZYM® exactly as prescribed. Do not take more or less COTAZYM® than directed by your doctor.

INTERACTIONS WITH THIS MEDICATION

As with all other pancrelipase lipase preparations, interactions with COTAZYM® is possible. Therefore, tell your doctor all

the medications that you take, including prescription and nonprescription drugs, natural health products, vitamins and herbs.

PROPER USE OF THIS MEDICATION

- Take COTAZYM® exactly as prescribed by your healthcare provider.
- You should not switch COTAZYM® with any other pancreatic enzyme product without first talking to your doctor.
- Do not take more capsules in a day than the number your doctor tells you to take (total daily dose).
- Always take COTAZYM® with a meal or snack and enough liquid to swallow COTAZYM® completely. If you eat a lot of meals or snacks in a day, be careful not to go over your total daily dose.
- If the capsules are opened, try to avoid sprinkling them on dairy products such as milk, custard or ice cream.
- Your doctor may change your dose based on the amount of fatty foods you eat or based on your weight.
- Do not crush or chew COTAZYM® capsules or its contents, and do not hold the capsule or capsule contents in your mouth. Crushing, chewing or holding the COTAZYM® capsules in your mouth may cause irritation in your mouth or change the way it works in your body.

Usual dose:
Take 1 to 3 capsules with each meal and 1 capsule with each snack as directed by your doctor.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of pancreatic enzyme preparations including COTAZYM® include the following:

•Blood sugar increase (hyperglycemia) or decrease (hypoglycemia)
•Pain in your stomach (abdominal area)
•Frequent or abnormal bowel movements
•Gas
•Soar throat and cough
•Dizziness
•Vomiting

Other Possible Side Effects

COTAZYM® and other pancreatic enzyme products are made from the pancreas of pigs, the same pigs people eat as pork. 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 if you have any side effect that bothers you or does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

COTAZYM® may cause serious side effects including:

• Irritation of the inside of your mouth. This can happen if **COTAZYM®** is not swallowed completely.

• Increase in blood uric acid levels. This may cause worsening of swollen, painful joints (gout) caused by an increase in your blood uric acid levels.

• Allergic reactions, including trouble with breathing, skin rashes, or swollen lips.

Call your doctor right away if you have any of these symptoms.

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

HOW TO STORE IT

•Store COTAZYM® at room temperature below 25°C.
•Keep COTAZYM® in a dry place and in the original container.
• After opening the bottle, keep it closed tightly between uses to protect from moisture.
Keep COTAZYM® and all medicines out of the reach of children.

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 online 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, or
  - 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 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

This document plus the full product monograph, prepared for health professionals, can be found at: www.organon.ca or by contacting the sponsor, Organon Canada Inc. at: 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

Last revised: March 30, 2021