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ULTRASE®/ULTRASE® MT (PANCRELIPASE) CAPSULES VIOKASE® (PANCRELIPASE, USP)

Safe and Effective as Pancreatic Enzyme Supplementation

In July 2007, **Axcan Pharma Inc. (Mont-Saint-Hilaire, Quebec),** submitted a New Drug Application (NDA) for its pancreatic enzyme replacement therapy drug ULTRASE.® As ULTRASE® does not require overfill, it will be filled at 100 percent of label claim. The Food and Drug Administration (FDA) has already granted ULTRASE® a Fast Track designation. The formulation of ULTRASE® for which the NDA was submitted has been designed to meet the new guidelines set forth by the FDA for pancreatic enzyme replacement products. Initial guidelines were announced in April 2004, at which time the FDA declared that all exocrine pancreatic insufficiency drug products were to be considered new products and that manufacturers who wanted to continue marketing such drug products were to submit a NDA and receive approval by April 28, 2008. In April 2006, final guidelines were made available. The applications are required to contain results of studies proving the safety and efficacy of the products.

Pancreatic extract drug products such as ULTRASE® are indicated as replacement therapy to treat Cystic Fibrosis (CF) as well as other conditions associated with exocrine pancreatic insufficiency, including chronic pancreatitis, pancreatic tumors, or pancreatectomy. Approximately 90% of patients with CF require supplementation with pancreatic enzyme products to treat pancreatic insufficiency,[1] which leads to malabsorption.[2] The CF patient relies on the consistency of a known dose of a specific pancreatic enzyme product. Variation that can occur between capsules, batches of similar product or brands can provide inconsistent absorption of essential nutrients in persons with CF.[3] It is important that dosing be individualized for the needs of each specific patient. Data supporting these claims were provided as the basis of the FDA's requirement for new approval of pancreatic enzyme drug products. These data included in vitro and in vivo studies demonstrating variations in bioactivity among pancreatic extract drug products that were labeled as containing the same enzyme activity.[4]

Pancreatic extract products marketed in the U.S. today include those marketed prior to the passage of the Federal Food, Drug and Cosmetic Act of 1938 and had been exempt from FDA regulation.[5] There are several companies that have manufactured and distributed microencapsulated pancreatic enzyme products without FDA approval.[3] Further, according to the FDA's Office of Generic Drugs, none of the companies making generic enzymes received FDA approval to sell those products.[3] It is no surprise that the Cystic Fibrosis Foundation has received several reports of treatment failures after pharmacy substitutions with generic products instead of brand name products.[4] "There are some companies marketing what they are calling generics," notes Michael W. Konstan, MD, Professor of Pediatrics, CF Specialist, Rainbow Babies and Children's Hospital (Cleveland, OH), "even though the FDA doesn't recognize them as generics. These companies are saying that their enzymes are equivalent to the branded enzymes, but the formulation or ratio of the various enzymes could be very different. For instance, some are enteric coated and some are not, which then affects their bioavailability." Dr. Konstan continues, "We also know that two patients may respond differently to the same enzyme. Therefore, you can't simply substitute one enzyme for another, even among the branded ones."

Phillip P. Toskes, MD, a Gastroenterologist who specializes in pancreatic diseases at the University of Florida, College of Medicine (Gainesville, FL), explains that pancreatic enzymes are not used appropriately or in the right dosage in practice quite commonly. "There is an art to this and there is a rationale why a certain enzyme should be used in a certain patient." Dr. Toskes explains: "Clinicians have to understand what it is they are trying to treat in the patient and which enzyme should be used for a given situation. For example, managing abdominal pain associated with chronic pancreatitis presents a challenge. A study done in our center compared Pancrease,® Creon® and VIOKASE® in regard to delivery of proteases into the proximal small intestine—the site of the feedback control mechanism for pancreatic exocrine secretion. VIOKASE® delivered appreciable amounts of protease, but Pancrease® and Creon® demonstrated little delivery of the enzymes in the

upper intestine because they didn't open up their enteric coat until they were beyond that part of the intestine. In this situation, you wouldn't use an enteric coated enzyme, but would use VIOKASE.® On the other hand, ULTRASE® is an excellent enzyme formulation to use for patients with diarrhea and steatorrhea. Thus, it's not that 'one-size fits all.'"

The Company's NDA is based on a clinical study program that included Phase III, multi-center, double-blinded, placebo-controlled crossover trials. In the initial two Phase III studies previously disclosed, patients with pancreatic insufficiency associated with CF received ULTRASE® MT12, ULTRASE® MT20, or placebo. The results of this study showed excellent effects on fat absorption with minimal adverse events. Baseline fat absorption levels without enzyme supplementation were 46.7% and 58.7% respectively in the ULTRASE® MT12 and ULTRASE® MT20 study groups. Mean fat absorption increased to 79.4% and 87.3% respectively for the ULTRASE® MT12 and ULTRASE® MT20 study groups.[2]

The Company also recently completed an additional Phase III clinical study, also included in the NDA, with the currently marketed ULTRASE® MT20 formulation. This multi-center, randomized, double-blind, crossover study was designed to compare the efficacy and safety of ULTRASE® MT20 to placebo in the correction of steatorrhea in patients with CF. Results of this study also demonstrated excellent effects on the primary efficacy parameter, i.e. fat absorption, with minimal adverse events.

Dr. Konstan, Lead Investigator for the study, which was conducted with the assistance of the Cystic Fibrosis Therapeutics Development Network, stated that the Axcan Pharma studies show very good efficacy. "They were able to substantiate their claim that ULTRASE® reduces steatorrhea using objective numbers from a calculation of a coefficient of fat absorption." The Company plans to have Dr. Konstan disclose detailed results of the study in the coming months, in the appropriate scientific forum.

ULTRASE® MT (pancrelipase) Capsules are orally administered capsules containing enteric-coated microspheres or minitablets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. ULTRASE® and ULTRASE® MT are indicated for patients with partial or complete exocrine pancreatic insufficiency caused by: cystic fibrosis, chronic pancreatitis, pancreatectomy, and Shwachman's Syndrome. Pancrelipase capsules are also effective in controlling steatorrhea caused by exocrine pancreatic insufficiency.

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. 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.

Colonic strictures have been reported in cystic fibrosis patients treated with both high- and lower-strength enzyme supplements. 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.

VIOKASE® (pancrelipase, USP), another pancreatic enzyme supplement available from Axcan Pharma, is of porcine origin and contains standardized lipase, protease, and amylase as well as other pancreatic enzymes. It is available in tablet and powder dosage forms for oral administration and is not enteric coated. VIOKASE® is indicated in the treatment of exocrine pancreatic insufficiency as associated with but not limited to cystic fibrosis, chronic pancreatitis, pancreatectomy, or obstruction of the pancreas ducts.

Adverse Effects: the dust or finely powdered pancreatic enzyme concentrate is irritating to the nasal mucosa and the respiratory tract. It has been documented that inhalation of the airborne powder can precipitate an asthma attack. The literature also contains several references to asthma due to inhalation in patients sensitized to pancreatic enzyme concentrates. Extremely high doses of exogenous pancreatic enzymes have been associated with hyperuricosuria and hyperuricemia. Overdosage of pancreatic enzyme concentrate may cause diarrhea or transient intestinal upset.

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To Learn More

For more information about ULTRASE,® VIOKASE,® or other Axcan Pharma® products, please call 1 (800)-950-8085; or visit the company's Web site at www.axcan.com.

References:

1. FitzSimmons, SC, The changing epidemiology of cystic fibrosis. J Pediatr. 1993 Jan;122(1):1-9.
2. Konstan, MW, et al. ULTRASE MT12 and ULTRASE MT20 in the treatment of exocrine pancreatic insufficiency in cystic fibrosis: safety and efficacy. Aliment Pharmacol Ther 2004; 20: 1365–1371.
3. Carroll, RC, et al., Pancreatic Enzyme Supplementation in Cystic Fibrosis Patients. US Pharmacists. Article can be found at http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/Pancreatic.htm&pub_id=8&article_id=824
4. FDA, Exocrine Pancreatic Insufficiency Drug Products; Draft Guidance for Submitting New Drug Applications; Notices, 2004; Vol. 69, No. 82; 23410-23414.
5. Hendeles L, Hochhaus G, Kazerounian S. Generic and alternative brand-name pharmaceutical equivalents: select with caution. Am J Hosp Pharm 1993;50:323-9.