Annex II

Scientific conclusions

Scientific conclusions

This referral concerns an application for marketing authorisation via the decentralised procedure for Micrazym 10 000 and 25 000 Ph. Eur. units, gastro-resistant capsules. The legal basis 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.

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.

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).

Overall summary of the scientific evaluation by the CHMP

The proposed formulation contains core excipients which do not influence local exposure, as it 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 to 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 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 and 25 000 Ph. Eur. Units gastro-resistant micro-pellets in capsules in all concerned Member States.

Grounds for the CHMP 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 established 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.