

**Second Meeting of the Subcommittee of the Expert Committee on the
Selection and Use of Essential Medicines**

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Application for the inclusion of Pancreatic Enzymes
in the WHO Model List of Essential Medicines

Submitted by

Cystic Fibrosis Worldwide

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1 Summary statement of the proposal for inclusion, change or deletion

This is a proposal for the inclusion of Pancreatic Enzymes in the pediatric medications section of the WHO model list of necessary medications.

Pancreatic insufficiency occurs when the pancreas does not secrete enough chemicals and digestive enzymes for normal digestion to occur. Pancreatic Enzyme replacement therapy is necessary when Pancreatic insufficiency occurs. When pancreatic insufficiency is severe, malabsorption (impaired absorption of nutrients by the intestines) may result, leading to deficiencies of essential nutrients and the occurrence of loose stools containing unabsorbed fat (steatorrhea). When there is severe malabsorption of nutrients, malnutrition is a predominant outcome. Severe pancreatic insufficiency occurs in cystic fibrosis, chronic pancreatitis, and surgeries of the gastrointestinal system in which portions of the stomach or pancreas are removed.

Virtually all CF patients (85%) require pancreatic enzyme supplements due to an inadequacy of their own pancreatic secretions (Morgan et al, 1999). Various preparations are available (Walters & Littlewood, 1996). The acid-resistant microsphere preparations (Creon 10,000, Pancrease) are significantly more effective than the older pancreatic enzyme preparations (e.g., Pancrex V and Cotazyme) (Beverley et al, 1987).

Cystic Fibrosis has been described as a disease in the Caucasian Population since late 1930 (Dorothy Andersen). In 2002 the WHO reported on “The molecular genetic epidemiology of cystic fibrosis” and it was clear that CF exists also in Africa, Latin America, Middle East and Asia. Due to the natural course of the disease and due to the medical communities lack of knowledge of the disease it is likely that CF is under-diagnosed in those areas.

2 Name of the focal point in WHO submitting or supporting the application

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3 Name of the organisation(s) consulted and/or supporting the application

Cystic Fibrosis Worldwide (including 52 international member CF Associations)
Cystic Fibrosis Europe
The European Cystic Fibrosis Society

4 International Nonproprietary Name (INN; generic name) of the medicine.

The active pharmaceutical ingredient is listed as
Pancreatin, pancrelipase; pancreas powder, pancreatic extract

5 Formulation proposed for inclusion, including adult and paediatric (if appropriate)

The formulation usually used for enzyme replacement therapy is a solid oral dosage form, preferably multiple unit dosage forms, e.g. capsules comprising of many gastro-resistant pellets which can easily mix with chime once the capsule shell is dissolved. Gastro-resistant coating of the pellets is considered mandatory to protect the acid instable pancreatic enzymes from irreversible denaturation by e.g. gastric acid during gastric passage.

Pediatric formulations should take care about patients ability to swallow drugs. Thus small gastro-resistant pellets are available as bulk presentation to be administered by a dosing spoon.

6 International availability – sources, if possible manufacturers

The 6 most commonly prescribed pancreatic enzyme replacement therapies in Europe-5 (France, Germany, Italy, Spain, UK), according to IMS Health (June 2006 MAT):

<u>Brand Name</u>	<u>Company</u>
Creon	Solvay
Mezym	Menarini
Ozym	Ferrer
Eurobiol	Mayoly-Spindler
Enzym-Lefax	Bayer
Panzytrat	Axcan

The 4 most commonly prescribed pancreatic enzyme replacement therapies in the US, according to IMS Health (June 2006 MAT):

<u>Brand Name</u>	<u>Company</u>
Pancrease	Johnson & Johnson
Creon	Solvay
Ultrase	Axcan
Viokase	Axcan

7 The drug is listed as a therapeutic group

8 Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Epidemiological information on disease burden

Pancreatic exocrine insufficiency is already present at birth in some 85% of cystic fibrosis patients, but it develops gradually over many years in diseases such as chronic pancreatitis or other diseases. The pathological consequences of (untreated) pancreatic exocrine insufficiency, whether arising from cystic fibrosis or other diseases are largely independent of the source of the insufficiency but rather depend upon the degree of the pancreatic insufficiency. Clinical consequences can be: diarrhea, maldigestion of nutrients (steatorrhea, azotorrhea), malnutrition, weight loss or poor weight gain, meteorism, pain, deficiency in fat-soluble vitamins, high prevalence of bacterial overgrowth, and increased susceptibility to disease.

8.1.1 Cystic fibrosis

Cystic fibrosis (CF) is the second most common genetic disease that leads to early death [Grosse, 2004]. CF affects people from all races, but is most commonly observed in Caucasians [ccf.org].

The condition is caused by mutations in a single gene of chromosome 7, which encodes the CF transmembrane conductance regulator (CFTR) (Sinaasappel 2002). The CFTR protein is a membrane-bound cAMP-regulated chloride channel, which regulates other cell membrane ion channels. This disease is characterized by abnormalities of electrolyte fluid, which provide evidence of a secretory defect that affects all epithelial cells (protein hypersecretion and precipitation and ductal plugging), e.g. in lungs, pancreas and the hepatobiliary tree (Durie and Forstner 1989, Durie 1992).

Approximately 85 to 90 % of all CF patients have clinical symptoms of maldigestion and require oral enzyme substitution already from the day of birth (Durie 1989). Clinical symptomatology is depending also on genotype and phenotype associates (Durie 1992). Most patients with cystic fibrosis carry mutations at the CFTR gene which are associated with malfunction of the pancreas.

Since malabsorption due to pancreatic exocrine insufficiency causes intolerance of fat, patients are at risk of low energy intake in addition to increased fecal nutrient loss (Steinkamp et al. 2002). Pancreatic exocrine insufficiency is of early onset and severe in most people with CF, and if untreated leads to severe malnutrition and growth failure (Littlewood and Wolfe 2000).

Patients with CF are advised to take a high percentage of the total caloric intake as fat to increase energy intake (plus 35-40%; see Dockter 1994). The 1992 consensus report of the Cystic Fibrosis Foundation on Nutritional Assessment and Management in Cystic Fibrosis stated that a more aggressive and effective nutrition program is requested because a lot of CF patients do not achieve the RDA (Recommended Dietary Allowances) of 130%-140% (Cowing Cannella et al.

1993). Individual needs may even be higher. Good nutritional status of CF patients can influence long-term survival and quality of life and may reduce the infection rate (Ramsey et al. 1992).

Essential fatty acid deficiency and fat-soluble vitamins may also occur in parallel (Chase et al. 1979, Lankisch and Creutzfeldt 1984). These recommendations can only be achieved with high caloric intake due to dietary fat increase (Dockter 1994, Collins et al. 1997).

8.1.2 Chronic pancreatitis

In chronic pancreatitis, unlike in cystic fibrosis, the pancreatic exocrine insufficiency arises subsequently to the loss of acinar cells; obstruction of the pancreatic ducts and ductules also plays a role (DiMagno and Pap 1994). The process in chronic pancreatitis is a gradual one; it takes 5 to 10 years for symptoms of maldigestion to occur (DiMagno and Pap 1994). Several mechanisms have been proposed, to describe the pathogenic events that lead to the development of chronic pancreatitis. They include the protein plug, toxic-metabolic, large duct obstruction, necrosis/fibrosis and the sentinel acute pancreatitis event theories (Khokhar et al 2004). It should be noted that these theories are incompletely understood and that they may not be mutually exclusive.

Two features that are common to all causes of CP are the development of ischemia and fibrosis.

A range of PEI prevalence rates among CP patients has been reported, from 22% to 94% (Dumasy et al., 2004; Lott, 1997; Eddes et al., 1999; Jarosz et al., 2003). The

rate of PEI in CP patients is dependent upon severity of the disease and length of time since diagnosis. The prevalence rate of PEI increases with disease duration. For example, a study by Dumasy et al. (2004) showed that five years from disease onset, 63% of CP patients developed PEI and at 10 years or more 94% developed PEI. Disease severity could be based on morphological changes in the pancreas, but there are no set guidelines on severity classification. One data source reported the rate of PEI at 30% in mild disease and 85% in severe disease (Lott, 1997). A study by Eddes et al. (1999), based on hospitalized patients, determined the rate of PEI was 56% among CP patients.

8.1.3 Post-pancreatic and gastric surgery

Pancreatic and gastric surgeries are most often used to alleviate pain or remove tumors or obstructions. One possible result following pancreatic or gastric surgery is PEI, with the degree of the resection determining the likelihood of PEI.

PEI rates for specific pancreatic surgeries were found in literature as follows: For total pancreatectomy and total gastrectomy, 100% of patients developed PEI (Van Berge Henegouwen et al., 1998; Stone et al., 1988; Friess et al., 1996).

If a bypass or drainage procedure was done, the resulting incidence of PEI was 4%.

If a Whipple procedure was performed, the range of PEI incidence was 21% to 50%; therefore, an average rate (35%) was applied to our estimated surgery patient population (Ghaneh et al., 1999; Evans et al., 1997).

If a partial pancreatectomy procedure was performed, the resulting PEI incidence ranged from 31% to 78%, with an average of 48% (Martin et al., 1996; Van Berge Henegouwen et al., 1998; Stone et al., 1988; Ong et al., 2000; Evans et al., 1997).

8.2 Assessment of current use

Pancreatin is approved by competent authorities as a safe and effective treatment of pancreatic exocrine insufficiency almost worldwide.

8.2.1 Status of Pancreatic Enzyme Preparations in the USA

Pancreatic enzyme preparations of porcine origin have been available in the United States for the treatment of exocrine pancreatic insufficiency (PEI) in children and adults with e.g. cystic fibrosis (CF) and chronic pancreatitis without requirement of a New Drug Application (NDA) because pancreatic enzyme products were available before the passage of the 1938 Federal Food, Drug, and Cosmetic Act. However, in 2004 the Federal Register Note was issued which require all pancreatin (pancrelipase) products (PEPs= pancreatic enzyme products) to be approved by the FDA by 2008. A guidance was issued for exocrine pancreatic insufficiency drug products for submitting the NDA (Indication submitted to be approved is "maldigestion due to exocrine pancreatic insufficiency")

8.2.2 Approved Regulatory Indications in Europe

The indication approved in Europe is treatment of pancreatic exocrine insufficiency in paediatric and adult patients.

(Pancreatic exocrine insufficiency is often associated with, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- pancreatic and gastric surgery
- other conditions)

8.2.3 Approved Regulatory Indications in Australia

Pancreatin is indicated as pancreatic enzyme replacement in conditions associated with pancreatic exocrine insufficiency (PEI) such as cystic fibrosis, chronic pancreatitis, post pancreatectomy, post-gastrointestinal bypass surgery (eg. Bilroth II gastroenterostomy) and ductal obstruction.

8.2.4 Approved Regulatory Indications in the Developing World

The indication approved throughout the Developing World is treatment of pancreatic exocrine insufficiency in paediatric and adult patients.

Pancreatic exocrine insufficiency is often associated with, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- pancreatic and gastric surgery
- other conditions

8.2.5 Use in developing world

Use of pancreatic enzymes in the developing world is insufficient and leaves many patients who suffer from diseases such as cystic fibrosis and chronic pancreatitis without access to this life saving medication. The reason for insufficient use is due to patient's inability to afford this life saving medication and lack of support from health programs through the local governments. In most diagnosed cases of cystic fibrosis and chronic pancreatitis, patients are informed of the need for and prescribed pancreatic enzymes but are unable to purchase this medication. Through recent patient analysis in countries such as India, the Republic of Georgia and Lebanon, it was found CF patients are taking low doses of pancreatic enzymes and therefore suffer from malnutrition and experience high levels of pain after eating. In order to combat this problem it is essential that health officials recognize the need for this life saving medication and include it in social health and welfare programs.

8.3 Target population

Pancreatic Exocrine Insufficiency (PEI) may be due to various underlying diseases like e.g. Cystic fibrosis (CF), Chronic Pancreatitis (CP), Post-Pancreatic surgery (PY) and Gastrectomy (GY), etc. There are several other diseases whose causal relationship to PEI is not finally established, but a remarkable co-incidence has been noticed like Shwachman- Diamond-Syndrome or Celiac Disease (Leeds 2007). The pathological mechanism may vary according to the disease status but is resulting in insufficient endogenous digestive enzyme supply to the intestine subject to pancreatic enzyme replacement therapy (PERT). PEI is assessed by evaluating pancreatic activity using pancreatic function tests. Direct pancreatic function tests are pancreas stimulations tests like e.g. the secretin pancreozymin test. Indirect pancreatic function tests are e.g. stool fat excretion, fecal chymotrypsin, human fecal elastase 1 or the pancreolauryl-test (Layer and Keller 2002, Chowdry and Forsmark 2003). As steatorrhea is the most prominent clinical manifestation of PEI and stool fat content can be reliably measured in standardized fashion in short-term clinical trials. The coefficient of fat absorption (CFA) is a generally accepted surrogate endpoint for efficacy of pancreatic enzyme supplementation and represents the gold standard (Layer and Keller 2002). Furthermore, stool parameters and clinical symptomatology describe the clinical picture of PEI.

8.3.1 Cystic fibrosis

Cystic fibrosis (CF) is one of the most common lethal genetic (autosomal recessive) disorders affecting all populations. It is caused by a genetic defect in the CF transmembrane conductance regulator (CFTR) which is located on the long arm of chromosome 7. The generally accepted incidence is an estimated 1 case in every 2000 live births for homozygotes for the CF gene of Caucasian descent. Severe mutations account for 92 % of CF patients with roughly 85 % of CF patients predicted to be pancreatic insufficient (Ratjen and Döring 2003).

The diagnosis of CF should be based on one or more characteristic phenotypic features, a history of CF in a sibling or a positive newborn screening using genetic testing or sweat tests plus laboratory findings (Rosenstein et al 1998 Consensus statement on the diagnosis of CF)..

The pathological changes of the pancreas, beside obstruction, include destruction of acinar cells, fibrosis and microcyst formation. The symptomatology of pancreatic exocrine insufficiency may present dramatically, especially in growing children, with malnutrition accompanied with body weight loss and failure to thrive. Poor clinical outcomes are associated with undernutrition in patients with CF. Therefore, special attention to nutrition has to be given to these patients (Ramsey et al. 1992, Borowitz et al. 2002, Sinaasappel et al. 2002, Consensus reports).

In cystic fibrosis there is a clear relation between malnutrition and deteriorating lung function (Durie and Forstner 1989). The long-term survival and well-being of these patients also closely correlates with their nutritional status (Kraemer et al. 1978, Corey et al. 1988). More specifically, patients with lipid maldigestion and associated under-nutrition have a worse prognosis in terms of growth, pulmonary function and long-term survival than those without (Gaskin et al. 1982).

Untreated pancreatic exocrine insufficiency affects the life-expectancy of patients with CF (Gaskin et al. 1998). Wasting was shown to be a significant predictor of survival in patients with CF independent of lung function, arterial blood oxygen and carbon dioxide tension (Sharma et al. 2001). Different investigations showed the association between malnutrition, lung disorders and survival curves (Koletzko et al 1994, Steinkamp et al. 2002). Steinkamp et al. reported that patients with malnutrition had significantly lower mean values of vital capacity, arterial oxygen pressure and forced expiratory volume in 1 second and higher serum IgG. *Pseudomonas aeruginosa* infection was also associated with decreased pulmonary function. Malnourished adolescents aged 12-18 years experienced a serious decline in FEV1 of about 20 % predicted, whereas mean FEV1 values remained stable at above 80 % predicted in adolescents of normal weight. Longitudinal follow up showed that malnourished patients of all ages and those with *Pseudomonas aeruginosa* infection had significantly worse lung function than their normally nourished counterparts and a greater yearly loss of FEV1 % predicted. During 1 year of observation, adolescents who experienced a > 5 % predicted decrease in weight for height had a concomitant mean loss of FEV1 of 16.5 % predicted during that year whereas patients who gained relative weight had a parallel increase in FEV1 of 2.1 % predicted.

The improvement in clinical care of CF patients has changed the disease from a pediatric entity to a disease spectrum starting in childhood but expected to progress well into adulthood (Jackson and Pencharz 2003). Much of this improvement has been attributed to the essential factor of better nutrition (Corey et al. 1988, Steinkamp et al 2002).

8.3.2 Chronic pancreatitis

Chronic pancreatitis (CP) is morphologically characterized by an irregular fibrosis with destruction and permanent loss of exocrine parenchyma which may be either focal, segmental or diffuse (calcifications are present in the majority of patients). Obstructive CP is a distinctive form, characterized by uniform dilatation of the ductal

system proximal to the occlusion of one of the major ducts. The occurrence of the disease is steadily increasing upon various etiologies, e.g. toxic-metabolic causes like alcohol consumption, biliary diseases with an incidence of 4 -8 new cases per 100,000 population per year and a prevalence of 13 cases per 100,000 population in western countries (Lankisch and Banks 1997, Lankisch et al. 2002).

The diagnosis of CP is performed using imaging procedures like ultrasonography, computed tomography, Endoscopic Retrograde Cholangiopancreatography and radiologic imaging (Malfertheiner et al. 1997).

Beside pain, a characteristic feature of CP is progressively decreasing pancreatic enzyme output resulting in pancreatic exocrine insufficiency.

Although PEI etiology is different in CF and CP, they are the same in terms of impaired secretion of pancreatic enzymes and the symptomatology of these patients with PEI is similar. Ultimately, PEI results in malnutrition with increased depletion of lean body mass, increased susceptibility to infection, decreased muscle force, reduced exercise tolerance and altered pulmonary function. Adequate treatment with digestive enzymes lowers the rate of morbidity and mortality in patients.

8.3.3 Pancreatic and gastric surgery

Surgical procedures are performed in patients with chronic pancreatitis mainly because of pain and/or inflammatory/necrotizing tissue resulting in partial pancreatectomy (van Hoozen et al. 1997). Another reason for pancreatectomy may be pancreatic cancer. Pancreatic exocrine insufficiency may be a result of the pancreatectomy (Neoptolemos et al. 1999, Ganesh and Neoptolemos 1999).

The consequence of PEI is nutrient maldigestion with symptoms like abdominal pain, diarrhea and body weight loss. To reduce nutrient maldigestion, sufficient enzyme activity must be delivered into the duodenal lumen simultaneously with the meal.

The main reason for Gastrectomy these days is no longer ulcer but gastric cancer. Though the incidence of carcinoma of the stomach and associated mortality has steadily declined in recent years, it remains the second most common cause of death from malignant disease worldwide (highest incidence in Japan). Survival rates for patients with gastric cancer have increased and accompanying symptoms like maldigestion, body weight loss and abdominal pain become more and more overt. A primary or secondary pancreatic exocrine insufficiency is being discussed as causes of the maldigestion (Gullo et al. 1979, Büchler et al. 1989; Friess et al 1996). Primary pancreatic exocrine insufficiency is due to a diminished functioning of the exocrine pancreatic parenchyma. In secondary pancreatic exocrine insufficiency patients show normal pancreatic enzyme output. However, this is accompanied by a pancreaticocibale asynchronism resulting in an insufficient mix of the pancreatic juice with the chyme and a reduced stimulation of the pancreas (MacGregor et al. 1977, Friess et al. 1993).

8.3.4 PEI due to other conditions

Other conditions like Shwachman Diamond Syndrome, Diabetes mellitus, Acute Pancreatitis etc. may also lead to pancreatic exocrine insufficiency.

9 Treatment details

9.1 General

PEI can be caused by various underlying diseases including CP, pancreatic resection and CF. However, they are not different in terms of indicating symptoms of maldigestion and malabsorption due decrease of pancreatic exocrine secretion caused by the underlying diseases. Investigation on treatment of PEI with enzyme

replacement therapy has been done with PEI patients due to CF and CP (representing non-CF diseases) that is considered as the main population of PEI patients. The most detailed description of the therapy is described in the section of CP in the textbooks for internal medicine and in a treatment manual. In the section of CP in Cecil Textbook of Medicine 21st Edition and that in Oxford Textbook of Medicine 4th Edition, it is mentioned that PEI occurs when pancreatic secretion of digestive enzyme is reduced. In these two textbooks as well as in Harrison's Principles of Internal Medicine 15th Edition, in the section of CP, it is described that the treatment for PEI is done with enzyme replacement therapy. Furthermore, it is also described in the section of CF in all three textbooks that treatment for PEI is done with enzyme replacement therapy. There are similar descriptions in the guidelines and in the treatment manual.

Internationally accepted textbooks for internal medicine:

- Harrison's Principles of Internal Medicine 15th Edition
- Cecil Textbook of Medicine 21st Edition
- Oxford Textbook of Medicine 4th Edition
- Reliable treatment manual: The Washington Manual of Medical Therapeutics 30th Edition

Guidelines for the diagnosis and management of cystic fibrosis are provided by the WHO Human Genetics Programme and the International Cystic Fibrosis Association, 1996 as well as from the Cystic fibrosis Trust, UK (<http://www.cftrust.org.uk/>)

9.2 Dosing

9.2.1 General Dosing Information

Pancreatic Enzyme Replacement Therapy Capsules is orally administered and contains delayed-release porcine-derived pancrelipase.

Doses should be taken during meals or snacks, or as prescribed by the healthcare provider. Pancreatic Enzyme Replacement Capsules should always be taken with food. The number of capsules and capsule strength given with meals or snacks should be estimated by assessing which dose minimizes steatorrhea and maintains good nutritional status.

When swallowing of capsules is difficult, the capsules may be carefully opened and the contents added to a small amount of low acidic soft food with a pH less than 5.5, such as applesauce, pudding, mashed or pureed bananas or carrots at room temperature. The soft food should be swallowed immediately without chewing and followed with a glass of water or juice to ensure swallowing.

9.2.2 Dosing In Patients With Cystic Fibrosis

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conference in 2002. Pancreatic Enzyme Replacement Capsules should be administered in a manner consistent with the recommendations of the Conference as follows:

Weight-based enzyme therapy should begin with a starting dose of 1,000 lipase units/kg/meal for children less than 4 years of age to 500 units/kg/meal with titration to 2,500 units/kg/meal or less than 4,000 lipase units/g fat/day (Consensus reports: Borowitz et al. 1995, FitzSimmons et al., 1997; Borowitz et al., 2002). Adequate control of gastrointestinal symptoms can be achieved at dosages of 10000 lipase units/kg body weight or only slightly more, and a normal nutritional state and growth

rate maintained in most patients with cystic fibrosis (Consensus reports: Littlewood and Wolfe 2000, Sinaasappel et al. 2002).

Dosage should be adjusted according to severity of disease, control of steatorrhea and maintenance of good nutritional status. Doses in excess of 2,500 lipase units/kg/meal should be used with caution and only if their benefit is documented by 3-day fecal fat.

9.2.3 Dosing In Patients With Chronic Pancreatitis / Pancreatic and gastric surgery

Dosage should be individualized by patient according to the degree of maldigestion and the fat content of the meal. The required dose for a main meal (breakfast lunch or dinner) ranges from about 20,000 to 75,000 Ph. Eur. U of lipase and for in-between snacks from about 5,000 to 25,000 Ph. Eur. U of lipase. The usual initial starting dosage for Pancreatic Enzyme Replacement Therapy is 10,000 – 25,000 Ph. Eur. Lipase units per main meal. However, patients may need higher doses to minimize steatorrhea and maintain good nutritional status. Customary clinical practice suggests that at least 20,000 – 50,000 Ph. Eur. Units of lipase should be given with the meals. and should be doubled if required for adequate lipolytic digestion (Layer et al. 2001).

This recommendation is in accordance with the Consensus report of the German Society for Digestive and Metabolic Diseases, (*Z. Gastroenterol* , 1998,36; 359-367) which describe that the dosage of pancreatic enzyme preparations should be adjusted to meet individual patient's needs.

9.2.4 Dosing in patients with other diseases leading to PEI

Dosing in patients with other conditions that may lead to exocrine pancreatic insufficiency (e.g., Shwachman-Diamond Syndrome, acute necrotizing pancreatitis, Billroth II gastroenterostomy) should be determined by the degree of maldigestion and caloric needs of each individual patient.

Summary of comparative effectiveness in clinical setting

Cystic fibrosis

CFW Advisors used Medline as the basis for searches in addition to information available on file.

ENZYME TRIALS

Konstan MW, Stern RC, Trout JR et al. Ultrase MT 12 and Ultrase MT20 in the treatment of exocrine insufficiency in cystic fibrosis; safety and efficacy. *Aliment Pharmacol Ther* 2004;20:1365-1371

Two doses of one formulation of enteric coated pancreatic enzymes: Ultrase M12 (12 000 units lipase per capsule) and Ultrase MT 20 (20 000units lipase per capsule) were compared with a placebo in two separate safety and efficacy studies.

Mean total fat, protein and carbohydrate did not differ significantly between the groups. A significant difference in both fat and protein absorption occurred with the enzyme therapy groups. The Ultrase MT12 and Ultrase MT20 groups experienced a mean fat and protein absorption of 79.4% and 83.8% and 87.3% and 88.6% respectively. No adverse events related to study drug were reported.

Kalnins D, Ellis L, Corey M et al. Enteric-coated pancreatic enzyme with bicarbonate is equal to standard enteric-coated enzyme in treating malabsorption in cystic fibrosis. *J Pediatr Gastroent Nutr* 2006;42:256-261.

The efficacy of an enteric coated buffered pancreatic enzyme (EC buffered PE) containing 1.5mmol bicarbonate per capsule was compared with a conventional enteric coated enzyme (EC-PE).

There was no significant difference in percent malabsorption of energy (19.4% vs 19%), fat (20.7% vs 20.2%), or nitrogen (10.4% vs 10.7%) between the EC buffered PE product and the conventional EC-PE product. However patients taking the EC buffered PE received less enzyme based on actual enzyme activity measured in vitro.

Brady MS, Garson JL, Krug SK et al. An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic fibrosis: a prospective randomized study. *J Am Diet Assoc* 2006;106:1181-1186.

The efficacy of an enteric coated highly buffered pancreatic enzyme (2.5mmol bicarbonate per capsule) was compared with a conventional enteric coated enzyme (EC-PE).

Mean fat excretion decreased significantly in each subject during periods when given the highly buffered pancrelipase compared to periods when given the non-buffered EC-PE (fat excretion 18.2% vs 24.9% respectively).

Brady MS, Rickard K, Yu PL, Eigen H. Effectiveness and safety of small vs. large doses of enteric coated pancreatic enzymes in reducing steatorrhea in children with cystic fibrosis: a prospective randomized study. [Pediatr Pulmonol](#). 1991;10(2):79-85

Among cystic fibrosis (CF) centers, usual doses of enteric coated (EC) pancreatic enzymes vary from one to six capsules per meal based upon arbitrary criteria for stool and growth patterns. Large doses of non-EC enzymes are associated with increased serum urate (SU) and urinary uric acid (UUA) but data are unavailable for EC enzymes. This study compared the effectiveness and safety of a relatively

large dose (patient's usual dose) versus a small dose (1/4 usual dose) of EC enzymes in nine nourished children with CF, regarding decreasing fecal fat and stool nitrogen losses and maintaining normal SU and UUA concentrations. A crossover study design randomly assigned large or small doses to two consecutive 7 day treatment periods within each child. Large doses of EC enzymes reduced steatorrhea and increased SU and UUA. SU was normal with both treatments and UUA was normal, i.e., 17 of 18 values were between the 10th and 95th percentiles for healthy children eating a normal diet. When fat excretion was greater than 10% with small doses of EC enzymes, large doses resulted in reduced fat excretion and normal UUA. These data suggest that large doses of EC enzymes reduce steatorrhea and are safe in patients who have malabsorption with small doses.

Stead RJ, Skypala I, Hodson ME. Treatment of steatorrhea in cystic fibrosis: a comparison of enteric-coated microspheres of pancreatin versus non-enteric-coated pancreatin and adjuvant cimetidine [Aliment Pharmacol Ther.](#) 1988;2(6):471-82.

Enteric-coated microspheres of pancreatin were compared with non-enteric-coated pancreatin combined with cimetidine taken 40 min before meals in the treatment of patients with cystic fibrosis. Fourteen adults with steatorrhea due to cystic fibrosis were investigated in an open, randomized crossover study, over two consecutive 28-day treatment periods. Lipase intake was adjusted to each patient's previous requirements and was the same during both months; they were instructed to continue with their normal diet. Patients collected faeces for 72 h at the end of each month and completed diary cards daily throughout. Bowel actions were less frequent on enteric-coated microspheres of pancreatin than on non-enteric-coated pancreatin/cimetidine (1.7 vs. 2.4/day; P less than 0.001) and stool character was improved (P less than 0.001). Mean daily faecal weight was similar on enteric-coated microspheres of pancreatin to that on the combination (254 g vs. 291 g; N.S.), whereas daily faecal fat excretion tended to be less on enteric-coated microspheres of pancreatin (21 g vs. 27 g; N.S.), and percentage fat absorption tended to be greater (81% vs. 73%; N.S.). Mean body weight increased by 0.3 kg on enteric-coated microspheres of pancreatin and fell by 0.1 kg on the combination (N.S.). These data indicate that enteric-coated microspheres of pancreatin are at least as effective as non-enteric-coated pancreatin with cimetidine in the treatment of steatorrhea in cystic fibrosis.

Williams J, MacDonald A, Weller PH, Fields J, Pandov H. Two enteric coated microspheres in cystic fibrosis. [Arch Dis Child.](#) 1990 Jun;65(6):594-7

In a randomised single blind crossover study in children with cystic fibrosis and pancreatic insufficiency, two enteric coated microsphere preparations of pancreatin were compared on a capsule for capsule basis, by measuring the coefficient of fat absorption, nitrogen excretion, weight change, and symptom scores after four weeks' treatment with each preparation. Thirty nine subjects were randomly allocated to receive Pancrease followed by Creon or vice versa. Each individual subject received the same number of capsules per day in each study period. Data from 27 children (Pancrease/Creon, n = 13 and Creon/Pancrease, n = 14) were suitable for analysis. Results showed no significant differences between the two preparations in any variable studied. We conclude that there is no significant difference between Pancrease and Creon when compared on a capsule for capsule basis.

Santini B, Antonelli M, Battistini A et al. Comparison of two enteric coated microsphere preparations in the treatment of pancreatic exocrine insufficiency caused by cystic fibrosis. Dig Liver Dis. 2000;32(5):406-11

BACKGROUND: Pancreatic exocrine insufficiency is a common condition in patients with cystic fibrosis. Large amounts of pancreatic enzyme supplements are required to reduce malabsorption but patient compliance is not always optimal. AIMS: To compare patients' preference and the efficacy of two enteric coated microsphere preparations in patients with cystic fibrosis. PATIENTS: Patients with pancreatic exocrine insufficiency due to cystic fibrosis. METHODS: Patients were assigned to the crossover treatment with Creon or Pancrease for 1 week and then to the alternative treatment. Patients had to follow a fixed diet (at least 2 g fat/kg) and had to assume 1000 units lipase/g fat. The evaluation parameters were: patients' preference, acceptance of therapy, stool fat excretion, stool weight, gastrointestinal symptoms, and tolerance. RESULTS AND CONCLUSIONS: Of the 33/60 patients who expressed a preference for one of the two treatments, 30 preferred Creon while only 3 patients preferred Pancrease ($p < 0.001$). No difference between the two treatments was observed regarding stool characteristics, gastrointestinal symptoms and tolerance. The mean number of capsules taken daily was reduced by 35% with Creon. The results of this study showed a preference in favour of Creon probably due to the reduction of daily capsule intake of 35%, supporting digestion as well as Pancrease.

Shah A, Dinwiddie R, Madge S, Prescott P, Hudson G. High dose Nutrizym 22 in cystic fibrosis. Eur J Pediatr. 1993 Sep;152(9):763-4

New high dose pancreatic enzyme preparations could be potentially helpful to cystic fibrosis (CF) patients. The purpose of this study was to compare the efficacy of the new high dose pancreatic enzyme preparation, Nutrizym 22 with the standard preparation Nutrizym GR. Twenty-five CF children (aged 7-16 years) entered the study and 22 completed it; 3 did not, due to non-compliance. All were taking Nutrizym GR for at least 2 weeks before entering the study. A randomised double blind, crossover method using standard Nutrizym GR or double strength Nutrizym 22 capsules was carried out over two consecutive 14-day periods. Crossover analyses of variance showed no statistically significant differences in actual weight gain, appetite, abdominal pain, stool consistency or faecal fat during the prestudy and study periods. It is concluded that half the capsule numbers of the high strength preparation are just as effective as the standard capsule dosage.

P J Robinson, A Olinsky, A L Smith, and S B Chitravanshi. High compared with standard dose lipase pancreatic supplement Arch Dis Child. 1989 January; 64(1): 143-145.

Cotazym-S-Forte, a new pancreatic supplement containing 10,000 BP units of lipase activity per capsule, was compared with a standard dose pancreatin supplement (Pancrease) with 5000 BP units lipase activity in a randomised crossover trial. The number of capsules of Cotazym-S-Forte administered was half the usual number of Pancrease capsules and was associated with the same degree of fat absorption as Pancrease.

Solvay conducted several placebo and/ or reference controlled clinical studies (reported or reported/published).

Two placebo-controlled studies (S2233101/S2233102, Stern et al. 2000) have been performed in CF patients (children/adolescents and adults) in a double-blind, parallel-group design. The patients were treated individually during the open-label Creon MMS run-in period. Patients with a CFA above 80 % when treated with PERT were included and were randomized to either remaining on this dose during the trial of 5-7 days, or receiving placebo.

Table 1: CFA (%) in placebo-controlled Creon studies in CF

		Protocol No.					
		S2233101			S2233102		
Period	Statistic	Creon MMS	Placebo	p-value	Creon MMS	Placebo	p-value
Baseline	N	18	19		18	18	
	Mean	87.4	87.1		89.2	87.8	
	SD	4.7	4.4		4.7	5.1	
Treatment	N	18	19		18	18	
	Mean	84.1	52.2		87.2	50.9	
	SD	9.3	24.4		7.2	31.0	
Change	N	18	19		18	18	
	Mean	-3.3	-34.9	<0.001 ^a	-2.0	-36.9	<0.001 ^a
	SD	7.6	22.2		3.8	28.4	

^a Comparison of Creon MMS versus placebo (ANOVA)

The two CF studies (S2233101 and S2233102) were designed as withdrawal studies with an individualized Creon MMS run-in period followed by Creon MMS or placebo treatment in a double-blind manner. The mean changes from baseline in CFA were significantly smaller in the Creon MMS group compared to placebo. This finding reveals the efficient treatment of CF patients with Creon MMS compared to placebo (table 1).

Two reference-controlled, cross-over studies (K245.5004/S2483002) have been performed in CF patients investigating the equivalent efficacy of Creon MMS versus Creon MS (10000 and 25000) for 2 weeks therapy. Both trials showed that Creon MMS and Creon MS are effective in the therapy of fat maldigestion with Creon MMS reaching 81.9% CFA and 89.1 % CFA respectively..

Additionally, two studies with Creon 10000 MMS in an open-label design (K245.5002 /S2453105) for 2-4 weeks have been performed to investigate the patient preference for Creon MMS (capsule size 2) over the Creon MS product (capsule size 0) in CF patients. In both studies, it was shown that the vast majority of patients preferred Creon MMS. In study K245.5002, 55 of 69 patients expressed a preference. Creon 10000 MMS was preferred by 39 patients (71 %) versus 16 patients (29 %) which expressed their preference for Creon M S (p= 0.003). The global acceptance of the therapy was very good. In study S2453105, a total of 51 patients expressed a preference. Creon MMS was preferred by 47 patients (87 %) out of the 54 patients who completed both crossover periods. Creon 8000 MS was preferred by 4 patients (7 %) and 3 were undecided (p < 0.001). The mean CFA in this study was above 90 % in both treatment groups.

Two infant studies (S2453118, S2483003) in patients aged less than 3 years have been performed with a special infant preparation (Creon for Children/Creon Micro), one of which was a cross-over study in comparison with Creon 10 000 mms (Creon 12 0000 in France) (S245 3118).

Creon for Children (S2483003) was efficacious regarding improvement of the CFA (from 58.0% at baseline to 84.7%, $p = 0.0013$), stool fat excretion and fecal energy loss in infants aged 1-24 months with pancreatic exocrine insufficiency due to CF. No relevant changes in hematology or biochemical parameters were observed. The height for weight percentile remained close to 100%. Safety and tolerability was good.

When comparing Creon 10 000 to the infant preparation (S2453118) parents' preference was higher for the infant preparation (Creon for Children/Creon Micro) as for Creon® 10 000 (Creon 12000 in France) in very young cystic fibrosis subjects of 6-36 months. The efficacy of Creon® for children and Creon® 12000 U as measured by CFA, fat intake and excretion, energy intake and excretion, stool weight, and clinical symptomatology was very similar on the basis of comparable lipase dose administration. The safety and tolerability was good and similar for both treatments.

9.3 Chronic Pancreatitis and Post-Pancreatic Surgery

Solvay conducted several placebo and/or reference controlled clinical studies (reported or reported/published).

Two double-blind, randomized, placebo-controlled, parallel-group, multicenter studies have been performed with Creon MMS (study numbers: 223.2.01, K245.5005) in patients with PEI due to chronic pancreatitis.

In study 223.2.01 and in study K245.5005, 26 respectively 31 patients were included in the evaluation of the CFA. No CFA values were assessed at baseline for study K245.5005. Therefore, the comparison of Creon MMS and placebo was done for the end of the treatment period.

Table 2 CFA (%) in placebo-controlled Creon studies in CP

		Protocol No.					
		223.2.01			K245.5005		
Period	Statistic	Creon MMS	Placebo	p-value	Creon MMS	Placebo	p-value
Baseline	N	12	14		NA	NA	
	Mean	49.9	55.9		NA	NA	
	SD	30.4	13.4		NA	NA	
Treatment	N	12	14		16	15	0.004 ^b
	Mean	86.6	68.0		81.5	60.3	
	SD	9.2	17.3		14.6	21.9	
Change	N	12	14		NA	NA	
	Mean	36.7	12.1	0.0185 ^a	NA	NA	
	SD	30.2	18.8		NA	NA	

^a Comparison of Creon MMS versus placebo: (ANOVA)

^b Comparison of Creon MMS versus placebo: (two sided t-test with Satterthwaite's adjustment)

NA = not assessed

One double-blind, cross-over, reference-controlled study to prove the efficacy of Creon 10000 MMS and Creon MS was performed (K245.5003) in CP patients. In both treatment groups (N=22) the CFA was in the mean about 80 % showing similar efficacy of both Creon products.

One double-blind, cross-over, reference-controlled study (S2483001) was performed to show the efficacy of Creon 25000 MMS and Creon 25000 MS in 20 patients after pancreatectomy. The mean CFA was about 83 % in both treatment groups and showed similarity in terms of efficacy.

One study (S2453102) investigated the effects of Creon 20000 MMS in gastrectomy patients. Trends towards a better fat digestion on Creon as compared to placebo was seen in the few number of patients investigated.

11. Summary of comparative evidence on safety

(Estimate of total patient exposure to date/Description of adverse effects/reactions/Identification of variation in safety due to health systems and patient factors/Summary of comparative safety against comparators)

Solvay's Pancreatin products are currently approved in 71 countries for the treatment of pancreatic exocrine insufficiency as a consequence of different medical conditions. Exposure of patients to pancreatin is currently estimated at about 180 000 patient-years per year.

The overall reporting rate of adverse drug reactions (ADRs) to pancreatin preparations is very low. About 25 % of the reported ADRs are considered serious. The most commonly reported adverse events encompass the following MedDRA System Organ Classes (SOC):

- gastrointestinal disorders, which contribute about 40 % of all ADRs,
- general disorders and administration site conditions (~15 %),
- skin and subcutaneous tissue disorders (~10.0 %),
- investigations (~7 %),
- nervous system disorders (~5 %),
- immune system disorders (~2 %).

The majority of the more frequent gastrointestinal events, abdominal pain, diarrhea, flatulence, oral complaints, constipation, nausea, and vomiting are also occurring as symptoms of the underlying disease; oral complaints occasionally are related to application errors. Pruritus, urticaria and rash are relatively rare events.

The low number of adverse drug reaction reports does not allow any detailed analyses regarding differences in ethnicity, gender, age, indication for use or health system. Alike, no differences regarding drug safety have become known for pancreatin preparations of different manufacturers.

In conclusion, therapy with Solvay's pancreatin preparations can be regarded as safe in the treatment of exocrine pancreatic insufficiency which is frequently associated with (amongst others) cystic fibrosis and chronic pancreatitis.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

Range of costs of the proposed medicine

It should be recognized that there are significant inter-individual differences when considering the dosages of pancreatic enzymes required. In order to standardize this, the figures quoted below are based on the

cost of 100 capsules of Creon 10000. Creon is the most commonly prescribed pancreatic enzyme replacement therapy in the World.

United States -		€82.98
Europe-5 (consisting of France, Germany, Italy, Spain, UK)	-	€17.05-25.93
Australia	-	€20.79
Developing World (using India as an example)	-	€23.10

- Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)
- It is not possible to provide comparative cost-effectiveness data as no alternative treatment option is available. These products are designed as a replacement therapy for chronic conditions, rather than as a cure or as a preventative measure.

Summary of regulatory status of the medicine

Pancreatin (Pancreas powder, Pancrelipase) products are approved as medicinal products or equivalents in most regions of the world (the European Union, Canada, South and Middle America, Australia, Near and Far East countries, South Africa and Asian countries including India and China).

In Japan up to now no high strength preparations are available.

In 2007 in the USA Pancreatin (Pancrelipase) products are available which are not yet approved by the FDA. This is supposed to change in 2008 when all pancreatin products by Federal Rule will have to be FDA approved to continue or start marketing

13. Availability of pharmacopoeial standard

Pancreatin is monographed as Pancreas Powder Ph.Eur., Pancreatic extract BP and Pancrelipase USP

14. Proposed (new/adapted) text for the WHO Model Formulary

Name of the medicinal product/Qualitative and quantitative composition

Name	Manufacturer	Presentation	Lipase IU	Protease IU	Amylase IU
Enteric coated minimicrospheres (all Creon products USP units)					
Creon [®] Micro	Solvay	Per gram	50000	2000	36000
Creon [®] Micro	Solvay	100mg scoop	5000	200	3600
Creon [®]	Solvay	Per capsule	10,000	600	8,000

10,000					
Creon [®] 25000	Solvay	Per capsule	25,000	1000	18,000
Creon [®] 40000	Solvay	Per capsule	40,000	1600	25,000
Cotazyme -S	Organon	Per capsule	10,000	750	7,700 (BP)

Enteric-coated microspheres					
Pancrecarb MS-4	Digestive Care	Per capsule	4,000	25,000	20,000 (USP)
Pancrecarb MS-8	Digestive Care	Per capsule	8,000	45,000	40,000 (USP)
Pancrecarb MS-16	Digestive Care	Per capsule	16,000	52,000	52,000 (USP)
Creon 20	Solvay	Per capsule	20,000	75,000	66,400 (USP)
Ultrase capsules	Axcan Scandipharm	Per capsule	4,500	25,000	20,000 (USP)
Enteric-coated micro tablets					
Pancrease MT4	McNeil	Per capsule	4,000	12,000	12,000 (USP)
Ultrase MT 12	Axcan Scandipharm	Per capsule	12,000	39,000	39,000 (USP)
Pancrease HL	Janssen Cilag	Per capsule	25,000	1250	22,500 (BP)
Pancrease MT 10	McNeil	Per capsule	10,000	30,000	30,000 (USP)
Pancreas MT 20	McNeil	Per capsule	20,000	44,000	56,000 (USP)
Ultrase MT 20	Axcan Scandipharm	Per capsule	20,000	65,000	65,000 (USP)
Non-enteric coated powders					
Pancrex V per g powder	Paines & Byrne		25,000	1,400	30,000 (BP)
Viokase Powder	Axcan		16,800	70,000	70,000

	Scandipharm				(USP)
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Conversion table for units of enzyme activity (u. Units)

Amylase:

1 Ph Eur u. = 1 FIP u. = 1 BP u. = 4.15 USP u.

Lipase:

1 Ph Eur u. = 1 FIP u. = 1 BP u. = 1 USP u.

Protease:

There is no direct equivalence between BP and Ph Eur units. This is because the assay methods used measure protease in different ways. The BP method only measures "free" protease, while the Ph Eur method measures "bound" PLUS "free" protease. "Free" refers to active protease. "Bound" refers to the inactive precursor for protease. When pancreatin is released from the enteric-coated granules in the gut, the inactive "bound" protease precursor is rapidly converted to active "free" protease. Thus it could be argued that Ph Eur units are a more useful measure.

Clinical particulars

Therapeutic indications

Treatment of pancreatic exocrine insufficiency in paediatric and adult patients.

Pancreatic exocrine insufficiency is often associated with, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- postpancreatectomy
- gastrectomy
- pancreatic cancer
- post gastrointestinal bypass surgery (e.g. Billroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)
- Shwachman-Diamond Syndrome

Posology and method of administration

Method of administration

The posology aims at individual needs and depends on the severity of the disease and the composition of food.

It is recommended to take half or one third of the total dose (see below) at the beginning of the meal and the rest during it.

The capsules should be swallowed intact, without crushing or chewing, with enough fluid during meals or snacks. Where swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be carefully opened and the minimicrospheres added to soft food [pH < 5.0] that does not require chewing or taken with liquid [pH < 5.0]. Any mixture of the minimicrospheres with food or liquids should be used immediately and should not be stored.

It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation.

Posology in cystic fibrosis

Based upon a recommendation of the Cystic Fibrosis Consensus Conference, the US CF Foundation case-control study, and the UK case-control study, the following general dosage recommendation for pancreatic enzyme replacement therapy can be proposed:

- Weight-based enzyme dosing should begin with 1 000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four.
- Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status.
- Most patients should remain below or should not exceed 10 000 U/kg body weight per day.

Posology in other pancreatic exocrine insufficiency disorders

Dosage should be individualized by patient according to the degree of maldigestion and the fat content of the meal. The required dose for a main meal (breakfast lunch or dinner) ranges from about 20,000 to 75,000 Ph. Eur. U of lipase and for in-between snacks from about 5,000 to 25,000 Ph. Eur. U of lipase.

The usual initial starting dosage for Trademark® is 10,000 – 25,000 Ph. Eur. Lipase units per main meal. However, patients may need higher doses to minimize steatorrhea and maintain good nutritional status. Customary clinical practice suggests that at least 20,000 – 50,000 Ph. Eur. Units of lipase should be given with the meals.

Contraindications

Hypersensitivity to pancreatin of porcine origin or to any of the excipients.

Special warnings and special precautions for use

Based on epidemiologic evidence, fibrosing colonopathy is a rare, serious adverse event initially described in association with high-dose pancreatic enzyme use in pediatric cystic fibrosis patients. However, the underlying mechanism remains unknown. At its most advanced stage, this condition leads to colonic strictures. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be reviewed to exclude the possibility of colonic damage -especially if the patient is taking in excess of 10 000 units of lipase/kg/day.

Interaction with other medicinal products and other forms of interaction

There have been no reports of interactions with other drugs or other forms of interaction.

Pregnancy and lactation

Pregnancy

For pancreatic enzymes no clinical data on exposed pregnancies are available.

Animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected.

Caution should be exercised when prescribing to pregnant women.

Lactation

No effects on the suckling child are anticipated since animal studies suggest no systemic exposure of the breastfeeding woman to pancreatic enzymes. Pancreatic enzymes can be used during breastfeeding.

Effects on ability to drive and use machines

There is no evidence that Trademark® has any effect on the ability to drive or operate machines.

Undesirable effects

Gastrointestinal disorders

Abdominal pain, constipation, abnormal stool, diarrhoea and nausea/vomiting.

Skin and subcutaneous tissue disorders

Allergic or hypersensitivity reactions of the skin were reported

Overdose

Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Trademark® contains porcine pancreatin formulated as enteric-coated (acid-resistant) minimicrospheres within gelatine capsules. The capsules dissolve rapidly in the stomach releasing hundreds of minimicrospheres, a multi-dose principle which is designed to achieve good mixing with the chyme, emptying from the stomach together with the chyme and after release, good distribution of enzymes within the chyme. When the minimicrospheres reach the small intestine the coating rapidly disintegrates (at pH > 5.5) to release enzymes with lipolytic, amylolytic and proteolytic activity to ensure the digestion of fats, starches and proteins. The products of pancreatic digestion are then either absorbed directly, or following further hydrolysis by intestinal enzymes.

15 Pharmacokinetic properties

Animal studies showed no evidence for absorption of intact enzymes and therefore classical 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.

Preclinical safety data

Preclinical data show no relevant acute, subchronic or chronic toxicity. Studies on genotoxicity, carcinogenicity or toxicity to reproduction have not been performed.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

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