COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Micrazym 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units, gastro-resistant hard capsule (pancreatin)

NL/H/5258/001-2/DC

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This module reflects the scientific discussion for the approval of Micrazym 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units, gastro-resistant hard capsule. The procedure was finalised on 16-05-2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
LALA	Locally Applied, Locally Acting
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Micrazym 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units gastro-resistant hard capsule, from All-Gen Pharmaceuticals & Generics B.V.

The product 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.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. The procedure was referred to the CMD(h) with a negative outcome. It was then referred to the CHMP, where it was determined that the benefits outweighed the risk.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of pancreatin. For this type of application, the MAH needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. The MAH submitted a justification for bridging between their product and the product used in the literature, Creon 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units gastro-resistant hard capsules (RVG: 10655-6, licenced in 1984), based on comparable composition of the two formulations.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Czechia, Denmark, Finland, France, Germany, Ireland, Luxembourg, Northern Ireland, Norway, Slovakia, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

The two product strengths can be distinguished by the different size and colour of the tablets.

Micrazym 10.000 Ph. Eur. Units is a 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. Each capsule contains as active substance pancreatin corresponding to 8.000 Ph. Eur. Units of amylase, 10.000 Ph. Eur. Units of lipase and 600 Ph. Eur. Units of protease.

Micrazym 25.000 Ph. Eur. Units is a hard gelatin capsules of size 00 (length 23.5 ± 0.4 mm) with an orange cap and transparent body, filled with cylindrical, spherical or irregularly shaped gastro-resistant pellets (micro pellets) of light brown to brown colour. Each capsule contains

as active substance pancreatin corresponding to 18.000 Ph. Eur. Units of amylase, 25.000 Ph. Eur. Units of lipase and 1.000 Ph. Eur. Units of protease.

The excipients are:
Pellets - cetyl alcohol, poloxamer.
Gastro-resistant coating - methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 %, macrogol-4000, talc, simeticone, methyl cellulose, sorbic acid.

The two tablet strengths are dose proportional.

The gastro-resistant hard capsule is packed in white high density polyethylene (HDPE) bottle with a white polypropylene (PP) screw cap containing a coloured white insert block made of low density polyethylene (LDPE) with desiccant inside (silica gel). Each bottle is overpacked in a carton box.

II.2 Drug Substance

The active substance is pancreatin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). It consists of a mixture of several pancreatic enzymes (proteases, amylase, lipase), and other co-extracted (and possibly partly denatured/degraded) components of animal origin. The frozen tissues are obtained from swine that fulfil the requirements for the health of animals suitable for human consumption in accordance to the EU Rules for product of animal origin, collected from approved EEC slaughterhouses in EU countries. The active substance is a slightly brown, amorphous powder which is partly soluble in water and is practically insoluble in ethanol (96%).

Manufacturing process
The manufacturing process consists of grinding, homogenisation, activation, followed by a number of extraction steps with a solvent, followed by centrifugation, drying, milling and sieving, resulting in the intermediate. The intermediate undergoes blending and filling to form the active substance. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 30 months when stored under the stated conditions.

Virus inactivation
The studies supporting virus removal demonstrate that the DS manufacturing process results in significant removal of enveloped viruses. As this is not the case for non-enveloped viruses the homogenized raw material is tested for HEV and EMCV. To exclude risks of HEV

transmission with Micrazym, material that is tests positive for HEV is not qualified for production. Material that tests positive for EMCV is additionally tested for infectivity after processing and not qualified for production if positive. (Re)Validation of the analytical procedures for HEV and EMCV has not been performed and a commitment has been provided to present the results post-approval. In addition, a test for Rotavirus A should be included and an analytical procedure needs to be developed and validated. The integrated evaluation of viral safety and the studies supporting virus removal/evaluation are considered acceptable. The representativeness of the studies for the proposed process has been sufficiently justified. The safety evaluation of the product with respect to non-enveloped viruses has lead to the introduction of controls of the ubiquitous porcine viruses PPV and PCV in the intermediates of the drug substance during monitoring only. Validation of the analytical procedure (qPCR) has not been performed and a commitment has been provided to present the results post-approval. A commitment for Rotavirus A testing/validation has also been made.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form, its development and the choice of excipients is adequately described in accordance with the relevant European guidelines. The suitability of the formulation for the paediatric population has also been adequately described.

Data on enzyme activity of the literature reference products has been provided, as well as a discussion on the potential effect of excipients, as these differ from the formulations of the literature reference products. The provided *in vitro* dissolution study, performed with a suitable dissolution method shows similar dissolution profiles. The bridge between the test product and literature reference products has been adequately established for both strengths after discussion in the CMD(h) and CHMP.

Manufacturing process

The manufacturing process is a non-standard process which consists of six steps: preparation of raw materials, core pancreatin pellets production, coating of pellets, encapsulation, and filling and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. or USP requirements, or in-house specifications. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, enzymatic activity assay, dissolution, average mass and uniformity of mass, uniformity of dosage unit, residual organic solvents, water content, elemental impurities and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control

of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for three primary production batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for six (three of each strength) batches stored at 25°C/ 60% RH (12 months). Accelerated studies were not performed according to ICH Q5C "Stability testing of biotechnological/biological products" it is acceptable to provide real-time/real-temperature stability studies for products where active substance is proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues which is pancreas powder obtained from porcine pancreas The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability study demonstrated that the product is not sensitive to light. The labelled storage conditions are "store below 25°C. After opening use within 3 months" "and keep the bottle tightly closed in order to protect from moisture".

In-use stability data have been provided demonstrating that the product remains stable for 90 days following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for gelatin have been provided and compliance with the "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products" has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Micrazym has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made, due no later than 6 months after marketing authorisation is granted:

- The MAH commits to perform revalidation of qPCR testing for HEV and EMCV (homogenate, specific matrix) and submit the results of the validation.
- The MAH commits to perform revalidation of Infectivity test for EMCV at semi-finished pancreatin matrix and submit the results of the validation.
- The MAH commits to develop and validate the qPCR for PPV and PCV and submit the description of the analytical procedure and the results of the validation.

- The MAH commits to develop and validate a qPCR test for Rotavirus A on homogenate matrix and on semifinished pancreatin. A Positive qPCR test for Rotavirus A will result in batch disqualification.
- The MAH commits to perform a risk calculation for potential HEV contamination based on detection limits of the qPCR for HEV (homogenized pancreas) and process inactivation capacity.
- The MAH commits to perform an additional virus validation study focussing on two non-enveloped model viruses (HAV and EMCV) for the heating step under worst case conditions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The product Micrazym is an enzyme preparation from porcine pancreas intended to be replacing pancreatic enzymes in cases of pancreatic enzyme insufficiencies. Pancreatic enzyme products are commonly used in patients with exocrine pancreatic insufficiency (EPI), including cystic fibrosis, pancreatic surgery, and chronic pancreatitis (Kuhn et al. ,2010; Mössner & Keim, 2011; Sikkens et al., 2010; Trang et al., 2014). EPI can result in decreased absorption of nutrients, steatorrhea, bloating, nausea, pain, diabetes mellitus, abnormal gastric motility, and decreased weight. Maintaining adequate nutrition in patients with cystic fibrosis and EPI can be challenging, as pancreatic insufficiency can occur in 85-90% of the cases (Littlewood et al., 2006). Poor nutrition in patients with cystic fibrosis may result in decreased lung function (Konstan et al., 2003). Patients with chronic pancreatitis or pancreatectomy and EPI may also experience nutritional concerns such as deficiencies in the fat-soluble vitamins A, D, E, and K (Dutta et al. 1982). In turn, this may lead to long-term health-related issues (Giuliano et al., 2011; Imrie et al., 2010; Mössner & Keim 2011; Sikkens et al., 2010).

Pancreatic enzyme replacements are usually of bovine or porcine origin. Generally the name “pancreatin” was used for preparations derived from bovine, and pancrelipase is porcine derived, however, pancreatin is sometimes used to imply porcine derived enzymes (Bauer & White, 1947). Therefore care should be taken when this name is used to make sure that the enzyme derived is from pigs or bovine. As Micrazym is porcine derived, it is important to make as much as possible all preclinical comparisons with porcine derived products. In addition, the main difference between bovine and porcine pancreatic enzymes is the activity of lipase, which is generally higher in pancreatic enzymes of porcine origin, hence the reason pancreatic enzymes for replacement therapy have been largely replaced by porcine derived.

III.2 Pharmacology

Pancrelipase contains a mixture of pancreatic enzymes obtained from porcine pancreas that are used as replacement in pancreatic exocrine inefficiency (PEI). *In vitro* studies showed that pancrelipase, which contains lipase, amylase and protease, is able to break down starch, lipids and proteins (Beck, 1973; Giuliano et al., 2011; Whitcomb & Lowe, 2007). Due to the sensitive nature of enzymes, different branded and generic enzymes had variable activities when tested

in vitro, even between batches (Kuhn et al., 2007). It is acknowledged that potency between different batches of branded and generic drugs can be variable since the enzymes are animal extracts. Nevertheless, *in vitro* activity of pancreatic enzymes has been adequately discussed for the purpose of the non-clinical assessment in a well-established use application.

In vivo models of pancreatic insufficiency indicate that pancrelipase was able to break down starch, lipids and proteins. A study performed in a rat pancreatitis model assessed the effect of pancrelipase on lipid digestion and measured faecal fat content (Naikwade et al., 2009). Faecal fat absorption was reduced in the pancreatitis rats and administration of pancrelipase resulted in enhanced hydrolysis of fats. In a Guinea swine PEI study, enzyme substitution in a pancreatic duct ligation (PDL) model dose-dependently improved the inhibited digestion of particularly fats and proteins, and less for starch (Imondi et al., 1972). In a mini pig study, PDL resulted in a significant reduction of digestibility of crude fat and crude protein, which was concentration-dependently restored upon pancrelipase replacement (Tabeling et al., 1999). In this study, crude proteins were digested in smaller amounts. In conclusion, the results of these studies indicate that pancrelipase supplementation restores the digestibility of fat. Effects on protein digestion were less pronounced. In addition, results indicate that amylase from saliva may contribute to the digestion of starch in addition to the pancreatic amylase.

Two literature studies have been submitted to support secondary pharmacodynamics that indicate that pancrelipase helps in gut maturation. In young rats, signs of gut maturation after administration of Creon included an increase in small intestine length, proximal and distal small intestine weight, adult type enterocytes and pancreas weight (Prykhodko et al., 2015). Creon treatment in piglets was found to increase the crypt mitotic index, villi height and crypt depth, also signs of growth stimulation of the small intestine (Slupecka, 2012). An increase in adult-type enterocytes was also observed in the distal jejunum epithelium. Enzyme treatment did not affect pancreas weight but increased mitotic division of pancreatic acini, indicating gastrointestinal tract development. The MAH discussed that the observed effects in this study are likely to be more important in animal rearing.

Safety pharmacology studies in line with ICH S7A/B have not been performed. A three week acute toxicology study in rats receiving 4% uncoated pancreatin powder in their daily meal revealed that uncoated pancreatic powder caused adverse salivary gland enlargement (Mangos et al., 1969). This effect was not reproduced after intragastric administration of pancrelipase indicating that the effect on salivary gland enlargement was likely due to a reflex arc in the pharynx and is not associated with the presence of pancrelipase in the small intestine. Additionally, gland enlargement was not observed when the pancrelipase powder was heated and administered normally via the oral route, indicating that denaturation of pancrelipase powder prevented gland enlargement. Rats that were administered 4% coated pancreatic powder in their daily meal showed a less pronounced effect on glandular weight increase. Possible reasons that gland weight was still increased compared to the control include impurities of powder in the products, or destruction of part of the coating in the mouth. This effect has not been reported in humans.

There is limited data on pharmacodynamic drug-drug interactions. Submitted literature describes a decrease in iron absorption upon pancrelipase administration in both control rats and rats with exocrine pancreatic destruction, without presenting anaemia (Brozovic et al.,

1966). The increase in iron absorption that was detected in rats with a destroyed pancreas, was reduced to within normal limits by pancrelipase administration. This implies that pancrelipase may interact with iron absorption in the gut, either physiologically as well as when iron supplementation is given, and is a known clinical effect.
In an *in vitro* study protease inhibitors, used in HIV, could inhibit lipases (Wignot et al., 2004). However, *in vivo* studies confirming these findings are lacking.

The non-clinical literature overview presents data derived from experiments with pancrelipase of porcine origin. The primary, secondary and safety pharmacology have been adequately discussed based on available literature for the purpose of a well-established use application.

III.3 Pharmacokinetics

In a single dose study with oral administration of pancrelipase (400 mg/kg) in hamsters with pancreatic cancer, no differences were revealed in absorption of enzymes in blood between treated animals and control animals (Saruc et al., 2012). Similarly, repeated doses (400 mg/kg for 65 days) in hamsters did not result in evidence of absorption of the pancreatic enzymes.
Single dose intraperitoneal (IP) injections of pancrelipase in dogs did result in elevated enzyme levels. However, absorption via IP is not relevant since the product is administered via the oral route in clinical practice.
The absorption of Creon in pigs, using repeated and increasing oral dosing in control, pancreatectomized and PDL pigs, revealed no absorption of lipase or trypsin (Gewert et al., 2004).
The presented literature on the use of pancreatin given to pigs or hamsters support that pancrelipase is not absorbed in the systemic circulation when administered orally. This was evidenced in healthy animals as well as in pancreatic duct ligated and pancreatectomized animals.

Oral pancrelipase is not systemically absorbed. Enzymes in pancrelipase exert their therapeutic effect solely in the GI tract. Hence, no literature studies have been submitted for the distribution to tissues of pancrelipase after oral administration. One publication has been discussed where dogs received pancreatic enzymes after IV administration. Pancreatic enzymes distributed well in plasma, and to a lesser extent in whole blood and to blood cells. However, this study is not considered relevant due to the different route of administration compared to the clinical use.

Pancrelipase is assumed to be degraded in the GI tract into peptide fragments and amino acids, similar as naturally secreted pancreatic enzymes and other enzymes (Appert et al., 1972). Therefore, no non-clinical literature studies have been submitted for the metabolism of pancrelipase after oral administration, which is considered adequate for the non-clinical PK assessment for the purpose of a well-established use application.

Pancrelipase is assumed to be eliminated through faeces as it is not absorbed. In addition, naturally secreted pancreatic enzymes also pass through the faeces. No literature overview has been submitted for the excretion of porcine pancrelipase in animals when given orally, which is acknowledged. Excretion or elimination studies after IV infusion has been evaluated

in dogs and pigs. The results from these studies on IV elimination are variable, most likely due to interspecies variation (Gewert et al., 2004; Hayakawa et al., 1992a; Yacoub et al., 1969). These studies are not considered to be relevant for Micrazym, which is intended to be orally administered.

The submitted literature data are adequate to assess the non-clinical absorption, distribution, metabolism and elimination of pancrelipase for the purpose of a well-established use application.

III.4 Toxicology

Pancrelipase given in a single oral dose of either 1 g/kg or 400 mg/kg to Syrian Gold hamsters revealed no overt signs of toxicity in lungs, pancreas, liver or kidneys and no effects on body weight or pancreas weight (Saruc et al., 2012).

Syrian Gold hamsters with were given 400 mg/kg porcine pancreatic enzymes (PPE) via oral gavage four times a day for 15 days or 400 mg/kg/day via drinking water for 65 days (Saruc et al., 2012). In both studies, no toxicity was revealed in the pancreas, liver, kidneys and lungs. From the literature study it was apparent that in the 65-day experiment, the treatment group exhibited significant loss of body weight, plasma insulin levels and a significant reduction in the size of islets and number of insulin producing cells. The MAH considers that the observed effects are attributed to the fact that high amounts of PPE are given to healthy hamsters. In addition, in other animal and human studies, weight loss was not observed by PPE. Therefore, the observation in this single study is not likely to be clinically relevant.

In a rat 90 day repeat dose toxicity study with an acid resistant pancreatin, histopathological results indicated no effects on heart, brain, adrenals, lungs, oesophagus, stomach, duodenum, small intestine, large intestine, and kidney (Naikwade et al., 2009). Although the literature submitted by the MAH is limited, these studies were not suggestive of overt toxicity of pancrelipase, except for lower plasma insulin and reduced number of beta cells. The results of this study were discussed to be not clinically relevant.

No literature studies on genotoxicity have been reported. The MAH considers it unlikely that pancreatic enzymes are genotoxic because they are endogenous enzymes and do not bind to DNA. This is acknowledged. In addition, CVMP reports no mutagenic effect of pancreatin of animal origin using tests such as the Ames, Saccharomyces-D7-cells, DNA repair system, EUE cell and S9-supernatants for liver microsomal fractions (EMEA/MRL/062/96-Final) (EMEA 1996a).

No literature studies on carcinogenicity have been reported. The MAH considers it unlikely that pancreatic enzymes are carcinogenic, because pancrelipase is composed of endogenous, naturally occurring enzymes. This is acknowledged.

There are no literature studies reported on non-clinical reproductive and developmental toxicity studies. The MAH considers that the likelihood of reproductive and developmental toxicity is low since the product exists of enzymes that do not reach the systemic circulation. Hence, no effects on foetus are expected. This is acknowledged.

No literature studies on local tolerance and other toxicity studies are submitted by the MAH. However, a toxic *in vitro* effect in malignant and non-malignant pancreatic cells has been described following treatment with the PPE preparation, as used in the hamster single dose and repeated dose toxicity studies (Saruc et al., 2012). Cells became necrotic, and this effect was found to be attributed to calcium chloride, a contaminant present in the PPE preparation. No other literature studies that were submitted contained this specific PPE preparation.

The provided non-clinical overview on toxicology is adequate for the purpose of a well-established use application, though it should be considered that clinical experience with pancreatic enzyme products describes a more complete view on the safety aspects.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Micrazym is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

This product has been granted a marketing authorisation for well-established use. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Micrazym is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Pancreatic enzymes act locally in the GI tract and no absorption is needed for their action. Therefore, pharmacokinetic data are not available and no bioequivalence study was performed by the MAH.

The formulation is a non-solution, where after administration no systemic levels can be measured, and is acting locally in the lumen of the gastro-intestinal tract. Therefore, it should be ascertained that the drug is released in the gastro-intestinal tract. The formulation contains core excipients which do not influence local exposure, as is the case for literature reference

product Creon. Dissolution data between Micrazym and Creon using *in vitro* dissolution data applicable for gastro-resistant pellets, i.e. 2 hours pretreatment at pH 1.2 followed by dissolution at pH 1.2 and at pH 4.5 did not show a release of the drug for both formulations. Furthermore, after a 2 hour acid pre-treatment followed by pH 6.0 and a 2 hour acid pre-treatment followed by pH 6.8 comparable dissolution has been shown between Micrazym and Creon. The impact of hydrodynamic forces in the stomach, which may result in loss of pellet integrity and potential dose dumping, has been addressed, showing *in vitro* that the forces at which this happens are much lower than those observed in resistance to crushing on pellets for both Micrazym and Creon. Moreover, a comparable resistance was observed for Micrazym and Creon. Additionally, the pellet size does not prevent the transit trough the stomach in case of a (partly) filled stage, as observed with single unit formulations. This data indicates that an impact of higher hydrodynamic forces in the stomach is unlikely to impact the release of the drug. The *in vitro* dissolution data shows that the drug will be released at the local gastro-intestinal pHs were the place of action is.

IV.3 Pharmacodynamics

Pancrelipase is used as a digestant (ATC-Code A09AA - enzyme containing preparations) for replacement therapy in the symptomatic treatment of malabsorption syndrome caused by established pancreatic insufficiency of organic origin. The main goal of treatment with pancreatic extracts is control of maldigestion. In addition, replacement therapy may provide pain relief although this effect is less clearly demonstrated. The primary function of the enzymes present in the product is to hydrolyse proteins, starches and lipids.

Fats are emulsified before break down such that the lipases are in contact with as many triglyceride molecules as possible. Hydrolysis of fats by lipases occurs in three steps. In the first step a triglyceride molecule is converted to a diglyceride and a fatty acid portion in a rapid reaction, in the second less rapid step another fatty acid is split off the diglyceride and a monoglyceride remains. The remaining fatty acid in the monoglyceride is attached to the second carbon atom of the glycerol. The third step of the reaction, the conversion of monoglyceride to a free glycerol and a fatty acid, is extremely slow. Overall, the main products of triglyceride lipolysis are monoglycerides and fatty acids.

Protein break down to form amino acids or smaller peptides occurs by enzymatic cleavage of the proteins at the peptide bond. Specifically, protease enzymes such as trypsin and chymotrypsin, attack the peptide bond (CO-NH) and break it, releasing either amino acids or peptides. Different proteases have different specificities as to the amino acid peptide bond which they attack (Beck, 1973; Whitcomb & Lowe, 2007). The pancreas is the major source of proteases in the digestive system for the digestion of ingested proteins. The primary proteases are synthesized as inactive pro-enzymes (zymogens) and include trypsin, proelastase, procarboxypeptidase and other proteases. The trypsins, chymotrypsins and elastase are endopeptidase of the serine protease family of enzymes. Trypsin-like proteases hydrolyse peptides at the site of basic amino acids (lysine and arginine); chymotrypsin hydrolyses peptides involving aromatic amino acids (phenylalanine, tyrosine, tryptophan), and elastase splits the protein backbone at bonds at uncharged small amino acids (such as alanine, glycine, and serine) (Whitcomb & Lowe, 2007). The other major class of proteases are metalloproteinases, which include the carboxypeptidases. Carboxypeptidase-A attacks the

last amino acid of a target peptide chain when it is aromatic, neutral, or acidic amino acid, while carboxypeptidase-B attacks basic amino acids. The different isoforms of the enzymes (carb-A and -B) arise from different genes and function optimally under slightly different conditions. However, there is significant overlap in function, such that isolated mutations or deletions of specific pancreatic digestive enzyme genes result in no discernible phenotype (Whitcomb & Lowe, 2007).

The function of amylase is to break down sugars to monosaccharides which is the only form that can be transported by the intestinal mucosa, and hence the need for breaking down sugars or other carbohydrate forms. The disaccharides consisting mainly of sucrose and lactose are hydrolysed to monosaccharides by the intestinal brush border enzymes. Amylases are concerned only with the digestion of starch and glycogen, and is secreted by saliva but also by the pancreas. The digestion of starch and glycogen starts in the saliva, but the salivary α-amylase becomes inactivated when it reaches the acid pH of the stomach. After leaving the stomach, the remaining undigested starch and glycogen enter the duodenum, where they undergo further hydrolysis by pancreatic α-amylase. Starch contains amylose and amylopectin and α-amylase breaks it down to maltose and maltotriose (and dextrins if branched) which are then further hydrolysed to single glucose molecules. α-amylase, is a glycoprotein of 57 kDa, containing a single oligosaccharide chain, and makes up about 5-6% of the total pancreatic secretions (Stiefel & Keller, 1973). The predominant sources of α-amylase are the parotid glands and the pancreas. Unlike other pancreatic zymogens, amylase does not have an inactive proform. Substrate can bind with the first glucose residue in subsite 1 or 2, allowing cleavage to occur between the first and second or second and third glucose residues. Consequently, amylase preferentially cleaves interior α-1,4-glucose linkages (Whitcomb & Lowe, 2007). Neither terminal glucose residues nor α-1,6-linkages can be cleaved by α-amylase. The resulting products of α-amylase digestion are called dextrins, a mixture of maltose, maltotriose, and branched oligosaccharides of 6–8 glucose units that contain both α-1,4 and α-1,6 linkages. Human *in vitro* studies show that amylase is the only glycosidase in human pancreatic fluid (Stiefel & Keller, 1973). As such, it is essential for the digestion of dietary starch. As the intestinal epithelium only absorbs monosaccharides, dietary starch must be hydrolysed into glucose by the action of α-amylase.

Mechanism of action

Pancreas powder 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 in the duodenum and proximal small intestine, enzymes catalyse the hydrolysis of fats to monoglycerides, glycerol, beta-monoglycerides and free fatty acids; protein into peptides and amino acids; and starch into dextrins and short chain sugars such as maltose and maltriose, acting thereby like digestive enzymes physiologically secreted by the pancreas (Giuliano et al., 2011; Whitcomb & Lowe, 2007). Lipase hydrolyses fats into glycerol and fatty acids. In the normal situation, lipase interacts with colipase, phospholipase A2 and bile salts, most effectively in an alkaline environment. Bile salts and phospholipids are further required for the emulsification of fats prior to lipase hydrolysis, and transport of lipophilic digestive products

in micelles and for chylomicron formation (Roy et al., 1988). Amylase (endoamylase) converts starch into dextrins and sugars. Trypsin (endopeptidase) breaks down protein into peptides, proteases and derived substances. Pharmacodynamic effects in humans of pancreatic enzymes has been proved (Bruno et al., 1998).

IV.4 Clinical efficacy

From the pharmacokinetic analysis it can be concluded that the enzymes are released in the duodenum (comparable with the normal physiology) with the claimed enzymatic activity. The clinical comparable efficacy and safety is considered justified. Therefore, a clinical confirmative study is considered unnecessary (and not possible considering the legal basis - art 10a). Moreover, it is not expected that a clinical study is capable to provide sufficient reassurance that two medicinal pancreatin containing products are similar in efficacy and safety. Therefore, a clinical study will not add to the already provided justification.

The literature data cover a large timeframe from 1979 - 2016. This overview summarises 21 separate trials in various indications over the timeframe. The majority of the studies were performed in the eighties/mid-nineties for the indication chronic pancreatitis and cystic fibrosis and included small numbers of patients. The studies were performed with different formulations of pancreatin/pancrelipase/pancreas powder. Ten of these were placebo controlled studies performed in patients with cystic fibrosis, chronic pancreatitis or post-surgical conditions. The objective was to show superiority of Creon 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. The CFA (%, mean ± SD) was higher with Creon 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 Creon was similar to the mean CFA values for Creon in the placebo controlled studies. Treatment with Creon markedly improves the symptoms of pancreatic exocrine insufficiency including stool consistency, abdominal pain, flatulence and stool frequency, independent of the underlying disease.

Systematic review by Taylor et al. (2010) reviewed 12 clinical trials of pancreatic enzyme products (PEPs) in exocrine pancreatic insufficiency (EPI), conducted from 1983 to 2006. These studies found no consistent difference in fat malabsorption or gastrointestinal symptoms between different active treatments and demonstrated that pancreatic enzyme supplements are superior to placebo for fat absorption. Based on data from randomized cross-over trials, pancreatic enzyme supplements appear to improve fat malabsorption. No specific branded product or specific delivery system is superior for treatment of fat malabsorption in patients with exocrine pancreatic insufficiency. No data was identified on long-term use. Typically for pancreatic enzymes, approximately 25,000 to 40,000 Ph. Eur. Units of lipase is required to digest a meal. Ideally the correct amount of lipase should be divided and administered through the course of a meal or immediately after a meal, and dose adjustments made after several days to allow for sufficient time for the enzymes to work.

As comparability with Creon is demonstrated, the indication as generally accepted for Creon is therefore obvious. As argued by the MAH the indication of Creon focuses on the treatment

of CF (although other causes leading to EPI are included by listing the most relevant conditions leading to EPI) and not on the underlying condition. The proposal of the MAH is to focus the indication to the EPI. Based on the indication generally accepted for Creon and the submitted information of the MAH the following indication is considered acceptable:
"(trade name) 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"

IV.5 Clinical safety

Safety data from clinical studies consist of five clinical studies in which a detailed compilation of adverse events was given (Graff et al., 2010; Halm et al., 1999; Santini et al., 2000; Taylor et al., 2016). These safety studies include 201 patients treated with pancreatic enzyme products. The products included in these studies were Pancreatin (mini) microspheres (Creon 10.000), Pancrease, Panzytrat 25.000, Panzytrat 20.000 and Pansine 20. All proposed indications were included and all studies were active-controlled with maximal treatment duration of 4 weeks. The majority of adverse events were gastrointestinal problems, at least partially causally related to the pancreas enzyme products. Gastrointestinal events included diarrhea, vomiting and nausea. General disorders and administration site conditions were often not causally related to the therapeutic use of pancreas enzyme products. Regarding the uncommon and rare adverse events, skin and subcutaneous adverse events may be possibly related to the treatment, as rash and other exanthema may be expression of an allergy. A recent comprehensive compilation contains the following adverse reactions due to pancreatic enzyme products: abdominal pain, bowel fibrosis, bronchospasm, constipation, contact dermatitis, diarrhea, esophagitis, maculopapular rash, nausea, vomiting, oral ulceration, stomatitis, wheezing. Gastrointestinal effects occur in 1-10% of patients. Preparations that are retained in the mouth before swallowing can cause mucosal oral ulceration and stomatitis. Retention of the dosage form in the oesophagus could cause oesophagitis. Very large doses have been associated with hyperuricemia and hyperuricosuria (Ferrone et al., 2007). Pancrealipase causes skin rash (maculopapular rash) in 1% or less of patients. This appears to be part of a porcine hypersensitivity reaction to the pork protein in pancrealipase. Other hypersensitivity reactions such as sneezing and lacrymation have been reported, but are also rare. Pancreatic extract might inhibit folate absorption in patients with pancreas insufficiency as well as in healthy individuals.

In children with CF and treated with high doses PEP, the risk on developing colonic strictures is increased (Borowitz et al., 1995). The pathophysiology of the colonic damage in fibrosing colonopathy is not clear, but is associated with high-dose supplemental pancreatic enzymes, even though there are reports of it occurring before initiation of supplemental enzymes in CF. Therefore, it is recommended upper limit of 2.500 Ph. Eur Units lipase/kg/meal or 10.000 Ph. Eur. Units lipase/kg/day was established. This maximum is meant to prevent further disease and not maximize the absorption.

Pancreatic enzymes act locally in the gastrointestinal tract and are not likely to be systemically absorbed. Some of the constituent amino and nucleic acids are likely to be absorbed along with dietary proteins.

Although the summary of safety data is limited, especially concerning data derived from clinical trials, the listing of adverse events covers the accepted text of the innovator product. Most frequently reported adverse events are confined to the GIT (Gastrointestinal Tract) and can be considered mild, reflecting the local action of the enzymes and the fact that only degradation products (small peptides and amino acids) are absorbed.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Micrazym.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this application, no new clinical studies were conducted, reference is made to the clinical studies and experience with the innovator product Creon. The proposal of the MAH is to focus the indication to the EPI. Based on the indication generally accepted for Creon and the submitted information of the MAH the following indication is considered acceptable: "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" Risk management is adequately addressed. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Micrazym 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units gastro-resistant hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Creon 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units gastro-resistant hard capsules. Creon is a well-known medicinal product with an established favourable efficacy and safety profile.

The Board followed the advice of the assessors.

The procedure was discussed in the CMD(h) meeting on 13 December 2023. The main disagreement between the RMS and the divergent CMSs concerned the sufficiency of *in vitro* dissolution data to establish a bridge demonstrating the similarity of the products applied for and the product described in the referred literature, to support the efficacy and safety of the product in the case of this WEU application, which concerns a gastro-resistant formulation. This was partly based on different understanding of the degree of applicability of the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting (LALA) products in the gastrointestinal tract (CHMP/EWP/239/95 Rev.1, Corr.1). The CMSs remained of negative opinion after the discussion period and therefore no agreement was reached.

The procedure was referred to the CHMP on 21 December 2023.The CHMP was of the view that the data submitted by the MAH was sufficient in this specific case to establish the bridge between the product applied for and the medicine product described in literature, and concluded that the products can be considered as similar in spite of the existing differences, thereby fulfilling the requirements for a well-established use application. The CHMP concluded that the benefits of Micrazym outweigh its risks, and recommended the granting of the marketing authorisation for Micrazym 10 000 Ph. Eur. Units and 25 000 Ph. Eur. Units gastro-resistant hard capsules in all concerned Member States.

The member states, on the basis of the data submitted and the conclusion of the CHMP, considered that essential similarity has been demonstrated for Micrazym 10.000 Ph. Eur. Units and 25.000 Ph. Eur. Units gastro-resistant hard capsule with the reference product, and have therefore granted a marketing authorisation.

The decentralised procedure was finalised with a positive outcome on 16-05-2024.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.