

PRODUCT INFORMATION

PANCREASE[®]* MT 4
PANCREASE[®]* MT 10
PANCREASE[®]* MT 16

Pancrelipase Delayed-Release Capsules, USP

Digestant

NOT A PRODUCT MONOGRAPH

This Product Information is the exclusive property of Janssen Inc.
It may not be copied in whole or in part without the written
permission of Janssen Inc.

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

www.janssen.ca

DATE OF PREPARATION:
February 9, 1996

DATE OF REVISION:
November 29, 2011

Submission Control No: 060981-1

© 2010 JANSSEN Inc.

*All trademark rights used under license

PANCREASE[®] MT 4
PANCREASE[®] MT 10
PANCREASE[®] MT 16

Pancrelipase Delayed-Release Capsules, USP

Digestant

DESCRIPTION

PANCREASE[®] MT capsules contain enteric-coated microtablets of pure porcine pancreatic enzyme concentrate - predominantly steapsin (pancreatic lipase), amylase, and protease - isolated by a patented process that ensures high enzyme purity and activity.

PHARMACOLOGIC CLASSIFICATION

Mechanism of Action

PANCREASE[®] MT microtablets resist gastric inactivation and deliver predictable, high levels of biologically active pancreatic enzymes (lipase, amylase, and protease) into the duodenum. The enzymes catalyze the hydrolysis of fats into glycerol and fatty acids, proteins into proteoses and derived substances, and starch into dextrans and sugars.

Pharmacokinetics

Absorption

The intestinal bioavailability of PANCREASE[®] MT 16 capsules[‡] was determined, *in vitro*, under simulated physiological conditions¹. PANCREASE[®] MT capsules were placed into a test tube containing an incubation medium consisting of 2.0 g NaCl, 9.2 g NaH₂PO₄ and distilled water (total volume: 1 litre). Employing a disintegration tester, the contents of the test tube were shaken at a constant speed of 30 rpm at an incubation temperature of 37°C. The pH of the mixture was adjusted by adding 4N HCl or 4N NaOH.

To simulate the acidic conditions of the stomach during a meal, a pH of 4.0 was initially established and gradually reduced in increments of 0.5 at 30-minute intervals to a pH of 2.5. To simulate the relative alkalinity of the intestine, the preparation was then transferred to a buffer where a pH of 6.6 was maintained. While the preparation was exposed to the buffer, release of pancreatic lipase, the marker enzyme, was measured as a function of time. The lipase content of the incubation medium was determined

[‡] This study, conducted in West Germany, used Panzytrat[®] 20000 (Nordmark Arzneimittel GmbH, Uetersen, West Germany) which contains microtablets that are the same formulation as those of PANCREASE[®] MT 16.

every 15 minutes for 120 minutes. More than 90% of the enzyme activity of the PANCREASE[®] MT capsules was released at 15 minutes with peak levels (97%) occurring at 30 minutes. The results demonstrate that PANCREASE[®] MT capsules are nearly 100% bioavailable and rapidly release high levels of pancreatic enzymes.

Excretion

Unused enzymes in PANCREASE[®] MT capsules are excreted in the feces. Digested enzymes are absorbed and are subsequently excreted in the urine.

INDICATIONS AND CLINICAL USE

PANCREASE[®] MT capsules are indicated for the treatment of steatorrhea secondary to pancreatic insufficiency in disorders such as cystic fibrosis or chronic pancreatitis.

CONTRAINDICATIONS

PANCREASE[®] MT capsules are contraindicated in patients known to be hypersensitive to pork protein and in patients with acute pancreatitis or with acute exacerbations of chronic pancreatic diseases.

WARNINGS

Should hypersensitivity occur, discontinue medication and treat the patient symptomatically.

Cases of fibrotic stricture formation in the ascending colon have been reported in cystic fibrosis patients with the use of high potency enzyme supplements in high doses (6,500 - 50,000 BP lipase units[‡]/kg/meal). If symptoms suggestive of gastrointestinal obstruction occur, the possibility of bowel strictures should be considered.

[‡] 1 BP lipase unit is approximately equal to 1 USP lipase unit⁴

PRECAUTIONS

To protect the enteric coating, microtablets should not be crushed or chewed. Where swallowing of capsules is difficult, they may be opened and the contents may be shaken onto a small quantity of a soft food which does not require chewing (e.g. applesauce, dessert gelatin, etc.), and swallowed immediately. Contact of the microtablets with foods having a pH greater than 7.3 (e.g. milk, custard, ice cream, and many other dairy products) can dissolve the protective enteric coating and destroy enzyme activity.

To avoid irritation of the mouth, lips, and tongue, opened PANCREASE[®] MT Capsules should be swallowed immediately before regular feedings or meals to minimize the likelihood that the microtablets are retained in the mouth. Proteolytic enzymes present in pancrelipase, when retained in the mouth, may begin to digest the mucous membranes and cause ulcerations.

Any change in pancreatic enzyme replacement therapy (e.g. dose or brand of medication) should be made cautiously and only under medical supervision.

Pregnancy and Lactation

Teratology studies in rats (single dose level of 329 mg/kg/day) and rabbits (up to 259 mg/kg/day) did not indicate any embryo/fetal toxicity or teratogenic effects. No fertility or peri-/postnatal studies have been performed in animals.

No adequate, well-controlled studies have been conducted in pregnant women. PANCREASE[®] MT Capsules should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 cannot be excluded.

ADVERSE REACTIONS

Clinical evidence indicates that PANCREASE[®] MT pancrelipase capsules are well tolerated. Post-marketing, the most frequently reported adverse effects are gastrointestinal in nature and include diarrhea, abdominal pain, intestinal obstruction, vomiting, intestinal stenosis, and constipation. Frequently reported adverse events in other body systems include dermatitis.

Extremely high doses of exogenous pancreatic enzymes have been associated with hyperuricemia and hyperuricosuria when the preparations given were pancrelipase in powdered or capsule form or pancreatin in tablet form^{2,3}.

Cases of fibrosing colonopathy have been reported in cystic fibrosis patients (see WARNINGS).

OVERDOSAGE

There have been no reports of accidental or purposeful overdosage with PANCREASE[®] MT capsules. Pancrelipase microtablets are classified as nontoxic by the Poisindex[®] Information System, and serious toxicity from overdose is unlikely. Should toxicity occur, treat symptomatically.

DOSAGE AND ADMINISTRATION

General Guidelines

Patients with pancreatic insufficiency should consume a high-calorie, unrestricted fat diet appropriate for their age and clinical status. A nutritional assessment should be performed regularly as a component of routine care, and additionally when the dosage of pancreatic enzyme replacement is changed.

Dosage should be adjusted according to the severity of the exocrine pancreatic enzyme deficiency. The number of capsules or capsule strength given with meals and/or snacks should be estimated by assessing which dose minimizes steatorrhea and maintains good nutritional status. In some patients with pancreatic enzyme deficiency, satisfactory responses have been achieved with dosages (expressed in USP units of lipase) similar to the ones stated below. However, dosages should be adjusted according to the response of the patients. Dosage should be adjusted based on 3-day fecal fat studies.

Dose increases, if required, should be made slowly, with careful monitoring of response and symptomatology. It is important to ensure adequate hydration of patients at all times while administering PANCREASE[®] MT capsules.

There is considerable variation among individuals in response to enzymes with respect to control of steatorrhea; therefore, a range of doses is suggested.

Infants (up to 12 months)

Fat Consumption Scheme

2,000-4,000 USP lipase units per 120 mL of formula or per breast-feeding. This provides approximately 450-900 lipase units per gram of fat ingested (based on 4.5 grams of fat per 120 mL standard cow's milk-based formula). Higher doses are used in infants because, on average, infants ingest 5 grams of fat per kilogram of body weight per day, whereas adults tend to ingest about 2 grams of fat per kilogram per day.

Children (over 12 months) and Adults

Weight-based Scheme

Less than 4 years: Begin with 1,000 USP lipase units/kg/meal to a maximum of 2,500 lipase units/kg/meal.

Over 4 years and Adults: Begin with 400 USP lipase units/kg/meal to a maximum of 2,500 lipase units/kg/meal.

Enzyme doses, expressed as lipase units/kg/meal, should be decreased in older patients, since they weigh more but tend to ingest less fat per kilogram. Usually, half the mealtime dose is given with a snack. The total daily dose should reflect approximately three meals and two snacks per day.

If doses greater than 2,500 lipase units/kg/meal (4,000 lipase units/gm fat/day) are required to control malabsorption, further investigation is warranted to rule out other causes of malabsorption. Doses greater than 2500 units/kg/meal should be used with caution and only if they are documented to be effective by 3-day fecal fat studies. It is unknown whether doses above 2,500 lipase units/kg/meal are safe.

Doses above the recommended dosing range have been associated with colonic strictures, particularly in children. Patients currently on higher doses (>2,500 lipase units/kg/meal or 4,000 lipase units/gm fat/day) should be re-evaluated and the dosage either immediately decreased or titrated downward to the lowest effective clinical dose as assessed by 3-day fecal fat excretion.

AVAILABILITY OF DOSAGE FORMS

PANCREASE[®] MT 4 capsules, yellow opaque, clear hard gelatin capsule, imprinted "MT 4" on clear cap, and "McNEIL" on body, containing: lipase 4,000 USP units, amylase 12,000 USP units and protease 12,000 USP units. Capsules are filled with off-white microtablets.

PANCREASE[®] MT 10 capsules, pink opaque, clear hard gelatin capsule, imprinted "MT 10" on clear cap, and "McNEIL" on body, containing: lipase 10,000 USP units, amylase 30,000 USP units and protease 30,000 USP units. Capsules are filled with off-white microtablets.

PANCREASE[®] MT 16 capsules, salmon opaque, clear hard gelatin capsule, imprinted "MT 16" on clear cap, and "McNEIL" on body, containing: lipase 16,000 USP units, amylase 48,000 USP units and protease 48,000 USP units. Capsules are filled with off-white microtablets.

Bottles of 100 capsules for each dosage form.

Stability and Storage Recommendations

Keep bottle tightly closed. Store between 10°C-25°C in a dry place. Dispense in tight container. Do not refrigerate.

PHYSICAL AND CHEMICAL PROPERTIES

Macroscopic Appearance

Pancrelipase, the enzyme component of PANCREASE[®] MT capsules, is a light beige granulate containing some lighter off-white particles.

Similarity to Other Compounds

PANCREASE[®] MT capsules closely relate to other lipase-enriched pancrelipase preparations and to pancreatin. PANCREASE[®] MT capsules differ from conventional pancreatic enzyme preparations in that the pancreatic enzymes are prepared as small enteric-coated microtablets (2 mm diameter). The pH-sensitive coating reduces or prevents inactivation of the enzymes by the acidic environment of the stomach.

The extremely small size of the microtablets promotes rapid and uniform dispersion with food in the stomach and emptying into the duodenum with the chyme. In addition, a patented pancrelipase extraction process ensures that the microtablets contain high-potency, biologically active pancreatic enzymes, including activated proteases.

Physical and Chemical Compatibilities

To protect the enteric coating, the microtablets should not be crushed or chewed. Diminished clinical effectiveness could result if the microtablets are crushed.⁵ If patients have difficulty swallowing capsules, the PANCREASE[®] MT capsules may be opened and the microtablets may be shaken onto a small quantity of a soft food which does not require chewing (e.g. applesauce, dessert gelatin, etc.), and swallowed

immediately. Contact of the microtablets with foods having a pH greater than 7.3 (e.g. milk, custard, ice cream, and many other dairy products) can dissolve the protective enteric coating.

The concurrent use of cimetidine or antacid therapy has not been demonstrated to improve the efficacy of enteric-coated pancreatic enzyme preparations such as PANCREASE[®] MT capsules.

The pancrelipase powder is partly soluble in water and practically insoluble in alcohol or ether.

General Stability

Temperature

The enteric coating and the potency of the pancreatic enzymes may be adversely affected by high temperature.

Moisture

The enteric coating and the potency of the pancreatic enzymes may be adversely affected by high humidity.

pH Stability

The enteric-coated microtablets are completely resistant to gastric acid, as indicated by testing for 2 hours in 0.1 N HCl (simulated gastric fluid). *In vitro*, the microtablets begin to dissolve above a pH of 5.5, with nearly 100% dissolution occurring within 30 minutes at a pH of 6.0. Exposing the microtablets to simulated intestinal fluid (pH 6.6) results in a 93% enzyme release within 15 minutes.¹

Excipients

PANCREASE[®] MT capsules contain the following inactive ingredients: cellulose, crospovidone, gelatin, iron oxide, magnesium stearate, methacrylic acid copolymer, polydimethylsiloxane, sodium lauryl sulfate, silicon dioxide, talc, titanium dioxide, triethylcitrate, wax, and other trace ingredients.

ANIMAL TOXICOLOGY

Acute Toxicity

No untoward signs of acute toxicity were observed in Beagle dogs dosed orally by capsule with enteric-coated pancrelipase microtablets for 10 days at a dosage of 5 g/kg.

CLINICAL EXPERIENCE

Clinical studies have demonstrated the efficacy of PANCREASE[®] MT capsules[‡] in the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and in patients with acquired pancreatic enzyme deficiencies. In these studies PANCREASE[®] MT capsules (16,000 units of lipase) was often compared with Kreon capsules[‡] (8,000 USP units of lipase) containing enteric-coated granules. PANCREASE[®] MT capsules were as effective as Kreon capsules, and the higher enzyme content of enteric-coated pancrelipase microtablets permitted a reduction in the number of capsules required per day.

Clinical Studies in Cystic Fibrosis

Two open 10-day studies^{6,7} compared the efficacy of PANCREASE[®] MT capsules and Kreon capsules in a total of 27 patients with cystic fibrosis. In both studies, fecal weight, frequency, and fat content were used to assess efficacy. During each study the patients received Kreon capsules for the first 3 days and were then switched to PANCREASE[®] MT capsules for the remainder of the study. Although both preparations were equal in efficacy, most patients (89%) required only one-half the number of capsules per day while on PANCREASE[®] MT capsules.

Clinical Studies in Acquired Pancreatic Insufficiency

The efficacy of enteric-coated pancrelipase microtablets in the treatment of pancreatic enzyme insufficiency resulting from chronic pancreatitis was determined in two open studies.

The first study⁸ compared the effects of PANCREASE[®] MT capsules and Kreon capsules in an open, randomized crossover design. After an initial 3-day no-treatment period, 9 patients with severe pancreatic insufficiency accompanied by marked steatorrhea were treated with either Kreon capsules (six t.i.d.) or PANCREASE[®] MT capsules (three t.i.d.) for 5 consecutive days. The patients were then switched to the other preparation and the trial was continued for 5 consecutive days. Both preparations produced a significant ($p < 0.05$) reduction in fecal weight and fat content compared to the initial 3-day no-treatment period. The number of capsules taken per day was reduced by one-half with the use of PANCREASE[®] MT capsules.

In the second study,⁹ all enzyme replacement medications were withdrawn for at least 3 days from 11 patients with severe, chronic pancreatitis. They were then treated with PANCREASE[®] MT capsules (one

[‡] These studies, conducted in West Germany, used Panzytrat[®] 20000 (Nordmark Arzneimittel GmbH, Uetersen, West Germany) which is therapeutically equivalent to PANCREASE[®] MT 16.

[‡] Kreon[®] capsules, Kali-Chemie Pharma GmbH, Hannover, West Germany

t.i.d.) for 7 consecutive days. Efficacy was measured by determining fecal frequency, weight, and fat content immediately before and after treatment. PANCREASE[®] MT capsules produced a significant ($p < 0.05$) improvement in all efficacy parameters. In addition, a questionnaire administered at the end of the study revealed a reduction in the subjective symptoms (pain, diarrhea, nausea, emesis, flatulence) associated with pancreatic enzyme insufficiency.

REFERENCES

1. Otte M, Ridder P, Dageforde J: *In vitro* tests of pancreatic enzyme preparations. Deutsche Medizinische Wochenschrift 1987; 112(39):1498-1502.
2. Stapleton FB, Kennedy J, Nousia-Arvanitakas S, Linshaw MA: Hyperuricosuria due to high-dose pancreatic extract therapy in cystic fibrosis. New England Journal of Medicine 1976; 295:246-248.
3. Davidson GP, Hassel FM, Crozier D, et al: Iatrogenic hyperuricemia in children with cystic fibrosis. The Journal of Pediatrics 1978; 93:976-978.
4. Martindale: The Extra Pharmacopoeia 30th Edition, Reynolds, JEF ed., London: The Pharmaceutical Press, 1993; p. 1397, 1398.
5. Weber AM, de Gheldere B, Roy CC, et al: Effectiveness of enteric coated pancrease in cystic fibrosis (CF) children under 4 years old. Cystic Fibrosis Club Abstracts; May 1979; 18.
6. Stern M, Plettner C, Gruttner R: Pancreatic-enzyme replacement therapy in cystic fibrosis (CF): Clinical trial of a gastric-acid resistant pancreatin preparation in encapsulated microtablet form. Klinische Padiatrie 1988; 200:36-39.
7. Gottschalk B, Wiesemann HG, Stephan U: Comparison of two pancreatic enzyme preparations for the treatment of digestive insufficiency in cystic fibrosis. Monatsschrift Kinderheilkunde. To be published.
8. Lankisch PG, Lembcke B, Kirchoff S, et al: Therapy of pancreatogenic steatorrhea: Comparison of two acid-protected enzyme preparations. Deutsche Medizinische Wochenschrift 1988; 113:15-17.
9. Meyer J, Sulkowski U, Preusser P: Results of replacement therapy in insufficiency of the exocrine pancrease. Medizinische Welt 1987; 38:516-518.
10. Borowitz DS, Grand RJ, Durie PR, and the Consensus Committee: Use of Pancreatic Enzyme Supplements for Patients with Cystic Fibrosis in the Context of Fibrosing Colonopathy. The Journal of Pediatrics 1995; 127:681-683.
11. Pancreatic Enzymes - Evaluation of Current Practice in a Large Clinic. CF Conference 1995, 309