HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ULTRESA safely and effectively. See full prescribing information for ULTRESA.

ULTRESA (pancrelipase) delayed-release capsules, for oral use
Initial U.S. Approval: 2012

---------- INDICATIONS AND USAGE ----------

ULTRESA® is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. (1)

----------DOSAGE AND ADMINISTRATION ----------

ULTRESA is not interchangeable with any other pancrelipase product. (2)

Administration

- ULTRESA should be swallowed whole. Do not crush or chew the capsules and the capsule contents. For children or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food with pH of 4.5 or less such as applesauce or yogurt. (2.1)

Infants (up to 12 months)

- Infants may be given 4,000 lipase units per 120 mL of formula or per breast-feeding. (2.2)
- Do not mix ULTRESA capsule contents directly into formula or breast milk prior to administration. (2.1)

Children Older than 12 Months and Younger than 4 Years

- Begin with 1,000 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.2)

Children 4 Years and Older and Adults

- Begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.2)

Limitations on Dosing

- Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Delayed-Release Capsules: 4,000 USP units of lipase; 8,000 USP units of protease; 8,000 USP units of amylase (3)
- Delayed-Release Capsules: 13,800 USP units of lipase; 27,600 USP units of protease; 27,600 USP units of amylase (3)
- Delayed-Release Capsules: 20,700 USP units of lipase; 41,400 USP units of protease; 41,400 USP units of amylase (3)
- Delayed-Release Capsules: 23,000 USP units of lipase; 46,000 USP units of protease; 46,000 USP units of amylase (3)

----------CONTRAINDICATIONS ----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of ULTRESA exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day). (5.1)
- To avoid irritation of oral mucosa, do not chew ULTRESA or retain in mouth. (5.2)
- Exercise caution when prescribing ULTRESA to patients with gout, renal impairment, or hyperuricemia. (5.3)
- There is theoretical risk of viral transmission with all pancreatic enzyme products including ULTRESA. (5.4)
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. (5.5)

---------- ADVERSE REACTIONS ----------

- The most common adverse reactions (≥7% of patients treated with ULTRESA) are headache, pharyngolaryngeal pain, and epistaxis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact APTALIS Pharma US, Inc. / Forest Laboratories, LLC at 1-800-472-2634 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: MM/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ULTRESA (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

2 DOSAGE AND ADMINISTRATION

ULTRESA is not interchangeable with other pancrelipase products.

ULTRESA is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of ULTRESA should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet as described in the Limitations on Dosing below *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

2.1 Administration

Infants (up to 12 months)

ULTRESA should be administered to infants immediately prior to each feeding, using a dosage of 4,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Contents of the capsule may be administered with a small amount of applesauce, or other acidic food with a pH of 4.5 or less (e.g., commercially available preparations of bananas, or pears). Contents of the capsule may also be administered directly to the mouth and immediately give formula or breast milk to ensure complete ingestion.

Administration should be followed by breast milk or formula. Contents of the capsule **should not** be mixed directly into formula or breast milk as this may diminish efficacy. Care should be taken to ensure that ULTRESA is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

Children and Adults

ULTRESA should be taken during meals or snacks, with sufficient fluid. ULTRESA capsules should be swallowed whole. **ULTRESA capsules and capsule contents should not be crushed or chewed**.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on a small amount of soft acidic food with pH of 4.5 or less such as applesauce or yogurt at room temperature.

The ULTRESA-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth to avoid mucosal irritation.

Any unused portion of capsule contents should be discarded, and not used for subsequent dosing. The remaining exposed contents may lose potency and become less effective.

2.2 Dosage

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.[1,2,3] ULTRESA should be administered in a manner consistent with the recommendations of the Conferences provided in the following paragraphs, with one exception. The

Conferences recommend doses of 2,000 to 4,000 lipase units in infants up to 12 months. ULTRESA is available in a 4,000 lipase unit capsule. The recommended dose of ULTRESA in infants up to 12 months is 4,000 lipase units. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

Infants (up to 12 months)

Infants may be given 4,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Do not mix ULTRESA capsule contents directly into formula or breast milk prior to administration *[see Dosage and Administration (2.1)]*.

Children Older than 12 Months and Younger than 4 Years

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Adults

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed ULTRESA dose for an individualized full meal should be given with each snack. The total daily dosage should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

Limitations on Dosing:

Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1,2,3] If symptoms and signs of steatorrhea persist, the dosage may be increased by a healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age *[see Warnings and Precautions (5.1)]*. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

3 DOSAGE FORMS AND STRENGTHS

The active ingredient in ULTRESA evaluated in clinical trials is lipase. ULTRESA is dosed by lipase units. Other active ingredients include protease and amylase.

ULTRESA is available in 4 color coded delayed-release capsule strengths. Each ULTRESA delayed-release capsule strength contains the specified amounts of lipase, protease, and amylase as follows:

- 4,000 USP units of lipase; 8,000 USP units of protease; 8,000 USP units of amylase delayed-release capsules have a flesh opaque cap printed with "ULTRESA" and blue opaque body printed with "4000" in black.
- 13,800 USP units of lipase; 27,600 USP units of protease; 27,600 USP units of amylase delayed-release capsules have a white cap printed with "13800UL" and yellow body printed with "AXCA" in black.
- 20,700 USP units of lipase; 41,400 USP units of protease; 41,400 USP units of amylase delayed-release capsules have a gray cap printed with "20700UL" and white body printed with "AXCA" in black.
- 23,000 USP units of lipase; 46,000 USP units of protease; 46,000 USP units of amylase delayed-release capsules have a light gray cap printed with "23000UL" and yellow body printed with "AXCA" in black.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products.[4, 5] Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually with use over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture in children less than 12 years of age.[1] Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day *[see Dosage and Administration (2.2)]*.

Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

5.2 Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth. ULTRESA should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity *[see Dosage and Administration (2.1) and Patient Counseling Information (17.1)]* For patients who are unable to swallow intact capsules, the contents may be sprinkled on soft acidic food with pH 4.5 or less such as

applesauce or yogurt. The ULTRESA-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

5.3 Potential for Risk of Hyperuricemia

Caution should be exercised when prescribing ULTRESA to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

5.4 Potential for Viral Exposure from the Product Source

ULTRESA is sourced from pancreatic tissue from swine used for food consumption. Although the risk that ULTRESA will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

5.5 Allergic Reactions

Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued ULTRESA treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

6 ADVERSE REACTIONS

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) that are described elsewhere in the label include fibrosing colonopathy, hyperuricemia and allergic reactions *[see Warnings and Precautions (5.1, 5.3 and 5.5)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The short-term safety of ULTRESA was assessed in two clinical trials conducted in 40 patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). Study 1 was conducted in 31 patients, ages 8 years to 37 years; Study 2 was conducted in 9 patients, ages 7 years to 11 years.

Study 1 was a randomized, double-blind, placebo-controlled, crossover study of 31 patients, ages 8 to 37 years, with EPI due to CF. In this study, patients were randomized to receive ULTRESA at doses not to exceed 2,500 lipase units per kilogram per meal or matching placebo for 6 to 7 days of treatment, followed by crossover to the alternate treatment for an additional 6 to 7 days. The mean daily dose of ULTRESA was 6,270 lipase units per kilogram body weight per day. The mean exposure to ULTRESA during this study was 5.4 days.

The most common adverse reactions (≥7%) were headache, pharyngolaryngeal pain, and epistaxis. Table 1 enumerates adverse reactions that occurred in at least 2 patients (greater than or equal to 7%) treated with ULTRESA at a higher rate than with placebo in Study 1.

TABLE 1
Adverse Reactions Occurring in at Least 2 Patients (≥ 7%) in Cystic Fibrosis (Study 1)

Adverse Reaction	ULTRESA n=30 n (%)	PLACEBO n=31 n (%)
Headache	2 (7%)	1 (3%)
Pharyngolaryngeal Pain	2 (7%)	1 (3%)
Epistaxis	2 (7%)	0

Study 2 was an open-label study of 9 patients, ages 7 years to 11 years, with EPI due to CF. After a screening period of up to 15 days on individually-titrated doses of ULTRESA not to exceed 2,500 lipase units per kilogram per meal, patients entered a washout phase (no treatment) of up to 7 days before returning to a treatment phase of up to 12 days on the same individually-titrated dose of ULTRESA. Two patients discontinued during the washout phase leaving 7 patients in the treatment phase. The mean daily dose of ULTRESA was 6,361 lipase units per kilogram body weight per day during the last 4 days of the screening phase, and was 6,846 lipase units per kilogram body weight per day during the treatment phase. The mean duration of the treatment phase was 5.7 days.

Adverse reactions that occurred during treatment with ULTRESA were nasal congestion (14%), neck pain (14%), beta-hemolytic streptococcal infection (11%), ear pain (11%), and lymphadenopathy (11%).

6.2 Postmarketing Experience

Postmarketing data for ULTRESA has been available since 2003. The safety data is similar to that described below. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pancreatic enzyme products (delayed and immediate-release) with different formulations of the same active ingredient (pancrelipase) have been used for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis and other conditions, such as chronic pancreatitis. The long-term safety profile of these products has been described in the medical literature. The most serious adverse events included fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives, and pruritus. The most commonly reported adverse events were gastrointestinal disorders, including abdominal pain, diarrhea, flatulence, constipation and nausea, and skin disorders including pruritus, urticaria and rash.

7 DRUG INTERACTIONS

No drug interactions have been identified. No formal interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category C. Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ULTRESA should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ULTRESA is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.

8.4 Pediatric Use

The short-term safety and efficacy of ULTRESA were assessed in two clinical studies in pediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis; one study included patients aged 8 years to 17 years, and the other included patients aged 7 years to 11 years.

Study 1 was a randomized, double-blind, placebo-controlled crossover study of 31 patients with exocrine pancreatic insufficiency due to cystic fibrosis including 2 children aged 8 to 11 years, and 12 adolescents aged 12 to 17 years. The safety and efficacy in pediatric patients in this study were similar to that in adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Study 2 was an open-label study of 9 pediatric patients, ages 7 years to 11 years, with exocrine pancreatic insufficiency due to cystic fibrosis. Patients showed similar control of fat malabsorption as in the treatment arm of Study 1 *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience.

Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy and colonic strictures in children less than 12 years of age *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies of ULTRESA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There have been no reports of overdose in clinical trials or postmarketing surveillance with ULTRESA. Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Dosage and Administration (2) and Warnings and Precautions (5.1)]*. High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should be used with caution in patients with a history of hyperuricemia, gout, or renal impairment *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

ULTRESA is a pancreatic enzyme preparation consisting of pancrelipase, an extract derived from porcine pancreatic glands. Pancrelipase contains multiple enzyme classes, including porcine-derived lipases, amylases, and proteases.

Pancrelipase is a beige-white amorphous powder. It is miscible in water and practically insoluble or insoluble in alcohol and ether.

Each delayed-release capsule for oral administration contains enteric-coated beads (1.7 mm in diameter and 1.9 mm thick for 4,000 USP lipase units, approximately 2.0 mm in diameter and 2.0 – 2.4 mm thick for 13,800, 20,700, and 23,000 USP lipase units).

The active ingredient evaluated in clinical trials is lipase. ULTRESA is dosed by lipase units. Other active ingredients include protease and amylase.

ULTRESA contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydrogenated castor oil, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, talc, and triethyl citrate.

<u>4,000 USP units of lipase</u>; 8,000 USP units of protease; 8,000 USP units of amylase. The hypromellose delayed-release capsules have a flesh opaque cap and blue opaque body, printed with “ULTRESA” on the cap and “4000” on the body in black ink. The capsule shell contains hypromellose, titanium dioxide, FD&C Blue 1, red iron oxide, and capsule imprint ink.

<u>13,800 USP units of lipase</u>; 27,600 USP units of protease; 27,600 USP units of amylase. The hard gelatin delayed-release capsules have a white cap and yellow body printed with “13800UL” on cap and “AXCA” on the body in black ink. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and capsule imprint ink.

<u>20,700 USP units of lipase</u>; 41,400 USP units of protease; 41,400 USP units of amylase. The hard gelatin delayed-release capsules have a gray cap and white body printed with “20700UL” on cap and “AXCA” on the body in black ink. The capsule shell contains gelatin, titanium dioxide, black iron oxide, and capsule imprint ink.

<u>23,000 USP units of lipase</u>; 46,000 USP units of protease; 46,000 USP units of amylase. The hard gelatin delayed-release capsules have a light gray cap and yellow body printed with “23000UL” on cap and “AXCA” on the body in black ink. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and in capsule imprint ink.

The black radial imprinting on the capsule contains iron oxide black as colorant, shellac, and propylene glycol. It may also contain strong ammonia solution, and potassium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pancreatic enzymes in ULTRESA catalyze the hydrolysis of fats to monoglycerides, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltotriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

12.3 Pharmacokinetics

The pancreatic enzymes in ULTRESA are enteric-coated to minimize destruction or inactivation in gastric acid. ULTRESA is designed to release most of the enzymes *in vivo* at pH greater than 5.5. Pancreatic enzymes are not absorbed from the gastrointestinal tract in appreciable amounts.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with pancrelipase.

14 CLINICAL STUDIES

The short-term efficacy and safety of ULTRESA were evaluated in 2 studies conducted in 40 patients, ages 7 to 37 years, with exocrine pancreatic insufficiency associated with cystic fibrosis.

Study 1 was a randomized, double-blind, placebo-controlled, crossover study of 31 patients, ages 8 to 37 years, with exocrine pancreatic insufficiency due to cystic fibrosis. The final analysis population was limited to 24 patients, who completed both treatment periods and had stool results available for each treatment period. Patients were randomized to receive ULTRESA (at a dose not to exceed 2,500 lipase units per kilogram per meal or snack) or matching placebo for 6 to 7 days of treatment followed by crossover to the alternate treatment for an additional 6 to 7 days. The mean dose during the controlled treatment periods was 6,270 lipase units per kilogram per day. All patients consumed a high-fat diet (2 grams of fat per kilogram of body weight per day) during the treatment periods.

The coefficient of fat absorption (CFA) was determined by a 72-hour stool collection during both treatments, when both fat excretion and fat ingestion were measured. Each patient's CFA during placebo treatment was used as their no-treatment CFA value.

Mean CFA was 89% with ULTRESA treatment compared to 56% with placebo treatment. The mean difference in CFA was 35 percentage points in favor of ULTRESA treatment with 95% CI: (25, 45) and $p<0.0001$.

Subgroup analyses of the CFA results showed that mean change in CFA was greater in patients with lower no-treatment (placebo) CFA values than in patients with higher no-treatment (placebo) CFA values. There were similar responses to ULTRESA by age and gender.

The coefficient of nitrogen absorption (CNA) was determined by a 72 hour stool collection during both treatments, when nitrogen excretion was measured and nitrogen ingestion from a controlled diet was estimated

(based on the assumption that proteins contain 16% nitrogen). Each patient's CNA during placebo treatment was used as their no treatment CNA value.

In Study 1, mean CNA was 84% with ULTRESA treatment compared to 59% with placebo treatment. The mean difference in CNA was 26 percentage points in favor of ULTRESA treatment with 95% CI: (18, 33) and $p<0.0001$.

Study 2 was an open-label study of 9 patients, ages 7 years to 11 years (mean 10 years), with exocrine pancreatic insufficiency due to cystic fibrosis. The final analysis population was limited to 7 patients who completed both the washout and treatment phases of the study. After a 15 day screening period on individually-titrated doses of ULTRESA not to exceed 2,500 lipase units per kilogram per meal, patients in Study 2 entered a 7-day washout phase (no treatment) before returning to a 12-day treatment phase on the same individually-titrated dose of ULTRESA. The mean daily dose of ULTRESA during the treatment phase was 6,846 lipase units per kilogram body weight per day. All patients consumed a high-fat diet (2 grams of fat per kilogram of body weight per day) during both the washout phase and the treatment phase.

The mean coefficient of fat absorption (CFA) was determined during the washout phase (no treatment) and during the ULTRESA treatment phase. Mean CFA was 35% during the washout phase and was 83% during the ULTRESA treatment phase.

15 REFERENCES

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4. Smyth RL, Ashby D, O'Hea U, et al. Fibrosing colonopathy in cystic fibrosis: results of a case-control study. *Lancet.* 1995; 346: 1247-1251.

5. FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *New England Journal of Medicine.* 1997; 336: 1283-1289.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULTRESA Delayed-Release Capsules

4,000 USP units of lipase; 8,000 USP units of protease; 8,000 USP units of amylase

Each ULTRESA capsule is available as a two-piece hypromellose capsule with a flesh opaque cap printed with "ULTRESA" and blue opaque body printed with "4000" that contains light brown, bright, homogeneous micro-tablets of delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 58914-006-10)

ULTRESA Delayed-Release Capsules

13,800 USP units of lipase; 27,600 USP units of protease; 27,600 USP units of amylase

Each ULTRESA capsule is available as a two-piece gelatin capsule with a white cap printed with "13800UL" and a yellow body printed with "AXCA" that contains light brown, bright, homogeneous mini-tablets of delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 58914-003-10)

ULTRESA Delayed-Release Capsules

20,700 USP units of lipase; 41,400 USP units of protease; 41,400 USP units of amylase

Each ULTRESA capsule is available as a two-piece gelatin capsule with a gray cap printed with "20700UL" and a white body printed with "AXCA" that contains light brown, bright, homogeneous mini-tablets of delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 58914-019-10)

ULTRESA Delayed-Release Capsules

23,000 USP units of lipase; 46,000 USP units of protease; 46,000 USP units of amylase

Each ULTRESA capsule is available as a two-piece gelatin capsule with a light gray cap printed with "23000UL" and a yellow body printed with "AXCA" that contains light brown, bright, homogeneous mini-tablets of delayed-release pancrelipase supplied in bottles of:

- 100 capsules (NDC 58914-005-10)

Storage and Handling

Avoid excessive heat. ULTRESA capsules should be stored in a dry place in the original container. Store at room temperature 20-25°C (68-77°F). After opening, keep the container tightly closed between uses to protect from moisture.

ULTRESA is dispensed in bottles containing a desiccant. The desiccant packet should not be eaten or thrown away. The desiccant packet will protect the product from moisture.

Do not crush ULTRESA delayed-release capsule or the capsule contents.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Dosing and Administration

- Instruct patients and caregivers that ULTRESA should only be taken as directed by their health care provider Patients should be advised that the total daily dose should not exceed 10,000 lipase units/kg body weight/day unless clinically indicated. This needs to be especially emphasized for patients eating multiple snacks and meals per day. Patients should be informed that if a dose is missed, the next dose should be taken with the next meal or snack as directed. Doses should not be doubled. *[see Dosage and Administration (2)]*

- Instruct patients and caregivers that ULTRESA should always be taken with food. Patients should be advised that ULTRESA delayed-release capsules must not be crushed or chewed as doing so could cause

early release of enzymes and/or loss of enzymatic activity and irritation of the oral mucosa. Patients should swallow the intact capsules with adequate amounts of liquid at mealtimes. If necessary, the capsules contents can also be sprinkled on soft acidic foods. *[see Dosage and Administration (2)]*

- Any unused portion of capsule contents should be discarded, and not used for subsequent dosing. The remaining exposed contents may lose potency and become less effective. *[see Dosage and Administration (2)]*

17.2 Fibrosing Colonopathy

Advise patients and caregivers to follow dosing instructions carefully, as doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal (10,000 lipase units/kg body weight/day) have been associated with colonic strictures (a rare bowel disorder) in children below the age of 12 years. *[see Dosage and Administration (2) and Warnings and Precautions (5.1)]*

17.3 Allergic Reactions

Advise patients and caregivers to contact their health care provider immediately if allergic reactions to ULTRESA develop.

17.4 Pregnancy and Breast Feeding

- Instruct patients to notify their physician if they are pregnant or are thinking of becoming pregnant during treatment with ULTRESA. *[see Use in Specific Populations (8.1)]*

- Instruct patients to notify their physician if they are breast feeding or are thinking of breast feeding during treatment with ULTRESA. *[see Use in Specific Populations (8.3)]*

Marketed by:
Aptalis Pharma US, Inc
100 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Manufactured by:
Aptalis Pharma S.r.L.
Pessano, Italy 20060

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MEDICATION GUIDE
ULTRESA® (ul-tres-a)
(pancrelipase)
delayed-release capsules

Read this Medication Guide before you start taking ULTRESA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about ULTRESA?

ULTRESA may increase your chance of having a rare bowel disorder called fibrosing colonopathy. This condition is serious and may require surgery. The risk of having this condition may be reduced by following the dosing instructions that your doctor gave you.

Call your doctor right away if you have any unusual or severe:

- stomach area (abdominal) pain
- bloating
- trouble passing stool (having bowel movements)
- nausea, vomiting or diarrhea

Take ULTRESA exactly as prescribed by your doctor. Do not take more or less ULTRESA than directed by your doctor.

What is ULTRESA?

ULTRESA is a prescription medicine used to treat people who cannot digest food normally because their pancreas does not make enough enzymes due to cystic fibrosis or other conditions.

ULTRESA capsules contain a mixture of digestive enzymes including lipases, proteases, and amylases from pig pancreas.

What should I tell my doctor before taking ULTRESA?

Before you take ULTRESA, tell your doctor about all of your medical conditions, including if you:

- are allergic to pork (pig) products
- have a history of intestinal blockage, or scarring or thickening of your bowel wall (fibrosing colonopathy)
- have gout, kidney disease, or a condition called high blood uric acid (hyperuricemia)
- have trouble swallowing capsules
- have any other medical condition

- are pregnant or plan to become pregnant. It is not known if ULTRESA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ULTRESA passes into your breast milk. You and your doctor should decide if you will take ULTRESA or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take ULTRESA?

- **Take ULTRESA capsules exactly as your doctor tells you.**
- You should not switch ULTRESA with any other pancreatic enzyme product without first talking to your doctor.
- Do not take more capsules in a day than the number your doctor tells you to take (total daily dose).
- Always take ULTRESA with a meal or snack and plenty of fluid. If you eat a lot of meals or snacks in a day, be careful not to go over your total daily dose.
- Your doctor may change your dose based on the amount of fatty foods you eat or based on your weight.
- **Do not crush or chew the ULTRESA capsules or their contents, and do not hold the capsule or capsule contents in your mouth.** Crushing, chewing or holding the ULTRESA capsules in your mouth may cause irritation in your mouth or change the way ULTRESA works in your body.

Giving ULTRESA to infants (up to 12 months of age):

1. Give ULTRESA right before each feeding of formula or breast milk.
2. Do not mix ULTRESA capsule contents directly into formula or breast milk.
3. Open the capsule and sprinkle the contents on a small amount of soft acidic food such as applesauce, pureed bananas or pears. These foods should be the kind found in baby food jars that you buy at the store, or other foods recommended by your doctor. You may also sprinkle the capsule contents directly into your infant's mouth and immediately give formula or breast milk to ensure your infant has swallowed the medicine completely.
4. If you sprinkle the ULTRESA on food, give the ULTRESA and food mixture to your infant right away. Do not store ULTRESA that is mixed with food. Throw away any unused portion of capsule contents.
5. Give your infant enough formula or breast milk to completely swallow the ULTRESA capsule contents or the ULTRESA and food mixture.

6. Look in your infant's mouth to make sure that all of the medicine has been swallowed.

7. If you miss giving your infant a dose of ULTRESA, wait and give the prescribed dose of ULTRESA right before the next feeding of formula or breast milk. **Do not give 2 doses at one time.**

Giving ULTRESA to children and adults:

1. You should not divide the capsule contents into small amounts to give small doses of ULTRESA.
2. Swallow ULTRESA capsules whole and take them with enough liquid to swallow them right away.
3. If you have trouble swallowing capsules, open the capsule and sprinkle the contents on a small amount of soft acidic food including applesauce or yogurt. Ask your doctor about other foods you can mix with ULTRESA.
4. If you sprinkle ULTRESA on food, swallow it right after you mix it and drink plenty of water or juice to make sure the medicine is swallowed completely. Do not store ULTRESA that is mixed with food. Throw away any unused portion of capsule contents.
5. If you miss a dose of ULTRESA, wait until your next meal or snack and take your prescribed dose. Take your next dose at your usual time. **Do not take two doses at one time.**

What are the possible side effects of ULTRESA?

ULTRESA may cause serious side effects, including:

- See **"What is the most important information I should know about ULTRESA?"**
- **Irritation of the inside of your mouth.** This can happen if ULTRESA is not swallowed completely.
- **Increase in blood uric acid levels.** This may cause worsening of swollen, painful joints (gout) caused by an increase of uric acid levels in your blood.
- **Allergic reactions, including** trouble breathing, skin rash, itching, or swollen lips.

Call your doctor right away if you have any of these symptoms.

The most common side effects of ULTRESA include:

- headache
- throat pain
- nose bleeds

Other possible side effects:

ULTRESA and other pancreatic enzyme products are made from the pancreas of pigs, the same pigs people eat as pork. These pigs may carry viruses. Although it has never been reported, it may be possible for a person to get a viral infection from taking pancreatic enzyme products that come from pigs.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ULTRESA. For more information, ask your doctor or pharmacist.

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

You may also report side effects to Aptalis Pharma, US Inc. / Forest Laboratories, LLC at 1-800-472-2634.

How should I store ULTRESA?

- Store ULTRESA at room temperature 68°F to 77°F (20°C to 25°C). Avoid heat.
- ULTRESA capsules should be stored in a dry place in the original container.
- After opening the bottle, keep it closed tightly between uses to keep your medicine dry (protect it from moisture).
- The ULTRESA bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). **Do not throw away or eat the desiccant packet.**

Keep ULTRESA and all medicines out of the reach of children.

General information about the safe and effective use of ULTRESA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ULTRESA for a condition for which it was not prescribed. Do not give ULTRESA to other people to take, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ULTRESA. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about ULTRESA that is written for health professionals.

For more information, go to www.ultresa.com or call toll-free 1-800-472-2634.

What are the ingredients in ULTRESA?

Active ingredient: lipase, protease, amylase.

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydrogenated castor oil, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, talc, and triethyl citrate.

Capsule shell ingredients:
ULTRESA 4,000 USP units of lipase; 8,000 USP units of protease; 8,000 USP units of amylase contains hypromellose, titanium dioxide, FD&C Blue 1, red iron oxide, and capsule imprint ink.

ULTRESA 13,800 USP units of lipase; 27,600 USP units of protease; 27,600 USP units of amylase contains gelatin, titanium dioxide, yellow iron oxide, and capsule imprint ink.

ULTRESA 20,700 USP units of lipase; 41,400 USP units of protease; 41,400 USP units of amylase contains gelatin, titanium dioxide, black iron oxide, and capsule imprint ink.

ULTRESA 23,000 USP units of lipase; 46,000 USP units of protease; 46,000 USP units of amylase contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and capsule imprint ink.

The black radial imprinting on the capsule contains Iron oxide black as colorant, shellac, and propylene glycol. It may also contain strong ammonia solution, and potassium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:
Aptalis Pharma US, Inc
100 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Manufactured by:
Aptalis Pharma S.r.L.
Pessano, Italy 20060

Revised: Month/Year

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