

ULTRASE®

**('ul-trās)
(pancrelipase) Capsules
Enteric-Coated Microspheres**

Prescribing Information

DESCRIPTION:

ULTRASE® (pancrelipase) Capsules are orally administered and contain 250 mg of enteric-coated microspheres of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease.

Each ULTRASE® Capsule contains:

Lipase.....	4,500 U.S.P. Units
Amylase.....	20,000 U.S.P. Units
Protease.....	25,000 U.S.P. Units

Inactive ingredients: povidone, talc, sugar, methacrylic acid copolymer (Type C), triethyl citrate, simethicone emulsion.

CLINICAL PHARMACOLOGY:

ULTRASE® (pancrelipase) Capsules are designed to prevent inactivation by gastric acid thereby resulting in the delivery of high levels of biologically active enzymes into the duodenum. The enzymes catalyze the hydrolysis of fats into glycerol and fatty acids, starch into dextrins and sugars, and protein into proteoses and derived substances.

INDICATIONS AND USAGE:

ULTRASE® (pancrelipase) Capsules are indicated for patients with partial or complete exocrine pancreatic insufficiency caused by:

- Cystic fibrosis (CF)
- Chronic pancreatitis due to alcohol use or other causes
- Surgery (pancreatico-duodenectomy or Whipple's procedure, with or without Wirsung duct injection, total pancreatectomy)
- Obstruction (pancreatic and biliary duct lithiasis, pancreatic and duodenal neoplasms, ductal stenosis)
- Other pancreatic disease (hereditary, post traumatic and allograft pancreatitis, hemochromatosis, Shwachman's Syndrome, lipomatosis, hyperparathyroidism)
- Poor mixing (Billroth II gastrectomy, other types of gastric bypass surgery, gastrinoma)

Pancrelipase capsules are effective in controlling steatorrhea.¹⁻⁹

CONTRAINDICATIONS:

Pancrelipase capsules are contraindicated in patients known to be hypersensitive to pork protein. Pancrelipase capsules are contraindicated in patients with acute pancreatitis or with acute exacerbations of chronic pancreatic diseases.

WARNINGS:

Should hypersensitivity occur, discontinue medication and treat symptomatically.

PRECAUTIONS:

General

TO PROTECT ENTERIC COATING, MICROSPHERES MUST NOT BE CRUSHED OR CHEWED. Where swallowing of capsules is difficult, they may be opened and the microspheres added to a small quantity of a soft food (e.g., applesauce, gelatin, etc.) that does not require chewing, and swallowed immediately. Contact of the microsphere with foods having a pH greater than 5.5 can dissolve the protective enteric shell.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Methacrylic acid, a minor component of the methacrylic acid copolymer enteric-coating contained in ULTRASE® (pancrelipase) Capsules, has been reported to act as a teratogen in rat embryo cultures. However, the copolymer enteric-coating of ULTRASE® (pancrelipase) Capsules was not mutagenic by the Ames test, and it did not produce chromosome damage in a test for unscheduled DNA synthesis in rat hepatocytes.

Pregnancy: Category C.

Animal reproduction studies have not been conducted with ULTRASE® (pancrelipase) Capsules. It is not known whether ULTRASE® (pancrelipase) Capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ULTRASE® (pancrelipase) Capsules should be given to a pregnant woman only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

It is not known whether ULTRASE® (pancrelipase) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ULTRASE® (pancrelipase) Capsules are administered to a nursing mother.

ADVERSE REACTIONS:

The most frequently reported adverse reactions to products containing pancrelipase are gastrointestinal in nature. Less frequently, allergic-type reactions have also been observed. Extremely high doses of exogenous pancreatic enzymes have been associated with hyperuricosuria and hyperuricemia when the preparations given were pancrelipase in powdered or capsule form, or pancreatin in tablet form.

Colonic strictures have been reported in cystic fibrosis patients treated with both high- and lower-strength enzyme supplements.¹⁰ A causal relationship has not been established. The possibility of bowel stricture should be considered if symptoms suggestive of gastrointestinal obstruction occur. Since impaired fluid secretion may be a factor in the development of intestinal obstruction, care should be taken to maintain adequate hydration, particularly in warm weather.¹¹

"Fibrosing colonopathy" is a term used to describe a condition seen in patients with CF who have taken high amounts of pancreatic enzyme supplements (>6,000 lipase U/kg/meal). At its most advanced, this condition leads to colonic strictures.

1. In whom should one consider the diagnosis of fibrosing colonopathy?
 - a. Patients with cystic fibrosis who have evidence of partial or complete obstruction, bloody diarrhea or chylous ascites.
 - b. Patients who have two of the following three symptoms:
 - abdominal pain
 - ongoing diarrhea
 - poor weight gain
 ESPECIALLY if they have:
 - taken >6,000 lipase U/kg/meal
 - age less than twelve years
 - history of meconium ileus
 - prior intestinal surgery
 - history of recurrent DIOS
 - "inflammatory bowel disease"¹²

DOSAGE AND ADMINISTRATION:

The enzymatic activity of ULTRASE[®] (pancrelipase) Capsules is expressed in U.S.P. units. The smallest effective dose should be used. Dosage should be adjusted according to the severity of the exocrine pancreatic insufficiency. Begin therapy with one or two capsules with meals or snacks and adjust dosage according to symptoms. 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. Dosages should be adjusted according to the response of the patient. Where swallowing of capsules is difficult, they may be opened and the microspheres added to a small quantity of a soft food (e.g., applesauce, gelatin, etc.) that does not require chewing, and swallowed immediately. It is recommended that the total dose of pancrelipase being ingested for a meal or snack be dispersed equally (with fluids) before, during, and after the meal or snack.

SUGGESTIONS FOR THE USE OF PANCREATIC ENZYMES IN CYSTIC FIBROSIS¹²

1. Patients should be receiving optimal diet for age and clinical status, recognizing that those with failure to thrive or malnutrition require additional calories and other nutrients for catch-up growth.
2. Nutrition assessment should be a part of routine clinical evaluations.
3. Initial dosing of pancreatic enzyme supplements should begin with 500 lipase U/kg/meal using enteric-coated microsphere products.
4. Patients should be reassessed 2-4 weeks after initiation of therapy. The following items should be assessed:
 - Clinical status, e.g., abdominal symptoms and exam;
 - Nutritional intake and growth (height, weight, head circumference);
 - Character of stools - greasy, oily (for information, not for decision making);
 - Quantitative 72-hour fecal fat when indicated but not less than annually (perform on a normal diet for age);
 - Fat soluble vitamin measures.
5. Corollaries to dosing suggestions:
 - a. Dose may be altered in a stepwise fashion according to the response of the patient (see 4. above).
 - b. Dose approaching 2,000 lipase U/kg/meal would indicate the need for further investigation (see below). Patients presently on higher doses should be reevaluated; either immediately decrease the dose or titrate down to a lower dose range at, or below, 2,000 lipase U/kg/meal. Doses >6,000 lipase U/kg/meal have been associated with colonic strictures.
 - c. Pancreatic supplements mixed with applesauce or other acidic food substances should be administered immediately, not stored.
 - d. Enteric-coated microspheres should not be crushed.
 - e. Enzyme doses (as lipase U/kg/meal) tend to decrease with advancing age.
 - f. Patients should accept only product brands prescribed by their physician.
 - g. Adjustment of dosage is the responsibility of the physician. Patients should be advised not to adjust doses without consulting their physician. Changes in product or dosage may require an adjustment period.
 - h. Complaints transmitted by phone should be investigated thoroughly before dose is adjusted. If indicated, this investigation should include 72-hour fecal fat testing.
 - i. Pancreatic supplements should be stored in a cool, dry place and checked regularly for expiration date.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

HOW SUPPLIED:

ULTRASE[®] (pancrelipase) Capsules

Gelatin capsules (opaque white and opaque white), imprinted "ULTRASE". Bottles of 100 (NDC 58914-045-10).

Store at controlled room temperature, between 15°C and 25°C (59°F and 77°F), in a dry place. Do not refrigerate.

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Rx only

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