EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Micrazym and associated names

Active substance: Porcine pancreas enzymes

Procedure number: EMEA/H/A29(4)/1535

Note: Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

An application was submitted under the decentralised procedure for Micrazym and associated names (active substance: porcine pancreas enzymes), 10 000 and 25 000 Ph. Eur. Units, gastro-resistant capsules in July 2020.

The legal basis under which the application was submitted is: Article 10(a) of Directive 2001/83/EC.

The application was submitted to the reference Member State (RMS): the Netherlands, and the concerned Member States (CMS): Austria, Belgium, Cyprus, Czechia, Denmark, Finland, Germany, Ireland, Luxembourg, Norway, Spain, Sweden and Slovakia.

The decentralised procedure NL/H/5258/001-002/DC started on 14 October 2020.

On day 210, major issues on the sufficiency of data to support the efficacy and the safety of the product, raised by Germany and Spain, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by the Netherlands on 17 August 2023. The CMDh 60 day procedure was initiated on 23 October 2023.

Day 60 of the CMDh procedure was on 21 December 2023 and as no agreement could be reached the procedure was referred to the CHMP.

Germany and Spain raised objections on the possibility to establish a bridge between the product applied for and the products described in the referred literature based on comparative in vitro dissolution data. These objections were considered to be a potential serious risk to public health. Therefore, on 21 December 2023, the RMS the Netherlands triggered a referral under Article 29(4) of Directive 2001/83/EC.

2. Scientific discussion

2.1. Introduction

Micrazym 10 000 and 25 000 Ph. Eur. units are gastro-resistant micro-pellets of porcine pancreas enzymes in capsules, which act locally in the gastro-intestinal tract and no systemic absorption is needed for their action.

The proposed indication is a replacement therapy 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. The main goal of treatment with pancreatic extracts is the control of maldigestion.

This procedure concerns an application for marketing authorisation via the decentralised procedure. The legal basis is Article 10(a) of Directive 2001/83/EC, whereby the applicant is required to demonstrate that the active substances of the medicinal product applied for have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I of the same Directive. When an active ingredient of a medicine meets the criteria of a well-established use (WEU), application for marketing authorisation may be based on results from the scientific literature. Pancreatic enzymes as contained in Micrazym have been considered to be in well-established medicinal use in the meaning of the above-mentioned Directive.

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).

2.2. Assessment of the issues raised as a potential serious risk to public health

The first point considered by the CHMP was on the potential clinical influence of the differences in size and shape of the pellets contained within the gastro-resistant capsules, as well as the potential impact of excipients differences on the release and action of the active substance locally in the gastro-intestinal tract as intended.

Influence of particle size:

Micrazym and the products described in the submitted literature present differences of capsule's content size, appearance and pellet size. The CHMP acknowledged that the differences in particle size may influence the retention time in the stomach, especially under fed conditions. However, as shown for Creon and Zennep (products containing the same active substance than Micrazym) in the study from literature submitted by the applicant, despite these differences in particle size, no dose-dumping was observed and both products appeared to present a recognised efficacy and an acceptable level of safety (Taylor, 2016). The pellet size in Micrazym is within the range of Creon and Zenpep.

Furthermore, the influence of particle size, comparing between pancreatin mini-microspheres and microspheres, on fat absorption was studied in the literature (Halm, 1999). The primary efficacy parameter was the coefficient of fat absorption which was calculated from fat intake and fat excretion. Although there was a difference in particle size, the coefficient of fat absorption was not different (see table 1).

Table 1 - Coefficient of fat absorption (CFA) with pancreatin mini-microspheres and microspheres

Parameter	Intention-to-treat analysis $n = 23$	Per protocol analysis $n = 18$
CFA, % (s.d.)		
Minimicrospheres	80.1 (13.6)	81.9 (10.6)
Microspheres	80.6 (17.5)	83.3 (12.1)
90% CI	0.92–1.12	0.92–1.06
P-value for equivalence	0.07	0.02

CFA denotes coefficient of fat absorption and 90% CI 90% confidence interval for the ratio minimicrospheres/microspheres (planned interval 0.905–1.105).

Release of the active substance:

The formulation of Micrazym is a non-solution, for which no systemic levels can be measured after administration. The formulation contains core excipients which do not influence local exposure, as it is the case for the products used in the literature studies referred to (e.g. Creon). The CHMP considered

that the excipients used in Micrazym are comparable to those used in most of the similar products containing porcine pancreas enzyme mentioned in literature (see table 2).

Table 2 - Comparison of excipients in different pancreatic enzymes products (PEP)

Creon	Panzytrat	Eurobiol	Panreaze HI	Zenpep (Enzepi)	Cotazym	Micrazym
cetyl alcohol						cetyl alcohol
						poloxamer 407
			hydrogenated castor oil	hydrogenated castor oil		
	colloidal silicon dioxide	colloidal anhydrous silica	colloidal silica	colloidal anhydrous silica		
	magnesium stearate	magnesium stearate	magnesium stearate	magnesium stearate		
			croscarmellose sodium	croscarmellose sodium		
	microcrystalline cellulose	microcrystalline cellulose	microcrystalline cellulose	cellulose microcrystalline		
	crospovidone	crospovidone				
macrogol-4000						macrogol-4000
	methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 %	methacrylic acid-ethyl acrylate copolymer (1:1)	methacrylic acid-ethyl acrylate copolymer		methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 %	methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 %
hypromellose phthalate				hypromellose phthalate		
	talc	talc	talc	talc	talc	talc
dimeticon 1000	simethicone emulsion	simethicone	simethicone		simethicone emulsion	simeticone emulsion: Dimeticone+ silicon dioxide Methyl cellulose Sorbic acid
triethyl citrate	triethyl citrate	triethyl citrate	triethyl citrate.	triethyl citrate	triethyl citrate	
	montane glycol wax	esters of montanic acid and ethane diol (hard wax E).				
gelatin capsule with colorants	gelatin capsule with colorants	gelatin capsule with colorants	gelatin capsule with colorants	hypromellose capsule with colorants	gelatin capsule with colorants	gelatin capsule with colorants

In addition, the applicant provided dissolution data for Micrazym and Creon using in vitro dissolution testing applicable for gastro-resistant pellets. The release of the active substance, porcine pancreas enzyme at pH under 4 would result in degradation of the enzymes (DiMagno, 1977; Kuhn, 2010; Ketwaroo, 2019). However, dissolution testing after 2 hours at pH 1.2 and 2 hours at pH 4.5, showed the active substance, for both formulations were not released. In addition, 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 several other approved products presented in scientific literature. The CHMP considered that these in vitro dissolution data show that the release of the active substance occurs at the local gastro-intestinal pHs where the place of action is intended.

In-vitro in-vivo correlation (IVIVC)

The second point considered by the CHMP was regarding the IVIVC. As the mechanism of action of pancreatic enzyme products (PEP) is based on enzymatic digestion of food components and the pH conditions can be altered in patients with pancreatic insufficiency, the divergent MSs considered that the in vitro dissolution testing data presented by the applicant are not sufficient to establish an IVIVC. The applicant claimed that the in vitro assay for pancreatic enzymes is a measurement of the binding capacity within the dosage form / until reaches equilibrium and measures the total binding capacity (strength) within dosage form in appropriate media digestion (equilibrium binding study); the comparative dissolution is the measurement of binding from released enzymes at predetermined points in-time (dynamic binding study). In addition, the applicant referred to the LALA Guideline (CPMP/EWP/239/95 Rev. 1, Corr.1*) which specifically states that "*in vitro studies based on their binding capacity (e.g. in vitro equilibrium and dynamic binding studies) are considered acceptable*

surrogates for the assessment of efficacy, as long as excipients are not critical and disintegration and dissolution profiles in the physiological pH range (as appropriate) are similar". Therefore, the applicant claimed that this statement indicates the sufficiency of the in vitro dissolution testing used in the case of Micrazym to establish an IVIVC.

The CHMP considered that the concept of binding capacity e.g. applicable to phosphate binders as per the LALA guideline cannot be translated one-to-one to the lipolytic binding used to measure enzymatic activity in the pancreatic enzyme assay. Therefore, the CHMP did not comment further on the nature of the IVIVC. However, the CHMP overall considered that the measurement of the lipolytic activity after dissolution, at different pHs relevant for this enteric coated formulation, and the determination of the lipolytic, amylolytic and proteolytic activity at defined pH are considered valid in vitro data to support the release and activity at the place of action. Therefore, also considering the broad therapeutic window of PEP, an in vivo study was not considered necessary.

Resistance to crushing:

Finally, the last point considered by the CHMP was the impact of hydrodynamic forces in the stomach that may result in loss of pellet integrity and thus a potential dose dumping in the event that the enzymes are released in pH<4. As described above, in this strongly acidic environment the enzymes would be degraded and thus the treatment would be non-efficacious. The applicant made reference to a published study, indicating that hydrodynamic forces may have an impact on the pellet integrity (Mudie, 2010). However, the forces at which this happens (approximately 1.89 N) are much lower than those observed in crushing resistance tests on pellets for both Micrazym and Creon that the applicant has performed (see table 3).

Table 3 – Average crushing force for Micrazym and Creon

Product	**Average Crushing force (Newtons, N)**	**Standard Deviation**
Micrazym 10,000	**21.26***	4.17
Creon 10,000	**19.43**	3.74
Micrazym, 25,000	**18.65**	3.35
Creon 25,000	**18.47**	1.99

In addition, a comparable crushing resistance was observed for Micrazym and Creon (see figure 2).

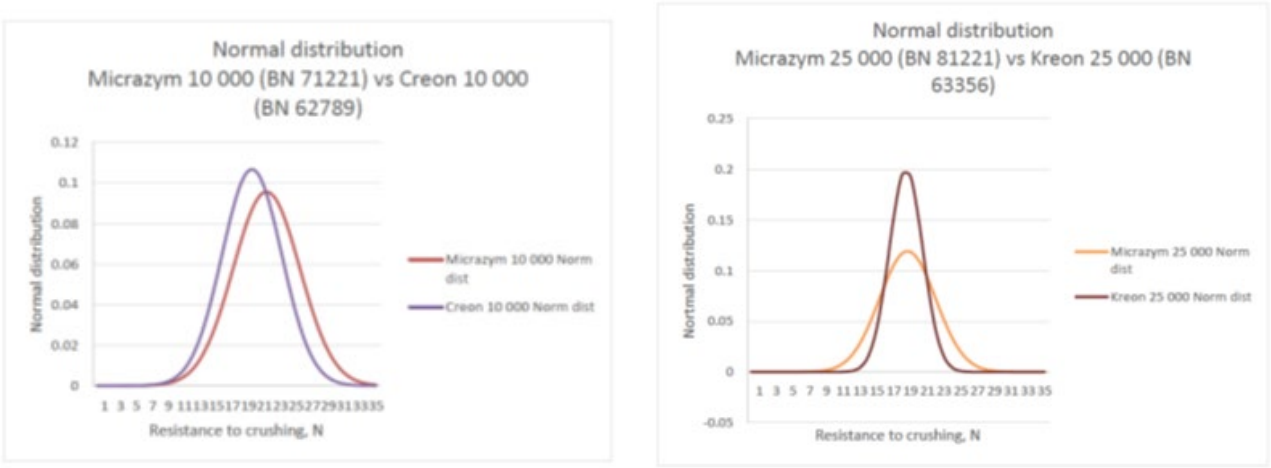

Figure 1 – Comparison of the crushing resistance between Micrazym and Creon

The CHMP considered this data sufficient to show that the impact of hydrodynamic forces in the stomach will not result in loss of pellet integrity.

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 CHMP noted that pancreatin (pancreatic enzymes, like the active substance in Micrazym) is mentioned in the LALA guideline. Whilst the scope of the guideline is limited to chemical entities, its principles are still intended to provide guideline for these biological active substances. The CHMP considered that the need for additional in vivo testing to establish a bridge as compared to the product in the chosen literature was not a prerequisite for this WEU application, as long as the data submitted, including published scientific literature and in vitro studies, are sufficient to demonstrate the release and action of the active substance locally in the gastro-intestinal tract as intended. On a case-by-case basis, as for this specific marketing authorisation application, this would justify deviating from the LALA guideline, including from the decision tree for products acting locally in the intestine.

3. Benefit-risk balance

This referral concerns Micrazym 10 000 and 25 000 Ph. Eur. Units, gastro-resistant micro-pellets of porcine pancreas enzymes in capsules. The legal basis for this procedure is Article 10(a) of Directive 2001/83/EC, whereby, as the well-established medicinal use of the active substance of Micrazym was considered to be demonstrated, with recognised efficacy and an acceptable level of safety, the application for marketing authorisation may be based on results from scientific literature.

The proposed formulation is a non-solution, for which no systemic levels can be measured after administration. It acts locally in the lumen of the gastro-intestinal tract. Therefore, it should be ascertained through the data provided that the active substance, porcine pancreas enzyme, is released in the gastro-intestinal tract at the intended site of action in the duodenum.

The proposed formulation contains core excipients which do not influence local exposure, as is also the case for the products used in the literature studies referred to. The gastro-resistant coating excipients contained in Micrazym are comparable to those in most of the products mentioned in submitted literature. Moreover, the comparison between authorised medicinal pancreatic enzyme products presented in scientific literature showed that, despite differences in capsule sizes and contents, all appeared to present a recognised efficacy and an acceptable level of safety.

In vitro dissolution data applicable to gastro-resistant pellets demonstrated that for Micrazym, like for Creon (one of the products referred to in the scientific literature), the active substance is not released at pH <4.5, thereby preventing the degradation of the enzymes prior to the intended site of action. Furthermore, comparable dissolution has been shown between Micrazym and Creon at pH 6 and 6.8 (after 2h pretreatment at pH 1.2), pH levels corresponding of the site of action. These in vitro dissolution data show that the active substance will be released at the local gastro-intestinal pH's where the place of action is (i.e. in the duodenum where the enzymes enter the gastrointestinal tract in physiological circumstances) and no further dissolution tests at other pH levels were considered necessary.

The CHMP acknowledged that the mechanism of action of pancreatic enzyme products (PEP) is based on enzymatic digestion of food components and that the pH conditions can be altered in patients with pancreatic insufficiency. However, the CHMP considered that the measurement of the lipolytic activity after dissolution, at different pHs relevant for this enteric coated formulation, and the determination of the lipolytic, amylolytic and proteolytic activity at defined pH are considered a valid in vitro test to support the release and activity at the place of action.

In conclusion, the CHMP considered that the data submitted, including published scientific literature and in vitro studies, are sufficient in this case to demonstrate the release and action of the active substance locally in the gastro-intestinal tract as intended, and thus a comparable efficacy and safety. Therefore, also considering the broad therapeutic window of PEP, the CHMP considered that there was no need for additional in vivo testing in the particular case of this locally acting biological active substance.

The CHMP was of the view that the data submitted by the applicant were sufficient in this specific case to establish the bridge between the product applied for and the medicinal 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 and 25 000 Ph. Eur. Units gastro-resistant micro-pellets in capsules in all concerned Member States.

4. Grounds for Opinion

Whereas,

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data submitted by the applicant, including published literature and in vitro dissolution data, in relation to the objections raised as potential serious risk to public health.
- The Committee considered that the provided data including in vitro dissolution data are sufficient to demonstrate the release and action of the active substance locally in the gastro-intestinal tract as intended.
- In the specific case of this well-established use application, the Committee was of the view that the data submitted establish a bridge between Micrazym and the product described in the scientific literature and therefore demonstrate their similarity.

The Committee, as a consequence, considers that the benefit-risk balance of Micrazym and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.

References

DiMagno EP et al., "Relation between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency", New England Journal of Medicines Vol. 288, 1977, (16) 813-815.

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Ketwaroo GA et al., "Rational Use of Pancreatic Enzymes for Pancreatic Insufficiency and Pancreatic Pain", Adv Exp Med Biol. 2019:1148:323-343

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Appendix 1

Divergent position

Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29(4)/1535

Micrazym and associated names (active substance: porcine pancreas enzymes)

Divergent statement

The following CHMP Members consider that the benefit/risk balance of Micrazym and associated names is not favourable based on the following grounds:

The *in vitro* data provided are not sufficient to allow transferability of the literature data to the product under evaluation for the following reasons:

- Similar contents of active substance and similar dissolution profiles at standard pH levels are not considered sufficient to establish a bridge between different gastro-resistant formulations with an active substance intended to act locally in the intestinal tract.
- There are potentially clinically relevant differences in the properties of the product applied for compared to the product used in the published studies to demonstrate efficacy. These pertain to qualitative and quantitative differences in excipients, including the pharmaceutical principle of acid resistance, differences in size and shape of the pellets included in the dosage form, and subtle differences demonstrated in the dissolution profiles at pH 6.0 and 6.8.
- An *in-vitro-in-vivo*-correlation for dissolution profiles under compendial conditions has not been established. Based on the facts that the product needs to be taken with food to assure synchronous emptying from the stomach as well as release in the duodenum, and the fact that the pH conditions and motility are greatly altered in patients with pancreatic insufficiency, the conducted dissolution tests are not considered to reliably simulate *in-vivo* conditions.

As a consequence, there is a need for additional *in-vivo* testing to assure similar clinical performance compared to the product in the chosen literature.

CHMP Members expressing a divergent opinion:

- Maria Conception Prieto Yerro
- Helena Panayiotopoulou
- Jan Mueller-Berghaus
- John Joseph Borg
- Martina Weise
- Sol Ruiz