To be sold by retail on the prescription of R.M.P. only

ENZAR

1. **Generic Name**
   Pancreatin Gastro Resistant Capsules B.P.
2. **Qualitative and quantitative composition**

   ENZAR 10000
   Each hard gelatin capsule contains:
   Pancreatin I.P. (as enteric coated pellets) equivalent to
   Lipase activity…..10000 Ph.Eur Units
   Amylase activity….6000 Ph.Eur Units
   Protease activity…..350 Ph.Eur Units
   Approved colours used in hard gelatin capsule shells.
   The excipients used are ready to use pellets of Pancreatin and Talc.

   ENZAR 40000
   Each hard gelatin capsule contains:
   Pancreatin I.P. (as enteric coated pellets) equivalent to
   Lipase activity…..40000 Ph.Eur Units
   Amylase activity….25000 Ph.Eur Units
   Protease activity…..1600 Ph.Eur Units
   Approved colours used in hard gelatin capsule shells.
   The excipients used are ready to use pellets of Pancreatin and Talc.

3. **Dosage form and strength**
   Dosage Form: Hard Gelatin Capsules
   Strength:

   ENZAR 10000

   Lipase activity – 10000 Ph Eur Units, Amylase activity - 6000 Ph Eur Units, Protease activity - 350 Ph Eur Units

   ENZAR 40000

   Lipase activity – 40000 Ph Eur Units, Amylase activity - 25000 Ph Eur Units, Protease activity - 1600 Ph Eur Units

4. **Clinical particulars**

   4.1 Therapeutic indication

   It is indicated for treatment of patient with exocrine pancreatin enzyme insufficiency**.**

   4.2 Posology and method of administration

   Adults (including the elderly) and children:
   Initially one or two capsules during or immediately after each meal. Dose increases, if required, should be added slowly, with careful monitoring of response and symptomatology.
   The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with acidic fluid or soft food, but without chewing.

This could be apple sauce or yoghurt or any fruit juice with a pH less than 5.5, e.g. apple, orange or pineapple juice. If the granules are mixed with fluid or food it is important that they are taken immediately and the mixture not stored, otherwise dissolution of the enteric coating may result. In order to protect the enteric coating, it is important that the granules are not crushed or chewed. 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.

It is important to ensure adequate hydration of patients at all times whilst dosing pancreatin. Fibrosing colonopathy has been reported in patients with cystic fibrosis taking in excess of 10,000 units of lipase/kg/day.

4.3 Contraindications

Hypersensitivity to the active ingredient or any of the excipients.

4.4 Special warnings and precautions for use

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/kg/day.

4.5 Drugs interactions

None known.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

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.

Lactation

No effects on the suckling child are anticipated since animal studies suggest no systemic exposure of the breast-feeding woman to pancreatic enzymes. Pancreatic enzymes can be used during breast-feeding.

If required during pregnancy or lactation ENZAR should be used in doses sufficient to provide adequate nutritional status.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

In reported clinical trials, more than 900 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 during clinical trials 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**
Gastrointestinal disorders	abdominal pain*	nausea, vomiting, constipation, abdominal distention, diarrhoea*		strictures of the ileo-caecum and large bowel (fibrosing colonopathy)
Skin and subcutaneous tissue disorders			rash	pruritus, urticaria
Immune system disorders				hypersensitivity (anaphylactic reactions).

*Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for abdominal pain and diarrhoea. Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations.

Allergic reactions mainly but not exclusively limited to the skin have been observed and identified as adverse reactions during post-approval use. Because these reactions were reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency.

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

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia. Supportive measures including stopping enzyme therapy and ensuring adequate rehydration are recommended.

5. Pharmacological properties

5.1 Mechanism of Action

Pancreatin improve the ability to metabolise starches, proteins and fats.

5.2 Pharmacodynamic properties

ENZAR contains pancreatin formulated as enteric-coated (acid-resistant) minimicrospheres within gelatine capsules.

The capsules dissolve rapidly in the stomach releasing plenty of minimicrospheres, a multidose 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.

When the minimicrospheres reach the small intestine the coating rapidly disintegrates (at pH > 5.5) to release enzymes with lipolytic, amylolytic and proteolytic activity to ensure the digestion of fats, starches and proteins. The products of pancreatic digestion are then either absorbed directly, or following further hydrolysis by intestinal enzymes.

Clinical efficacy:

In overall 30 reported studies for investigating the efficacy of pancreatin (pancreatin capsules with 10000, 25000 or 40000 Ph. Eur units of lipase and pancreatin 5000) 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 reported 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 faecal fat excretion. In the placebo-controlled PEI studies, the CFA (%, mean ± SD) was higher with pancreatin treatment (83.0 ± 12.6%) as compared to placebo (62.6 ± 21.8%). The median treatment duration was 7 days on both treatments. 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.

In reported placebo-controlled studies in which symptoms have been collected on diaries, the percentage of subjects with 'no abdominal pain' as most frequently reported rating was higher (73%) during pancreatin treatment than during placebo treatment (52%). The most frequently reported stool consistency was 'formed/normal' in 63% of the subjects during pancreatin treatment and in 17% of the subjects during placebo treatment. During pancreatin treatment, the percentage of subjects with 'no flatulence' as most frequently reported rating was higher (30%) than during placebo treatment (19%). The average number of daily stools was lower during pancreatin treatment than during placebo treatment (mean±SD: 1.89±0.87 vs 3.16±1.51).

In subjects with PEI due to CF in these studies, the percentage of subjects with 'no

abdominal pain' as most frequently reported rating was 94% during pancreatin treatment and 60% during placebo treatment. The most frequently reported stool consistency was 'formed/normal' in 73% of the subjects during pancreatin treatment and in 18% of the subjects during placebo treatment. The percentage of subjects with 'no flatulence' as most frequently reported rating was 37% during pancreatin treatment and 26% during placebo treatment. The average number of daily stools (mean±SD) was 1.78±0.78 during pancreatin treatment and 3.24±1.49 during placebo treatment.

In subjects with PEI due to CP in these studies, the percentage of subjects with 'no abdominal pain' as most frequently reported rating was 55% during pancreatin treatment and 46% during placebo treatment. The most frequently reported stool consistency was 'formed/normal' in 45% of the subjects during pancreatin treatment and in 18% of the subjects during placebo treatment. The percentage of subjects with 'no flatulence' as most frequently reported rating was 26% during pancreatin treatment and 13% during placebo treatment. The average number of daily stools (mean±SD) was 2.07±1.08 during pancreatin treatment and 2.89±1.55 during placebo treatment.

Paediatric population

In cystic fibrosis (CF) the efficacy of pancreatin was demonstrated in 288 paediatric patients covering an age range from newborns to adolescents. In all reported studies, the mean end-of treatment CFA values exceeded 80% on pancreatin comparably in all paediatric age groups.

5.3 Pharmacokinetic properties

Pharmacokinetic data are not available as the enzymes act locally in the gastro-intestinal tract. After exerting their action, the enzymes are digested themselves in the intestine.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No relevant pre-clinical safety data has been generated.

7. Description

Pancreatin is a preparation of mammalian pancreas containing protease, lipase and amylase activity. It may contain sodium. Pancreatin is a white to buff coloured amorphous powder; odoud meaty and unpleasant. Pancreatin is soluble in water producing a slightly turbid solution; practically insoluble in ethanol (95%); and in ether.

ENZAR 10000

Pancreatin Gastro-Resistant Capsules are green cap and clear transparent body size ‘4’ hard gelatin capsule filled with beige brown pellets. The excipients are ready to use pellets of Pancreatin and Talc.

ENZAR 40000

Pancreatin Gastro-Resistant Capsules are Orange cap & clear transparent body size '0EL' hard gelatin capsule, filled with beige brown coloured pellets. The excipients are ready to use pellets of Pancreatin and Talc.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

ENZAR is available in blister pack of 10 capsules.

8.4 Storage and handing instructions

Store in a cool, dry place.

Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine is available without prescription. However, you still need to take ENZAR carefully to get the best results from it. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- You must contact a doctor if your symptoms worsen or do not improve.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

What is in this leaflet:

9.1 What ENZAR is and what it is used for

The active ingredient in ENZAR is Pancreatin.

Pancreatin is a combination of enzymes normally produced by the pancreas which help to digest protein, fat, starch and sugars in the food that you eat.

ENZAR capsules are indicated for patients with exocrine pancreatic enzyme insufficiency such as: chronic pancreatitis, postpancreatectomy, post-gastrointestinal bypass surgery (e.g. Billroth II gastroenterostomy), ductal obstruction from neoplasm (e.g. of the pancreas or common bile duct). Enzyme replacement therapy in patients who do not produce enough pancreatic enzymes because of cystic fibrosis, chronic pancreatitis, postpancreatectomy, ductal obstructions caused by cancer of pancreas or common bile duct, pancreatic insufficiency; treatment of steatorrhea of malabsorption syndrome; postgastrectomy or after GI surgery; pancreatic function testing.

9.2 What you need to know before you use ENZAR

Do not take ENZAR if you:

- are allergic (hypersensitive) to pancreatin or any of the other ingredients of ENZAR. There are no known diseases that may prevent you from taking ENZAR.

Taking other medicines

ENZAR are not known to interfere with any other medicines that you may be taking. However if you are prescribed another medicine, inform the doctor you are taking ENZAR.

Pregnancy and breast-feeding

If you are pregnant, thinking of becoming pregnant or breast-feeding, discuss this with your doctor before taking your medicine as dose adjustments may be necessary. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

ENZAR do not interfere with your ability to drive or operate machinery.

9.3 How to use ENZAR

Dosage

Your doctor or pharmacist will advise you on the amount of ENZAR to take before each meal, although you may find with experience that you need to adjust the dose according to the size and type of meal that you eat. If loose pale stools (faeces) occur you may need to increase the dose. Always check with your pharmacist if you are not sure.

The following should provide a good starting point for adjustment of the dose:

- For infants, the contents of 1-2 capsules mixed with feeds.
- For older children and adults, 2-6 capsules (or their contents) with each meal or snack.

If the capsule contents are mixed with liquids or feeds, use within one hour.

If you take more ENZAR than you should

There are no special precautions to take, although the use of a barrier cream may help prevent possible irritation of the anus.

If you forget to take ENZAR

Simply skip that dose and take the next dose with your next meal or snack.

If you have any further questions on the use of this product, ask your pharmacist

9.4 Possible Side Effects

Like all medicines, ENZAR can cause side effects, although not everybody gets them.

It is possible that some people may be allergic (hypersensitive) to ENZAR. Allergic/asthmatic reactions have occasionally occurred on handling the capsule contents.

Signs of an allergy to something include rash, wheezing, breathlessness, swollen eyelids, face or lips, and in extreme cases collapse. In the unlikely event that you should get any of these symptoms soon after taking ENZAR, don't take any more. Tell a doctor straight away and take the packaging and this leaflet with you.

Rarely, high levels of uric acid in the blood and urine have been reported when extremely high doses of pancreatin have been taken.

Narrowing of parts of the bowel, and inflammation of the colon, have been reported in children with cystic fibrosis taking high doses of pancreatic enzyme supplements.
Some irritation of the skin of the mouth may occur if the capsules are chewed or the contents kept in the mouth. Irritation of the anus may also occur, which may be prevented by use of a barrier cream.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5 How to store ENZAR

- Keep out of the sight and reach of children.
- Do not use the tablets after the expiry date stated on the carton (EXP).
- Store in a cool, dry place.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What ENZAR 10000 contains:

- The active substance is Pancreatin I.P. (as enteric coated pellets) Equivalent to,
  Lipase activity…..10000 Ph.Eur Units
  Amylase activity….6000 Ph.Eur Units
  Protease activity…..350 Ph.Eur Units
- The excipients are ready to use pellets of pancreatin and Talc.

What ENZAR 40000 contains:

- The active substance is Pancreatin I.P. (as enteric coated pellets) Equivalent to,
  Lipase activity…..40000 Ph.Eur Units
  Amylase activity….25000 Ph.Eur Units
  Protease activity…..1600 Ph.Eur Units
- The excipients are ready to use pellets of pancreatin and Talc.

What are the contents of the pack

ENZAR is available in blister strips of 10 capsules.

10. Details of manufacturer

Manufactured by:
Windlas Biotech Pvt. Limited,
(Plant-2) Khasra No. 141-143 & 145, Mohabewala Industrial Area,
Dehradun – 248110, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No. 55/UA/SC/P-2013 issued on 02.04.2019

12. Date of revision

Mar 2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ENZAR/MAR-20/02/PI