ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 5,000 units gastro-resistant hard capsules

Enzepi 10,000 units gastro-resistant hard capsules

Enzepi 25,000 units gastro-resistant hard capsules

Enzepi 40,000 units gastro-resistant hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enzepi 5,000 units gastro-resistant hard capsules
One capsule contains 39.8 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		5,000 units*,
amylolytic activity:	not less than	1,600 units*,
proteolytic activity:	not less than	130 units*.

Enzepi 10,000 units gastro-resistant hard capsules
One capsule contains 83.7 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		10,000 units*,
amylolytic activity:	not less than	3,200 units*,
proteolytic activity:	not less than	270 units*.

Enzepi 25,000 units gastro-resistant hard capsules
One capsule contains 209.3 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		25,000 units*,
amylolytic activity:	not less than	4,800 units*,
proteolytic activity:	not less than	410 units*.

Enzepi 40,000 units gastro-resistant hard capsules
One capsule contains 334.9 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		40,000 units*,
amylolytic activity:	not less than	7,800 units*,
proteolytic activity:	not less than	650 units*.

* Ph. Eur. units

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule.

Enzepi 5,000 units gastro-resistant hard capsules
Hard capsules with a white opaque cap and a white opaque body, printed with “Enzepi 5” and containing light-brown gastro-resistant granules.

Enzepi 10,000 units gastro-resistant hard capsules
Hard capsule with a yellow opaque cap and a white opaque body, printed with “Enzepi 10” and containing light-brown gastro-resistant granules.

Enzepi 25,000 units gastro-resistant hard capsules
Hard capsule with a green opaque cap and a white opaque body, printed with “Enzepi 25” and containing light-brown gastro-resistant granules.

Enzepi 40,000 units gastro-resistant hard capsules
Hard capsule with a blue opaque cap and a white opaque body, printed with “Enzepi 40” and containing light-brown gastro-resistant granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pancreatic enzyme replacement treatment in exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (e.g. chronic pancreatitis, post pancreatectomy or pancreatic cancer).

Enzepi is indicated in infants, children, adolescents and adults.

4.2 Posology and method of administration

Posology
The dosage of Enzepi should be individualised based on clinical symptoms, the degree of steatorrhoea present, the fat content of the diet, or actual body weight. Therapy should be initiated at the lowest recommended dose and gradually increased under medical supervision with careful monitoring of the patient’s response and symptoms. Patients should be instructed not to increase the dosage on their own. Changes in dosage may require an adjustment period of several days.

Maximum recommended dose
The maximum recommended total dose is 2,500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day), or 4,000 lipase units/g fat ingested per day. Higher doses should be used with caution if warranted (see sections 4.4 and 4.9) and only if they are documented to be effective by 3day faecal fat measurements that indicate a significantly improved coefficient of fat absorption.
For each snack, half of the prescribed Enzepi dose for a full meal should be given. Enzyme doses expressed as lipase units/kg of body weight per meal must be reduced in older patients because they tend to ingest less fat per kilogram of body weight.

It is important to ensure adequate hydration of patients at all times whilst dosing Enzepi. Inadequate hydration may predispose to/or aggravate constipation.

Starting dose
Paediatric population below 1 year of age
For infants below 1 year of age the recommended starting dose is 5,000 lipase units per meal (generally 120 ml of milk) (see section Method of administration).

Paediatric population between 1 and less than 4 years of age
For children between 1 and less than 4 years of age the recommended starting dose is 1,000 lipase units/kg of body weight per meal.

Paediatric population aged 4 years or older and adults (including elderly)
For children aged 4 years or older, adolescents and adults the recommended starting dose is 500 lipase units/kg of body weight per meal.

Method of administration

For oral use.
Enzepi should be taken during meals or snacks, with a drink of water or juice.
Capsules should be swallowed whole and not chewed or crushed. Crushing, chewing, or mixing capsule contents with food or fluid with a pH greater than 5 or storing the food mixture (see below), can lead to a disruption of the protective gastro-resistant coating. This can result in early release of the enzymes in the oral cavity, irritation of the mucous membranes and may lead to loss of enzyme activity.

Patients unable to swallow capsules whole
For patients who are unable to swallow capsules whole, the capsules may be carefully opened and the contents mixed (without crushing) with small amounts of acidic soft food of pH 5 or less (e.g., fruit puree [apple/ pear], yoghurt, juice [orange/pineapple/apple]). Do not mix with water, milk, breast-milk, formula, flavoured milk or hot food. The Enzepi soft food mixture should be swallowed immediately without chewing and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that Enzepi is not retained in the mouth. The mixture must not be stored.

Paediatric population
For paediatric patients below 1 year of age, Enzepi must be administered immediately prior to each feed. The capsule should be carefully opened to empty the content (granules). The granules may be administered with a small amount of appropriate acidic food or directly into the mouth. Administration should be followed by breast-milk or formula to ensure complete ingestion. The contents of the capsule should not be mixed directly into formula or breast-milk as this may diminish efficacy. Care should be taken to ensure that Enzepi is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

4.3 Contraindications

Hypersensitivity to the active substance 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 lipase units/kg/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.

Potential for hyperuricaemia
Caution must be exercised when prescribing Enzepi to patients with a history of gout, renal impairment, or hyperuricaemia. Porcine derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

Potential for irritation to oral mucosa
Care should be taken to ensure that no medicinal product is retained in the mouth. Enzepi should not be crushed or chewed or mixed in foods having a pH greater than 5. These actions can disrupt the protective gastro-resistant coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity (see section 4.2).

Abnormal blood glucose levels

Consideration should be given to blood glucose monitoring in patients at risk of abnormal blood glucose levels as glycaemic control may be affected by administration of pancreatic enzyme replacement therapy (see section 4.8).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially `sodium-free´.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Pancreatic enzyme medicinal products do not cause pharmacokinetic and pharmacodynamic interactions based on their pharmacology, as they are not absorbed from the gastrointestinal tract. No clinically relevant interactions are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of this medicinal product in pregnant women. It is also not known whether this medicinal product can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Although, no preclinical investigations were carried out with Enzepi there is no evidence for any absorption of this medicinal product. Therefore, no reproductive or developmental toxicity is to be expected. The risk and benefit of this medicinal product should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and foetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

Breast-feeding
It is unknown whether this medicinal product is excreted in human milk. Nevertheless, undersirable effects on the breastfed newborn/infant are not anticipated since systemic exposure in breast-feeding women to the pancreatic enzymes present in Enzepi is not expected.

As a risk to newborns/infants cannot be excluded, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Enzepi therapy taking into account the benefit of breast-feeding for the child and the benefit of continued Enzepi therapy for the breastfeeding woman.

Fertility
No human data on the effect of Enzepi on fertility are available.

4.7 Effects on ability to drive and use machines

Enzepi has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
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).

The most common adverse reactions reported with Enzepi were gastrointestinal complaints [abdominal pain (16%); flatulence (12%); abdominal distention (7%); diarrhoea and vomiting (6%); constipation (5%); nausea (3%)], and headache occurring in approximately 6% of patients. In clinical trials, most of them were mild to moderate in severity.

Tabulated list of adverse reactions
Adverse reactions associated with pancreas powder obtained from clinical studies, post-marketing surveillance and some additional class effects are tabulated below. They are presented according to the

MedDRA System Organ Classification and are ranked under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	*Very common*	*Common*	*Not known*
Immune system disorders			Anaphylactic reaction** Drug hypersensitivity/ Hypersensitivity
Metabolism and nutrition disorders			Hyperuricaemia/ hyperuricosuria** Decreased appetite
Nervous system disorders		Headache	Dizziness
Respiratory, thoracic and mediastinal disorders			Dyspnoea*
Gastrointestinal disorders	Abdominal pain	Diarrhoea Vomiting Nausea Constipation Abdominal distension Flatulence Abdominal discomfort	Fibrosing colonopathy** Lip swelling and swollen tongue* Stomatitis Abdominal pain upper Dyspepsia Abnormal faeces Faeces discoloured Frequent bowel movements
Skin and subcutaneous tissue disorders			Swelling face Urticaria Rash generalised Rash Rash erythematous Pruritus
General disorders and administration site conditions			Fatigue Malaise
Investigations			Blood glucose decreased Blood glucose increased Weight decreased Weight increased

*Symptoms of allergic reactions.
**Class effects

Description of selected adverse reactions

In patients at risk of abnormal blood glucose levels glycaemic control may be affected by administration of pancreatic enzyme replacement therapy (see section 4.4). Cases of blood glucose fluctuations have been reported with Enzepi, most of them non-serious and recovered after diabetic treatment adjustment.

The most relevant class effects of the pancreatic enzyme products include fibrosing colonopathy, hyperuricaemia/ hyperuricosuria and anaphylactic reactions.

Paediatric population
In clinical trials, 110 children with CF (cystic fibrosis) aged 1 month and older received Enzepi at a dose that ensured stabilization of symptoms. The safety profile of Enzepi in the paediatric population was similar to that observed in adults.

Elderly people
No specific adverse reactions were identified in the elderly population. Frequency, type and severity of adverse reactions were similar in elderly people with pancreatic exocrine insufficiency 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 the national reporting system listed in Appendix V.

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). High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricaemia, and should be used with caution in patients with a history of gout, renal impairment or hyperuricaemia (see section 4.4). Supportive measures including stopping pancreatic enzyme therapy and ensuring adequate rehydration are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Enzepi belongs to the family of pancreatic enzyme products and contains a defined amount of lipase, amylase and protease that have been extracted from porcine pancreas and purified using a process designed to inactivate viruses.

Gastro-resistant granules are thoroughly mixed with chyme when the capsule dissolves in the stomach, without inactivating the acid-sensitive enzymes. It is only in the duodenum, which has a different environment with a pH value greater than 5, that these digestive enzymes are released from the granules. Then, enzymes catalyze the hydrolysis of fats to monoglycerides, glycerol, and free fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars such as maltose and maltotriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

Clinical efficacy
The efficacy of Enzepi has been evaluated in one active-comparator study and one placebo-controlled study conducted in 130 patients with EPI (exocrine pancreatic insufficiency) associated with CF. Moreover three supportive studies were conducted in 34 paediatric patients.

Data generated in the CF population with EPI can be extrapolated to the other causes of EPI such as chronic pancreatitis, post pancreatectomy or pancreatic cancer.

Study PR-005
The pivotal study PR-005 was conducted in Europe. It was a randomized, double-blind, active controlled, two-treatment, crossover study, comparing Enzepi to standard pancreatic enzyme treatment during 2 treatments periods. During the first treatment period, patients received either Enzepi or the comparator for

28 days, followed by a cross-over to the alternate treatment for a second 28 day period. For both treatment periods, patients received a dose as close as possible to their stabilized existing pancreatic enzyme product dose on the first day. Then, starting on the second day, the dose of assigned treatment could be changed (titrated up and/or titrated down) to stabilize the symptoms of EPI. Stabilization of the symptoms had to be obtained before the end of the first 14 days of each treatment period.

A total of 96 patients, aged 12 to 43 years, were randomized in the intent-to-treat population. During the study, patients were instructed to consume 100 g (± 15 g) of fat per day and to maintain a consistent dietary fat intake for meals and snacks. The primary efficacy endpoint was the coefficient of fat absorption over 72 hours (CFA-72h) which was calculated at the end of each treatment period, from the stools collected during the last 3 days of each treatment period. The collection was performed in an approved, controlled environment that enabled supervised dietary intake and quantitative stool collection.

Subjects achieved a mean CFA-72h of 84.08 with Enzepi and of 85.33 with comparator. The difference in means was -1.25 (95% CI, -3.62 to 1.12), with p=0.2972. Thus, Enzepi demonstrated both non-inferiority and equivalence to the comparator in fat absorption control (measured as CFA-72h) in adolescents and adults with CF-associated EPI.

Table 1 Analysis of coefficient of fat absorption over 72 hours (CFA72h) – completers population (study : PR005)

Variable statistic	Enzepi (N=83)	Standard treatment (N=83)
Summary statistics		
Mean (SD)	84.11 (11.073)	85.34 (9.099)
Median (minimum – maximum)	85.92 (47.4 – 99.5)	86.49 (53.5 – 97.3)
Model-based statistics (Enzepi minus Creon)		
LS mean (standard error)	84.08 (1.109)	85.33 (1.109)
Difference in LS means (95% confidence limits)	-1.25 (-3.62, 1.12)	
p-value	0.2972	

N: number of patients; SD: standard deviation; LS: least squares.
Model-based statistics are from a mixed effects linear model using CFA-72h as the response variable, fixed effect factors for treatment, period and treatment sequence, and subject within treatment sequence as a random effect.

Study EUR-1008-M
The supportive EUR-1008-M, conducted in the US, was a randomized, double-blind, placebo-controlled, crossover study of 34 patients, ages 7 to 23 years, with EPI due to CF. Patients were randomized to receive Enzepi or matching placebo for 6 to 7 days of treatment, followed by cross-over to the alternate treatment for an additional 6 to 7 days. All patients consumed a high-fat diet (greater than or equal to 100 grams of fat per day) during the treatment period.

The primary efficacy endpoint was the mean difference in the coefficient of fat absorption (CFA-72h) between Enzepi and placebo treatment. The CFA-72h was determined by a 72-hour stool collection during both treatments, when both fat excretion and fat ingestion were measured. Each patient's CFA-72h during placebo treatment was used as their no-treatment CFA-72h value.

Mean CFA-72h was 88% with Enzepi treatment compared to 63% with placebo treatment. The mean difference in CFA-72h was 26 percentage points greater with Enzepi treatment with a 95% Confidence Interval of (19, 32) and p<0.001.

Paediatric population

The short-term efficacy and safety of Enzepi were assessed in clinical studies in paediatric patients, ages 1 to 17 years, with EPI due to CF.

Study EUR-1008-M
EUR-1008-M was conducted in 34 patients with EPI due to CF, 26 of whom were children, including 8 children aged 7 to 11 years, and 18 adolescents aged 12 to 17 years. Results are presented above.
The safety and efficacy in the paediatric patients in this study was similar to the adult patients.

Study EUR 1009-M
EUR 1009-M was an open-label, single arm study in 19 patients, ages 1 to 6 years, with EPI due to CF. Approximately half of the patients were ages 1 to 3 years. Patients were transitioned to Enzepi from their usual PEP (pancreatic enzyme product) treatment. After a 4-14 days screening period on their usual PEP, patients received Enzepi at individually titrated doses ranging between 2,300 and 10,000 lipase units per kg body weight per day, with a mean of approximately 5,000 lipase units per kg body weight per day (not to exceed 2,500 lipase units per kilogram per meal) for 14 days. There was no wash-out period.

The primary efficacy endpoint was the percentage of "responders", defined as those patients without steatorrhoea (<30% faecal fat content) and without signs and symptoms of malabsorption after one and two weeks of treatment with Enzepi. Steatorrhoea was assessed from the faecal fat content measured by spot faecal fat testing on Days 11 and 18 compared with baseline (under usual PEPS).

The number of responders (patients with less than 30% faecal fat content and without signs and symptoms of malabsorption) at baseline was 10/19 (52.6%), 13/19 (68.4%) after 1 week of treatment (stabilization) and 11/19 (57.9%) after the second week of open-label treatment with Enzepi. The mean faecal fat content was similar at baseline (24.8%), after stabilization (27.0%) and after the second week of open-label treatment (27.3%).

Study PR-011
Study PR-011 was an open-label crossover study in 15 patients, ages 1 to 11 months, with EPI due to CF. Patients were randomized to receive Enzepi from an opened capsule mixed and administered with apple juice (in a syringe nurser) or apple sauce (using a spoon) for 10 days of treatment, followed by a cross-over to the alternate mode of administration for an additional 10 days.

The primary objective was to assess the acceptability of 2 modes of administration using an acceptability questionnaire that was completed by the caregiver. Twelve patients completed both assigned treatment arms and were evaluated. Overall, caregivers were satisfied with using apple sauce as a dosing method compared with apple juice.

Study PR-018
Study PR-018 was a 12-month open-label extension of Study PR-011. Patients were administered Enzepi at the same dose they were taking at the end of Study PR-011. The dose of Enzepi was adjusted during the 12-month study as the patient's grew and gained weight.

Twelve patients completed the study. Overall, an improvement was observed from baseline to study completion for growth indices including weight-for-age, length-for-age, and weight-for-length percentiles.

Elderly people
Clinical studies of Enzepi did not include sufficient numbers of subjects aged 65 and over to determine whether they respond different from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and young patients.

5.2 Pharmacokinetic properties

The pancreatic enzymes in Enzepi are gastro-resistant to minimise destruction or inactivation in gastric acid. Enzepi is designed to release most of the enzymes *in vivo* at pH greater than 5.5. Pancreatic enzymes are not absorbed from the gastrointestinal tract.

5.3 Preclinical safety data

No preclinical investigations were carried out with Enzepi. However as pancreatic enzymes are not absorbed from the gastrointestinal tract, no systemic toxicity is expected following oral administration of pancreas powder.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content (gastro-resistant granules)
Croscarmellose sodium
Hydrogenated castor oil
Colloidal anhydrous silica
Microcrystalline cellulose
Magnesium stearate
Hypromellose phthalate
Talc
Triethyl citrate

Capsule shell
Hypromellose
Carrageenan (E407)
Potassium chloride
Titanium dioxide (E171)
Carnauba wax
Purified water

Additionally for Enzepi 10,000 units gastro-resistant granules
Yellow iron oxide (E172)

Additionally for Enzepi 25,000 units gastro-resistant granules
Yellow iron oxide (E172)
Indigotine (E132)

Additionally for Enzepi 40,000 units gastro-resistant granules
Indigotine (E132)

Printing ink
Shellac
Propylene glycol
Indigotine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening: 6 months when stored below 25°C. Keep the bottle tightly closed and the desiccant in the bottle in order to protect from moisture.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottle containing desiccant sachets, closed with a lined polypropylene childresistant closure and a peel-off sealing liner.

Pack size of 20, 50, 100, and 200 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use in paediatric population
If required, carefully open the capsule and administer the contents (granules) to the patient as described in section 4.2.

Dispose of any accidentally crushed capsule.

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

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/001-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Nordmark Arzneimittel GmbH & Co. KG
Pinnauallee 4
25436 Uetersen
GERMANY

Name and address of the manufacturer(s) responsible for batch release

Adare Pharmaceuticals Srl
Via Martin Luther King 13
20060 Pessano Con Bornago
ITALY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - 5,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 5,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 39.8 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		5,000 Ph. Eur. units
amylolytic activity:	not less than	1,600 Ph. Eur. units
proteolytic activity:	not less than	130 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum of 6 months below 25°C in its tightly closed container.

Opening date :

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/001 20 gastro-resistant hard capsules
EU/1/16/1113/002 50 gastro-resistant hard capsules
EU/1/16/1113/003 100 gastro-resistant hard capsules
EU/1/16/1113/004 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enzepi 5,000

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - 10,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 10,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 83.7 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		10,000 Ph. Eur. units
amylolytic activity:	not less than	3,200 Ph. Eur. units
proteolytic activity:	not less than	270 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container.

Opening date :

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/005 20 gastro-resistant hard capsules
EU/1/16/1113/006 50 gastro-resistant hard capsules
EU/1/16/1113/007 100 gastro-resistant hard capsules
EU/1/16/1113/008 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enzepi 10,000

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - 25,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 25,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 209.3 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		25,000 Ph. Eur. units
amylolytic activity:	not less than	4,800 Ph. Eur. units
proteolytic activity:	not less than	410 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container.

Opening date :

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/009 20 gastro-resistant hard capsules
EU/1/16/1113/010 50 gastro-resistant hard capsules
EU/1/16/1113/011 100 gastro-resistant hard capsules
EU/1/16/1113/012 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enzepi 25,000

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - 40,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 40,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 334.9 mg of pancreas powder of porcine origin including the following enzymatic activities:

lipolytic activity:		40,000 Ph. Eur. units
amylolytic activity:	not less than	7,800 Ph. Eur. units
proteolytic activity:	not less than	650 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container.

Opening date :

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/013 20 gastro-resistant hard capsules
EU/1/16/1113/014 50 gastro-resistant hard capsules
EU/1/16/1113/015 100 gastro-resistant hard capsules
EU/1/16/1113/016 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enzepi 40,000

PARTICULARS TO APPEAR ON THE INNER PACKAGING

BOTTLE LABEL - 5,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 5,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains :

lipase:		5,000 Ph. Eur. units
amylase:	not less than	1,600 Ph. Eur. units
protease:	not less than	130 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/001 20 gastro-resistant hard capsules
EU/1/16/1113/002 50 gastro-resistant hard capsules
EU/1/16/1113/003 100 gastro-resistant hard capsules
EU/1/16/1113/004 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE LABEL - 10,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 10,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains:

lipase:		10,000 Ph. Eur. units
amylase:	not less than	3,200 Ph. Eur. units
protease:	not less than	270 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/005 20 gastro-resistant hard capsules
EU/1/16/1113/006 50 gastro-resistant hard capsules
EU/1/16/1113/007 100 gastro-resistant hard capsules
EU/1/16/1113/008 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE LABEL - 25,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 25,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains:

lipase:		25,000 Ph. Eur. units
amylase:	not less than	4,800 Ph. Eur. units
protease:	not less than	410 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/009 20 gastro-resistant hard capsules
EU/1/16/1113/010 50 gastro-resistant hard capsules
EU/1/16/1113/011 100 gastro-resistant hard capsules
EU/1/16/1113/012 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE LABEL - 40,000 unit strength

1. NAME OF THE MEDICINAL PRODUCT

Enzepi 40,000 units gastro-resistant hard capsules
Pancreas powder

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains:

lipase:		40,000 Ph. Eur. units
amylase:	not less than	7,800 Ph. Eur. units
protease:	not less than	650 Ph. Eur. units

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 gastro-resistant hard capsules
50 gastro-resistant hard capsules
100 gastro-resistant hard capsules
200 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew the capsules.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP
After first opening, the product may be stored for a maximum 6 months below 25°C in its tightly closed container.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1113/013 20 gastro-resistant hard capsules
EU/1/16/1113/014 50 gastro-resistant hard capsules
EU/1/16/1113/015 100 gastro-resistant hard capsules
EU/1/16/1113/016 200 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET

Package leaflet: Information for the patient

Enzepi 5,000 units gastro-resistant hard capsules
Enzepi 10,000 units gastro-resistant hard capsules
Enzepi 25,000 units gastro-resistant hard capsules
Enzepi 40,000 units gastro-resistant hard capsules
Pancreas powder

Read all of this leaflet carefully before you start taking 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 has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Enzepi is and what it is used for

Enzepi is a pancreatic enzyme replacement medicine for people whose bodies do not make enough of enzymes to digest food.

Enzepi contains a mixture of natural digestive enzymes which are used to digest food. These include lipases for digesting fat, proteases for digesting protein and amylases for digestions carbohydrates. The enzymes are taken from pig pancreas glands.

Enzepi is for use by adults, adolescents, children and infants with 'exocrine pancreatic insufficiency', a condition that makes the body less able to break down and digest food.

2. What you need to know before you take Enzepi

Do not take Enzepi
- if you are allergic to the active subtance or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Enzepi
- if you have ever had gout, kidney disease, or high uric acid levels in your blood (hyperuricaemia) or in urine (hyperuricosuria),
- if you have abnormal blood glucose levels.

Cystic fibrosis patients
A rare bowel condition called 'fibrosing colonopathy', where the intestine is narrowed, has been reported in patients with cystic fibrosis taking high doses of pancreatic enzymes. If you have cystic fibrosis and you are

taking pancreatic enzymes exceeding10,000 lipase units per kilogram body weight per day and have unusual abdominal symptoms (such as severe stomach pain, trouble passing stools, nausea or vomiting) or changes in abdominal symptoms, **tell your doctor straightaway**.

Severe allergic reaction
If an allergic reaction occurs, stop your treatment and talk to your doctor. An allergic reaction could include itching, hives or rash. Rarely, a more serious allergic reaction may include a feeling of warmth, dizziness and fainting, trouble breathing; these are symptoms of a severe, potentially life-threatening condition called 'anaphylactic shock'. If this occurs, **call for urgent medical attention straightaway**.

Mouth irritation
Enzepi capsules or its contents should not be crushed or chewed as they can cause irritation inside your mouth. Enzepi can only be sprinkled on certain food (see section 3).

Other medicines and Enzepi
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are breast-feeding or plan to breast-feed, or if you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known if Enzepi passes into your breast-milk. You and your doctor should decide if you will take Enzepi or breast-feed.

It is not known if Enzepi will affect your ability to get pregnant or if it harms your unborn baby.

Driving and using machines
Enzepi does not affect your ability to drive or use tools or machines.

3. How to take Enzepi

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The dose is measured in 'lipase units'.

Your doctor will adjust your dose which will depend on:
- the severity of your illness,
- how much fat is in your stools,
- your diet,
- your weight.

How much Enzepi to take
Infants (below 1 year of age)
The recommended starting dose for infants below 1 year of age is 5,000 lipase units per 120 ml of formula milk or breast-milk.

Children (between 1 and 4 years of age)
The recommended starting dose for children between 1 and 4 years of age is 1,000 lipase units per kg of body weight with each meal.

Children (over 4 years of age), adolescents and adults (including elderly)
The recommended starting dose for children over 4 years of age, adolescents (12 to 18 years) and adults is 500 lipase units per kg of body weight per meal.

If your doctor advises you to increase the number of capsules you take each day, you should do so slowly over several days. If you still have fatty stools (smelly, loose, oily, pale stools) or other stomach or gut problems (gastrointestinal symptoms), talk to your doctor as your dose may need to be adjusted again.

Do not take more capsules in a day than the amount your doctor has told you (total daily dose). Depending on what strength of Enzepi you take, your doctor will tell you how many capsules you need to take with each meal or snack.

Your total daily dose should not exceed 2,500 lipase units per kg of body weight per meal (or 10,000 lipase units per kg of body weight per day).

How to take Enzepi
Children (over 1 year of age), adolescents and adults
Enzepi should always be taken with a meal or snack. The capsules should be swallowed whole and take them with a drink of water or juice. If you or your child eat a lot of meals or snacks in a day, be careful not to go over your total daily dose of Enzepi.

If you or your child have trouble swallowing Enzepi capsules, open carefully the capsules and sprinkle the contents (granules) on a small amount of acidic food such as fruit puree (apple/ pear), yoghurt, or juice (orange/pineapple/apple). Do not mix the Enzepi granules with water, milk, breast-milk, formula feeds, flavoured milk or hot food. Ask your doctor about other foods you can sprinkle Enzepi granules on.

If you sprinkle the Enzepi granules on food, swallow the mixture or give it to your child straight after you have mixed it, followed by a drink of water or juice. Make sure the medicine and food mixture is swallowed completely and that no granules are left in your or your child's mouth.

Do not store Enzepi that has been sprinkled on food.

Enzepi capsules or the granules inside them should not be crushed or chewed and the capsules or the granules inside them should not be held in your or your child's mouth. Crushing, chewing or holding the Enzepi capsules in your or your child's mouth may cause irritation in your or your child's mouth or change the way Enzepi works in your or your child's body.

Infants (below 1 year of age)
For infants below 1 year of age, give Enzepi just before each feed of formula or breast-milk. Do not sprinkle the capsule contents directly into the formula or breast-milk. Carefully open the capsule and empty the granules on a small amount of acidic food (see above). If you sprinkle the Enzepi granules on food, give the medicine and food mixture to your child right away and do not store Enzepi that is sprinkled on food. Your child should take all the food mixture and should then drink enough liquid straight after to wash down all the medicine.

You may also sprinkle the granules directly into your child's mouth. Immediately give them milk, formula or breast-milk to drink to ensure the granules are completely swallowed and none remain in your child's mouth.

Look into your child's mouth to make sure that all the medicine has been swallowed.

If you take more Enzepi than you should
If you take more Enzepi than you should drink plenty of water and talk to your doctor as soon as possible.

If you forget to take Enzepi
Do not take a double dose or extra capsules to make up for a forgotten dose. Wait until your next meal, and take your usual number of capsules with your meal.

If you stop taking Enzepi
Keep taking your medicine until your doctor tells you to stop. Many patients will need to take pancreatic enzyme replacement medicines for the rest of their life.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

The most important serious side effects seen with other pancreatic enzyme replacement medicines are 'anaphylactic shock' and fibrosing colonopathy. The frequency of these two side effects is not known. Anaphylactic shock is a severe, potentially life-threatening allergic reaction that can develop rapidly. If you notice any of the following **seek urgent medical attention straightaway**:

- itching, hives or rash
- swollen eyes, lips, hands or feet
- feeling lightheaded or faint
- trouble breathing or swallowing
- dizziness, collapse or unconsciousness.

Repeated high doses of pancreatic enzyme replacement medicines can also cause scarring or thickening of the bowel wall that can lead to blockage of the intestines, a condition called fibrosing colonopathy. If you have severe stomach pain, trouble passing stools (constipation), nausea or vomiting, **tell your doctor straightaway**.

Other possible side effects may include:

Very common (may affect more than 1 in 10 people):

- stomach pain.

Common (may affect up to 1 in 10 people):

- abdominal discomfort or bloating
- flatulence/passing wind
- diarrhoea
- headache.

Not known (frequency cannot be estimated from the available data):

- abnormal/discoloured faeces (stools) or frequent bowel movements
- shortness of breath
- indigestion
- swelling, pain, soreness or irritation in the mouth
- tiredness or general feeling of being unwell (malaise)
- changes (increase or decrease) in blood glucose levels
- changes (increase or decrease) in body weight
- decreased appetite
- high uric acid level in the urine (hyperuricosuria)
- high uric acid level in the blood (hyperuricemia).

If you are diabetic, you should speak with your doctor, if you notice any changes in your blood glucose levels. A dose adjustment may be necessary.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enzepi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

After first opening, the medicine may be stored for a maximum of 6 months below 25°C in its tightly closed container. Keep the bottle tightly closed in order to protect from moisture. Do not discard the sachets (desiccant) from the bottle, these help protect your medicine from moisture. Do not eat or open the desiccant sachets.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enzepi contains

- The active substance is pancreas powder of porcine origin.

  Enzepi 5,000 units gastro-resistant hard capsules
  One capsule contains 39.8 mg of pancreas powder including the following enzymatic activities:
  - lipolytic activity: 5,000 units*
  - amylolytic activity: not less than 1,600 units*
  - proteolytic activity: not less than 130 units*

  Enzepi 10,000 units gastro-resistant hard capsules
  One capsule contains 83.7 mg of pancreas powder including the following enzymatic activites:
  - lipolytic activity: 10,000 units*
  - amylolytic activity: not less than 3,200 units*
  - proteolytic activity: not less than 270 units*

  Enzepi 25,000 units gastro-resistant hard capsules
  One capsule contains 209.3 mg of pancreas powder including the following enzymatic activites:
  - lipolytic activity: 25,000 units*
  - amylolytic activity: not less than 4,800 units*
  - proteolytic activity: not less than 410 units*

  Enzepi 40,000 units gastro-resitant hard capsules
  One capsule contains 334.9 mg of pancreas powder including the following enzymatic activites:
  - lipolytic activity: 40,000 units*
  - amylolytic activity: not less than 7,800 units*
  - proteolytic activity: not less than 650 units*

*Ph. Eur. units

- The other ingredients are:
  - Capsule content: croscarmellose sodium, hydrogenated castor oil, colloidal anhydrous silica, cellulose microcrystalline, magnesium stearate, hypromellose phthalate, talc, triethyl citrate.
  - Capsule shell :
    Enzepi 5,000 units: hypromellose, carrageenan (E407), potassium chloride, titanium dioxide E171, carnauba wax, water.
    Enzepi 10,000 units: hypromellose, carrageenan (E407), potassium chloride, titanium dioxide E171, carnauba wax, water, yellow iron oxide (E172).

Enzepi 25,000 units: hypromellose, carrageenan (E407), potassium chloride, titanium dioxide E171, carnauba wax, water, yellow iron oxide (E172), indigotine E132.
Enzepi 40,000 units: hypromellose, carrageenan (E407), potassium chloride, titanium dioxide E171, carnauba wax, water, indigotine (E132).

- Printing ink: shellac, propylene glycol, indigotine (E132).

What Enzepi looks like and contents of the pack
The Enzepi 5,000 units gastro-resistant hard capsule has a white opaque cap and a white opaque body with 'Enzepi 5' printed on it and contains light-brown gastro-resistant granules.

The Enzepi 10,000 units gastro-resistant hard capsule has a yellow opaque cap and a white opaque body with 'Enzepi 10' printed on it and contains light-brown gastro-resistant granules.

The Enzepi 25,000 units gastro-resistant hard capsule has a green opaque cap and a white opaque body with 'Enzepi 25' printed on it and contains light-brown gastro-resistant granules.

The Enzepi 40,000 units gastro-resistant hard capsule has a blue opaque cap and a white opaque body with 'Enzepi 40' printed on it and contains light-brown gastro-resistant granules.

Enzepi is supplied in plastic (HDPE) bottles with desiccant sachets, closed with a lined polypropylene childresistant closure and a peel-off sealing liner.
Pack size: one bottle of 20, 50, 100 or 200 gastro-resistant hard capsules.

Marketing Authorisation Holder
Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
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Dublin 17
Ireland

Manufacturer
Adare Pharmaceuticals Srl
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.