Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Micrazym 10000 units gastro-resistant capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant capsule contains pancreatin (as pancreas powder)* corresponding to:
Amylase 8 000 Ph. Eur. units
Lipase 10 000 Ph. Eur. units
Protease 600 Ph. Eur. units

*Produced from porcine pancreatic tissue.

Excipients with known effect
Ponceau 4R (E124): 0.16 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.
Hard gelatin capsules of size 2 (length 17.8 ± 0.4 mm) with a brown cap and transparent body, filled with cylindrical, spherical or irregularly shaped gastro-resistant pellets (micro pellets) of light brown to brown colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Micrazym is a replacement therapy indicated for the treatment of exocrine pancreatic insufficiency due to mucoviscidosis (cystic fibrosis) or other pancreatic diseases (chronic pancreatitis, after pancreatectomy, pancreatic cancer) in adults, adolescents and children.

4.2 Posology and method of administration

Posology

Dosing in paediatric and adult patients with cystic fibrosis:

Weight-based enzyme dosing should begin with 1000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four.

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

Most patients should remain below or should not exceed 10000 lipase units/kg body weight per day or 4000 lipase units/gram fat intake, and the patients should not exceed the dose 2500 lipase units/kg body weight/meal.

Dosing in other conditions associated with exocrine pancreatic insufficiency:

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

Method of administration

Micrazym capsules are administered orally.

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

The capsules should be swallowed intact, without crushing or chewing, with enough fluid during or after each meal or snack.

When swallowing of capsules is difficult (e.g., for small children or elderly patients), the capsules may be carefully opened and the gastro-resistant pellets added to acidic soft food [pH < 5.5] that does not require chewing, or to acidic liquid [pH < 5.5]. This could be apple sauce, yogurt or fruit juice with a pH less than 5.5, e.g. apple, orange or pineapple juice. This mixture should not be stored. The gastro-resistant pellets should not be mixed with water, milk or hot food. The soft food or liquid mixture should be swallowed immediately without chewing and followed with water or juice to ensure complete ingestion.

Crushing and chewing of the gastro-resistant pellets or mixing with food or fluid with a pH greater than 5.5 can disrupt the protective enteric coating. This can result in early release of enzymes in the oral cavity and may lead to reduced efficacy and irritation of the mucous membranes. Care should be taken that no product is retained in the mouth.

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

Fibrosing colonopathy has been reported in patients with cystic fibrosis taking in excess of 10 000 units of lipase per kilogram bodyweight per day (see section 4.4)

4.3 Contraindications

Hypersensitivity to the pancreatin of porcine origin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Fibrosing colonopathy
Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy, especially if the patient is taking in excess of 10 000 units of lipase/per kilogram bodyweight per day.

Anaphylactic reactions
Rarely, anaphylactic reactions have been reported with pancreatic enzyme products with different formulations of the same active ingredient (pancreas powder). If this reaction occurs, patients should be advised to discontinue treatment immediately and seek urgent medical assistance.
To reduce the risk of adverse reactions due to hypersensitivity, caution is advised in patients with allergy to porcine proteins.

Potential for irritation to oral mucosa
Care should be taken to ensure that no medicinal product is retained in the mouth. Micrazym should not be crushed or chewed or kept too long in the mouth and/or mixed in foods having a pH greater than 5.5. These actions can disrupt the protective gastro-resistant coating resulting in early release of enzymes, oral pain, irritation of oral mucosa, bleeding, ulcer formation in the mouth and/or loss of enzyme activity (see section 4.2).
Rinsing the mouth and drinking of a glass of water may help if there are preliminary signs of mouth irritation.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

This medicine is essentially 'sodium-free'.
The excipient Ponceau 4 R (E124) included in the capsules shell may cause allergic reactions.

Alcohol
Use of Micrazym concomitantly with heavy alcohol is not recommended for all the proposed strengths (see section 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of porcine pancreatic enzymes in pregnant women. There are no data from animal studies with respect to reproductive toxicity (see section 5.3), but animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. This medicinal product can be used during pregnancy if necessary, to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency.

Breastfeeding
No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to porcine pancreatic enzymes is negligible. Pancreatic enzymes can be used during breastfeeding.

Fertility
No effects on fertility are anticipated since pancreatic enzymes are not absorbed from the gastrointestinal tract.

4.7 Effects on ability to drive and use machines

Micrazym has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most important serious adverse reactions observed with pancreatic enzyme medicinal products are anaphylactic reactions (see section 4.4) and fibrosing colonopathy (see section 4.4).

In clinical trials, more than 1 000 patients were exposed to pancreatin. The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity.

The following adverse reactions have been observed with the below indicated frequencies:

Organ system	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Frequency not known (cannot be estimated from the available data)**
Immune system disorders				hypersensitivity*, anaphylactic reactions*
Gastrointestinal disorders	abdominal pain**	nausea, vomiting, constipation, abdominal distention, diarrhea**		strictures of the ileo-caecum and large bowel (fibrosing colonopathy)
Skin and subcutaneous tissue disorders			rash	pruritus, urticaria

* The following symptoms of hypersensitivity have been observed during post-approval use:
generalised rash, angioedema, lips swelling, oral mucosa and face swelling, burning and swelling around the eyes, asthmatic complaints. In addition, tachycardia and hypotension have been reported in the condition of an anaphylactic shock.

** Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for abdominal pain and diarrhea.

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations, see section 4.4 Special warnings and precautions for use.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and as a result in some cases colonic strictures (see sections 4.2 and 4.4).
Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Digestives, incl. enzymes; Enzyme preparations, ATC code: A09AA02

Mechanism of action
Micrazym contains porcine pancreatin formulated as enteric-coated (acid-resistant) pellets within gelatin capsules.

The capsules dissolve rapidly in the stomach releasing plenty of pellets, a multi-dose principle which is designed to achieve good mixing with the chyme, emptying from the stomach together with the chyme and after release, good distribution of enzymes within the chyme.

Clinical efficacy
Overall, 33 studies investigating the efficacy of pancreatin in patients with pancreatic exocrine insufficiency have been conducted. Eleven 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 pancreatin over placebo on the primary efficacy parameter, the coefficient of fat absorption (CFA).

The coefficient of fat absorption determines the percentage of fat that is absorbed into the body taking into account fat intake and fecal fat excretion. In the placebo-controlled PEI studies, the mean CFA (%) was higher with pancreatin treatment (83.0%) as compared to placebo (59.1%). In all studies, irrespective of the design, the mean CFA (%) at the end of the treatment period with Pancreatin was similar to the mean CFA values for pancreatin in the placebo-controlled studies.

Treatment with pancreatin markedly improves the symptoms of pancreatic exocrine insufficiency including stool consistency, abdominal pain, flatulence and stool frequency, independent of the underlying disease.

Paediatric population
In cystic fibrosis (CF) the efficacy of pancreatin was demonstrated in 340 paediatric patients covering an age range from newborns to adolescents. In all studies, the mean end-of-treatment CFA values exceeded 80% on pancreatin comparably in all paediatric age groups.

5.2 Pharmacokinetic properties

Alcohol
An in vitro study showed significant increases of pancreatin release from Micrazym capsules at 2 hours to approximately 48% of the label claim in the presence of 20 % alcohol. The effect of 5 % and 10 % alcohol on pancreatin release was observed at 2 hours to approximately 4 % and 6% of the label claim.

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

5.3 Preclinical safety data

Preclinical data show no relevant repeated dose toxicity. Animal studies show no evidence for absorption of porcine pancreatic enzymes from the gastrointestinal tract after oral administration. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets: cetyl alcohol, poloxamer (contains butylated hydroxytoluene).

Gastro-resistant coating: methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 % (contains sodium lauryl sulphate, polysorbate 80), macrogol-4000, talc, simeticone emulsion 30 % (contains methyl cellulose, sorbic acid).

Gelatin capsules, hard
Micrazym 10000 units: gelatin, ponceau 4R (E124), patent blue (E131), titanium dioxide (E171), quinoline yellow (E104).

Micrazym 25000 units: gelatin, sunset yellow FCF (E110), titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C. After opening use within 3 months.

Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Micrazym 10000 units is available in a 75 ml white HDPE bottle with a white PP screw cap containing a coloured white insert block made of low density polyethylene with desiccant inside (silica gel). Each bottle contains 100 capsules and is overpacked in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd.
12 Hamilton Drive
The Rock Road
Blackrock
Co. Louth
A91 T997
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of authorisation: 10th January 2025

10 DATE OF REVISION OF THE TEXT

Septemeber 2025