COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pantriozyme 25,000 units, hard gastro-resistant capsule

(pancreatin)

RVG: 34948

Date: 26 November 2018

This module reflects the scientific discussion for the approval of Pantriozyme 25,000 units, hard gastro-resistant capsule. The procedure was finalised on 2 June 2010. 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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Pantriozyme 25,000 units, hard gastro-resistant capsule, from Nordmark Arzneimittel GmbH & Co.KG.

The product is indicated for exocrine pancreatic insufficiency as occurring in:

- Cystic fibrosis of the pancreas
- Chronic pancreatitis
- Post pancreatectomy
- Partial or total gastrectomy

A comprehensive description of the indications and posology is given in the SPC.

Pancreatin is not absorbed following oral administration, but exerts its action locally in the gastrointestinal tract. Pancreatic enzyme products assist in breaking down in the small intestine the substances ingested as food. 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 milieu. 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 chylomicrons formation.

This national procedure concerns a well-established use application for pancreatine 300 mg. Creon 150 mg (NL License RVG 10656) is the innovator product of pancreatin and has been registered in the Netherlands by Abbott B.V. since 27 July 1988. Creon Forte 300 mg prolonged-release capsules (NL License RVG 16055) (Licensed 22 March 1994) resembles the proposed product the most, considering the product potency per capsule, which differs slightly from Pantriozyme: pancreatin 300 mg equivalent with 25.000 Ph. Eur. U lipase, 18.000 Ph. Eur. U amylase and 1.000 Ph. Eur. E protease. In the Netherlands a total of 20 pancreatin containing products are approved at the moment.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of pancreatin. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and

must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a well-established use application.

II. QUALITY ASPECTS

II.1 Introduction

Pantriozyme 300 mg is a hard gelatin capsule filled with microspheres containing 287 to 366 mg pancreatin, corresponding to:

- 25.000 I.E. lipase
- at least 18.125 I.E. amylase
- at least 1.050 I.E. protease

The gastro-resistant capsules are packed in an amber glass tablet container with a white PE snap-on cap with a sealing system.

The excipients are: methacrylic acid – ethyl acrylate – copolymer (1:1), triethyl citrate, talc, simethicone 20% emulsion.
The gelatin capsules also contain titanium dioxide (E171) and sodium lauryl sulphate.

II.2 Drug Substance

The active substance is pancreatin (= “pancreas powder”), an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a pancreas extract originating from pigs as animal source and comprises a mixture of enzymes with lipolytic, amylolytic and proteolytic activity. These enzymes are acid-sensitive and are irreversible inactivated with further decreasing pH-values below 4. The substance is an amorphous powder, which is partly soluble in water.

Manufacturing process
Assessment of the manufacturing process is based on a CEP assessment by the EDQM. Additionally the MEB assessed the limit for a residual solvent and the virus safety risk. These are adequately controlled.

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

Stability of drug substance
Stability data on the active substance have been provided for 4 batches in accordance with applicable European guidelines. The batches were stored at 25°C/60% RH and 40°C/75% RH. The retest period (6 months) and storage condition (store in the original package in order to protect from humidity) has been sufficiently justified.

II.3 Medicinal Product

Pharmaceutical development
Gastro-resistance has been sufficiently justified and is under control. A 10% overage drug substance (based on lipase activity) is included. Sufficient in vitro dissolution data have been provided. BE studies are not relevant as the product exhibits a local effect in the intestine.
The pharmaceutical development has been sufficiently described.

Manufacturing process
The process is non-standard (formation of pellets, enteric coating of the pellets and filling of these into empty capsules). Several questions were raised regarding missing process details and IPC limits regarding the activities of the coated pellets, and regarding the process validation (including regarding content uniformity); these points were sufficiently solved. Process validation data are present of sufficient representative batches.

Control of excipients
The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The intermediate product specifications (enteric coated pellets) includes tests for appearance, identity, assay/activity, dissolution, microbiological purity, loss on drying and these are justified. The finished product specification includes the same tests as the intermediate product specification, and additionally uniformity of mass and disintegration. The shelf-life specification is identical to the release specification except for assay: lower limits are including for the lipolytic activity than the amylolytic and proteolytic activities (as the lipolytic activity decreases). Batch analytical data from the proposed production site have been provided on sufficient representative batches, including production batches.

Stability of drug product
Stability data on the product have been provided for three batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). At all storage conditions a decrease in lypolytic activity is observed. At intermediate and long term conditions the results remain within specification.

Based on the results provided, the claimed shelf-life of 3 years when stored below 25°C, was granted. Furthermore, in-use stability was demonstrated for 26 months, when stored below 25°C. The product should be stored in the original container to protect from moisture and light.

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

Except for gelatin there are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product. Regarding gelatine, TSE Ph. Eur. Certificates of Suitability from the capsule supplier have been submitted. A theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Pantriozyme has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pancreatin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

III.2 Discussion on the non-clinical aspects

Pancreatin has been available on the European market for over 20 years. A non-clinical dossier has been provided, which sufficiently substantiates the well-established use of pancreatin regarding pharmacology, pharmacokinetics and toxicology. Adequate scientific publications were used. The Board agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pancreatic enzyme replacement therapy in the treatment of exocrine pancreatic insufficiency is known for several decades. The innovator product of pancreatin (Creon 150 mg (RVG 1065)) was approved in 1988 and today a total of 20 pancreatin products are approved in the Netherlands. The literature data summarised cover a large timeframe from

1983-2006, part of them do not comply with current GCP guidelines. A lot of studies lack some part of important information in their description hampering selection of pivotal studies. The majority of the studies are considered supportive.

The current submission summarises 76 trials in various indications over the period 1983-2006. 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.
A large proportion of the submitted studies included active-controlled studies. In most cases the active control consisted of the conventional enzyme preparations without acid protection. These studies were considered as supportive data.

IV.2 Pharmacokinetics

Animal studies showed no evidence for absorption of intact enzymes and therefore classic pharmacokinetic studies have not been performed. Pancreatic enzyme supplements do not require absorption to exert their effects. On the contrary, their full therapeutic activity is exerted from within the lumen of the gastrointestinal tract. Furthermore, they are proteins, and as such undergo proteolytic digestion while passing along the gastrointestinal tract before being absorbed as peptides and amino acids (IFHP 2006, Customized Monograph 2004).

A large portion of oral pancreatin given as immediate release preparations is inactivated by gastric juices and bacteria during the transit to the distal small intestine (Bruno et al. 1995). Several authors have demonstrated that enteric-coated pancreatic enzyme products are more effective than conventional (non-enteric-coated) preparations (Dutta et al. 1983, Lankisch et al. 1986, Schneider et al. 1985). As a consequence of the rapid and irreversible denaturation of pancreatic enzymes (including lipase which is the most sensitive) at pH values below 4.0, conventional preparations are inactivated by gastric acid. Enteric-coated preparations offer partial protection against acidic destruction of lipase. The pancreatin microspheres are coated with a pH-sensitive surface aimed to dissolve above a safe pH threshold in the duodenum (commonly 5.0-5.5) (Adler et al. 1993, Mundlos et al. 1990). Pancreatin granules sized 1.0-1.5 mm seem to empty together with dietary lipids as shown in a clinical investigation in 7 patients with chronic pancreatitis and exocrine pancreas insufficiency (Norregaard et al. 1996). Although the optimal particle size has not yet been firmly established a particle size range of approximately 1 to 2 mm appears to ensure a high digestive potency for enteric-coated pancreatin particles (Lippold 1998).

Lipase, amylase and protease are subject to intraluminal degradation by digestive proteases during the transit to the distal small intestine and are absorbed as peptides and amino acids. Lipase activity is lost most rapidly, amylase and proteases are more stable. After absorption, constituents are subsequently excreted in the urine. Unmetabolised pancreatin is excreted in the faeces (Customized Monograph 2004).

The pharmacokinetics of pancreatin in paediatric or elderly populations does not appear to differ from the pharmacokinetic parameters of young adults (Customized Monograph 2004). No information was provided on use in patients with renal or hepatic impairment.

Pancreatic enzymes as such are not absorbed and act locally; therefore the Board considers absence of pharmacokinetic studies acceptable. Plasma levels may play a role with regard to safety, but absence of these data is most likely not to be a problem for the current application as only degradation products (small peptides and amino acids) are absorbed.
The formulation is an enteric coated formulation as enzymes are unstable under acid conditions. Stability of the formulation under acid conditions is proven by in vitro dissolution tests, which is considered acceptable. For evaluation and assessment reference is made to the quality assessment report.

IV.3 Pharmacodynamics

Human pharmacodynamics
Pancreatin is used as a digestant (ATC-Code A09AA - enzyme containing preparations) used for replacement therapy of 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.

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Control of maldigestion
Pancreatic enzyme products assist in breaking down in the small intestine the substances ingested as food. 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 milieu. 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. Amylase activity is even sufficient in severe exocrine pancreatic insufficiency and is only important in respect to patients with cystic fibrosis (Henker et al. 1993). Trypsin (endopeptidase) breaks down protein into peptides, proteases and
derived substances.

Pancreatic synthesis and secretion of lipase is the first key enzyme to be impaired in pancreatic insufficiency. Furthermore, its luminal digestive action is hardly compensated by non-pancreatic mechanisms. As a consequence, steatorrhoea is generally more severe and occurs several years before clinical malabsorption of protein or starch. The most important

clinical goal of replacement therapy is to achieve a sufficient lipase activity in the duodenum and to restore gastrointestinal physiology as completely as possible.

Pain control

Inhibition of endogenous pancreatic enzyme secretion by oral pancreatic enzyme treatment by a feedback mechanism in humans was demonstrated by Walkowiak et al. (2003). Exogenous pancreatic enzymes, particularly protease (principally trypsin), may suppress cholecystokinin release and probably other gastrointestinal peptides which act as secretagogues on the exocrine pancreas (Mössner 1993). This observation could provide some support for the hypothesis that the administration of exogenous pancreatic enzymes may decrease pancreatitis-associated pain by suppression of the pancreatic secretion. Although administration of large amounts of proteases provided pain relief in some patients, the rationale for using enzymes to relieve pain in chronic pancreatitis has not been generally accepted.

The Board notes that the pharmacodynamic action of lipase is well known and its mode of action in lipid malabsorption is clearly and adequately explained. This also accounts for amylase and protease based on their mode of action. They may play a role in malnutrition. The deficiency of amylase and protease in exocrine pancreatic insufficiency is however, not clearly demonstrated.
The rationale for using enzymes to relieve pain has not been generally accepted.
It is acknowledged that a variety of drugs including amylase and protease are currently licensed for the same indications.

IV.4 Clinical efficacy

Chronic pancreatitis

The placebo-controlled double-blind studies by Paris (1993) and Cavallini et al. (1996) are described here into more detail as they included enzyme preparations with comparable units of lipase, used faecal fat excretion as the primary endpoint and included relatively high numbers of patients.
Paris (1993) studied the efficacy and tolerability of Panzytrat (2 capsules three times daily) compared to placebo in adult patients with chronic alcoholic pancreatitis and steatorrhoea. Information on age- and gender distribution was not available. There was a 7- to 9- day prestudy period and the treatment duration was 7 days. A total of 72 patients were randomised to either Panzytrat 25000 or placebo. 24 Panzytrat treated patients and 17 placebo-treated patients completed the study. Steatorrhoea pre-treatment was 52.7 g/day in Panzytrat treated patients and 27.6 g/day in placebo-treated patients.
Steatorrhoea post-treatment was 26.2 g/day and 29.8 g/day, respectively for Panzytrat- and placebo-treated patients. Panzytrat significantly reduced steatorrhoea and creatorrhoea compared to placebo. It should be noted that pre-treatment steatorrhoe was very different for both treatment groups. Its impact on the efficacy results is unknown.
Cavallini et al. (1996) studied the efficacy and tolerability of lipase rich enteric coated microtablet preparations containing 25000 Ph.Eur.U lipase (2 capsules three times daily) compared to placebo in patients with chronic pancreatitis. The study included 104 patients, 90 males and 14 females aged between 27 and 70 years. The lipase-containing preparations

significantly reduced fat excretion compared to placebo. Faecal fat less than 7 g/day was achieved in 54% of patients treated with Panzytrat compared to 19% of patients after treatment with placebo.
Other placebo-controlled studies were consistent in showing a decrease in faecal fat excretion. Placebo-controlled studies with pain as a primary efficacy endpoint were inconclusive: A significant reduction in pain as a result of the treatment was described by Isaksson & Ihse (1983), whereas Mössner et al. (1992) did not see any influence on the pain score.
Active controlled studies showed a stronger reduction of steatorrhoea, dyspeptic attacks and need for an analgesic (Spicak et al. 1992, Delchier et al. 1991, Schneider et al. 1985, Brackmann & Ruther 1984), a similar effect (Lankisch et al. 1986, Dutta et al. 1983) or better results with the conventional preparation (Marotta et al. 1989).

Some studies indicate a dose-dependent effect of an enteric-coated pancreatic enzyme preparation on steatorrhoea (Malesci et al. 1994, Pap & Varro 1988) with no improvement beyond 125,000 IU lipase/day (Pap et al. 1997), while others did not (Vecht et al. 2006).

The Board reckons that the summary adequately describes the studies performed demonstrating efficacy of pancreatic enzymes in the treatment of chronic pancreatitis with the clinically relevant primary endpoint faecal fat excretion. Although most studies included small numbers of patients and a wide variety of formulations were used, they support the conclusion that Pantriozyme can be used in patients with fat malabsorption to reduce faecal fat excretion in patients with chronic pancreatitis. Efficacy on the reduction of abdominal pain was not shown.

Cystic fibrosis
The placebo-controlled study by Stern et al. (2000) is considered a pivotal study for Pancreatine 25000 A and described into more detail. Stern et al. (2000) studied the efficacy and tolerability of pancrelipase minimicrospheres capsules (Creon 20, 20000 USP U lipase, 75000 USP U protease, 66400 USP U amylase) in CF patients with clinical exocrine pancreatic insufficiency and steatorrhoea and with a coefficient of fat absorption >80. The primary endpoint was fat absorption. Information on duration of treatment was not included. Initially 97 patients were given a high fat diet and stabilised with pancrelipase (open label phase), after which 74 patients were (1:1) randomised in the double blind placebo controlled trial, including 36 adults (mean age of 24 years) and 38 paediatrics (mean age 12 years). The placebo group experienced significantly more steatorrhoea than the pancrelipase group. Patients on placebo had a significant ($p < 0.001$) mean decrease in coefficient of fat absorption (adult, 36.9 percentage points; paediatric/adolescent, 34.9 percentage points) from open-label to double-blind treatment compared to pancrelipase patients (adult, 2 percentage points; paediatric/adolescent, 3.25 percentage points); this difference was caused by a greater ($p \leq 0.001$) increase in mean faecal fat excretion (grams per day) in the placebo groups compared to pancrelipase groups (adult: 61.9 versus 2.3; paediatric/adolescent: 45.4 versus 4.1). Change in mean stool frequency from open-label phase to double-blind phase was significantly different ($p \leq 0.002$) between treatment groups, with increases in placebo groups and no difference (adult) or further decrease (paediatric/adolescent) in pancrelipase groups.

Information on dose-responsiveness is limited. The active-controlled studies are considered as supportive. Several studies showed a stronger reduction of steatorrhoea (Henker et al. 1989, Ansaldi-Balocco et al. 1988, Dutta et al. 1988, Mitchell et al. 1982, Gow et al. 1981) compared with the conventional (not acid-protected) preparations.

The summary describes the studies performed demonstrating efficacy of pancreatic enzymes in the treatment of CF with the clinically relevant primary endpoint faecal fat excretion. The studies support the conclusion that Pantriozyme can be used in patients with fat malabsorption to reduce faecal fat excretion in CF patients.

Surgery

A limited number of studies was performed in patients with fat malabsorption after surgery, including three placebo-controlled studies. The largest one was a double-blind trial by Bragelmann et al. (1999) including 52 patients with steatorrhoea after total gastrectomy and with a faecal fat output ≥14 g/day. Patients were randomised (1:1) to treatment with 9 sachets of Panzytrat or placebo and the treatment duration was 14 days. The study included 38 males and 14 females and the average age was 56-57 years. The primary endpoint was fat malassimilation. In the total patient group, the median (interquartile range, IQR) for faecal mass and faecal fat output per day were (316 g (236-443) and 23.0 g (16.3-35.2), respectively. During the intervention, there was a non-significant decrease in median faecal mass end median faecal fat output in patients treated with Panzytrat, resulting in a non-significant trend to improved fat assimilation (20.8% before treatment (IQR 16.4-30.4) and 15.5% during treatment (IQR 9.2-24.9), respectively (p=0.1), whereas these parameters did not change in patients receiving placebo (19.4% before treatment (IQR 14.3-27.1) and 18.7% during treatment (IQR 11.7-29.1), respectively (p=0.4).
The other two placebo-controlled studies by Armbrecht et al. (1988) and Van Hoozen et al. (1997) included 15 and 11 patients. Armbrecht et al (1988) included patients after total gastrectomy for carcinoma of the stomach with a mean age of 64 years. Treatment with Pancreatin 3.6 g/day (Creon) for 7 days significantly reduced faceal fat excretion only in patients with massive steatorrhoea (free and esterified fatty acids > 350 mmol/72 hour); upper reference limit 60 mmol/72 hours). Van Hoozen et al. (1997) performed a placebo-controlled study in patients with local resection-longitudinal pancreaticojejunostomy. Patients received Pancreatin (Creon) for four weeks followed by 4 weeks of Pancreatin or placebo. Pancreatin supplementation significantly improved the coefficients of absorption of dietary fat and total energy over the next four weeks. Between four and eight weeks, pancreatin significantly improved protein absorption and nitrogen balance, whereas placebo worsened the absorption of dietary fat and total energy. Nutritional status was not significantly altered over the 8-week study period.

Limited data exist on the efficacy of pancreatic enzyme supplementation in patients with malabsorption after surgery. The provided data are inconclusive on the efficacy of pancreatin in this indication. It is, however, reasonable to assume that in this population supplementation of pancreatic enzymes should at least be able to (partly) improve fat absorption.

Dosing regimen

The proposed dose regimen is 1 capsule per meal. The dose of Pancreatin may be adjusted according to the severity of exocrine pancreatic insufficiency. The total daily dose should not exceed 15000 IE lipase per kg body weight.

The most important determinant of the effectiveness of pancreatic enzyme preparation is lipase. The lipase dosage necessary is about 100,000 Ph.Eur.U/day, equivalent to 20,000-40,000 Ph.Eur.U/meal.
Depending on the pancreatic enzyme preparation, this means 1-4 capsules for a main meal and 1-2 capsules for a snack (Lankisch 2001). There is no simple linear relationship between the dosage of supplemental lipase and corresponding faecal fat excretion though. The administration of enteric-coated pancreatin in dose schedules of 50,000, 100,000 and 150,000 U of lipase per day achieved a decrease in faecal fat excretion of 45, 60 and 70% respectively compared to faecal fat measurements with placebo in a group of patients with chronic pancreatitis (Kolbel et al. 1986).
In children with CF, high doses have been associated with the development of fibrosing colonopathy and therefore doses exceeding 10,000 U of lipase activity per kg body weight are discouraged (Martindale 2005).
There are no data on dosage adjustments in special patient groups like patients with hepatic or renal impairment. It appears that no dosage adjustments are needed (Customized Monograph 2004).

The proposed dosing regimen for Pantriozyme is in line with the literature data and similar to the dosing regimen for Creon Forte 300 mg.
There are no data provided on use in patients with hepatic or renal impairment.

IV.5 Clinical safety

Clinical trials

Safety data from clinical studies consist of 5 clinical studies in which a detailed compilation of adverse events was given (Santini et al. 2000, Halm et al. 1999, Schauerte 1998, Delbrück 1997, George et al. 1990). These safety studies include 953 patients treated with pancreatic enzyme products. Except for the reference of Schauerte 1998, a study synopsis was added to the summary of clinical safety. The products included in these studies were Pancreatin (mini) microspheres (Creon 10000), Pancrease, Panzytrat 25000, Panzytrat 20000 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 diarrhoea, 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.

Reviews

A recent comprehensive compilation contains the following adverse reactions due to pancreatic enzyme products (Customized Monograph 2004): abdominal pain, bowel fibrosis, bronchospasm, constipation, contact dermatitis, diarrhoea, esophagitis, maculopapular rash, nausea I 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 (AHFS 2006, Martindale 2005). Retention of the dosage form in the oesophagus could cause oesophagitis. Very large doses have been associated with hyperuricemia and hyperuricosuria. 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.

Pancrealipase powder is irritating to the nasal mucosa and respiratory tract, and may produce bronchospasm and wheezing. Contact dermatitis may occur in patients who get pancrealipase powder on their hands or skin (Customized Monograph 2004).

Interactions

Pancreatic extract significantly inhibited folate absorption in patients with pancreas insufficiency as well as in healthy individuals. (Martindale 2005).

Studies in special patient groups

No specific studies were submitted in children or elderly. Children with cystic fibroses on high doses of pancreatic enzyme preparations seem to have a higher risk on developing colonic strictures. Therefore it is recommended, unless special reasons exits, not to treat children with high doses, and to monitor carefully for gastrointestinal obstruction (Martindale 2005).

Animal reproduction studies have been performed with pancrelipase microspheres or microtablets and revealed no evidence of impaired fertility or harm to the foetus. Animal reproduction studies have not been performed with pancreatin and pancreatin should therefore be used during pregnancy only when clearly needed (AHFS 2006).

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. The possibility of the protein constituents appearing in the breast milk can not be excluded (Drug Consult 2004). Pancreatin should be used with caution in nursing women, since it is not known if the drug is distributed into milk (AHFS 2006).

Post-marketing experience

The submitted post-marketing experience is limited to spontaneous case reports on adverse reactions, which are in line with the adverse reactions already mentioned. No other information is provided on post-marketing experience with pancreatin products, including epidemiological studies.

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 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.
In addition, the updated SPC includes all changes requested by the assessor during the first assessment and is identical to that of the innovator.
The submitted post-marketing experience is limited and lacks information from epidemiological studies demonstrating well-established use.

IV.6 Discussion on the clinical aspects

Pantriozyme contains pancreatin which has been on the market in the European Community for more than 10 years. The present application is based on well-established use. The literature data discussed in the summary of clinical efficacy support the efficacy of Pantriozyme in fat malabsorption in patients with chronic pancreatitis or CF in short term use. The data do not provide substantial evidence for efficacy in patients after pancreatectomy and total or partial gastrectomy. It is, however, reasonable to assume that also in this population supplementation of pancreatic enzymes may be able to (partly) improve fat absorption. In addition, products with similar active ingredients, like Creon and Panzytrat, are already licensed for these indications. The dosing regimen is supported by literature data and identical to that of Creon Forte 300 mg.
Pancreatin is considered safe; most frequently reported adverse events are confined to the GIT and can be considered mild. They are adequately included in the updated SPC, identical to that of the innovator.
Data demonstrating efficacy only include short term studies. The MAH states that the efficacy of long-term treatment with pancreatin has been well shown over many years of widespread clinical use. However, this statement is not supported by data.
Based on the fact that:

1) numerous pancreatin products with comparable active ingredients are already approved in the Netherlands,
2) the claims in the SPC are consistent with the published literature and established clinical practice,
3) the SPC is identical to that of the innovator, the current application is considered approvable.

V. USER CONSULTATION

The package leaflet 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 test was performed with 20 participants. Fifteen questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In line with the results of the readability test and comments of the participants, a few minor suggestions for improvement were implemented. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pantriozyme 25,000 units, hard gastro-resistant has a proven chemical-pharmaceutical quality and is a well-established medicinal product. Based on the submitted dossier and further literature, Pantriozyme can be considered effective in the treatment of exocrine pancreatic insufficiency.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling include adequate information and are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered well-established medicinal use sufficiently demonstrated, and has therefore granted a marketing authorisation. Pantriozyme was authorised in the Netherlands on 2 June 2010.

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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
-	Transfer of the Marketing Authorisation.	N	1-2-2011	Approval	-
-	Submission of an updated Ph. Eur. certificate of suitability from an already approved manufacturer.	N	29-5-2011	Approval	-
-	Periodic Safety Update Report (PSUR) covering 03-06-2010 to 31-05-2011.	N	11-10-2011	Approval	-
-	Transfer of the Marketing Authorisation.	N	29-10-2018	Approval	-
-	Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	N	12-12-2018	Approval	-
-	Alignment PIL to SmPC	Y	07-01-2019	Approval	-