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ULTRASE®/ULTRASE® MT (PANCRELIPASE) CAPSULES

Safe and Effective Pancreatic Enzyme Supplementation

In July 2007 **Axcan Pharma Inc.** submitted a New Drug Application (NDA) for its pancreatic enzyme replacement therapy drug **ULTRASE® (pancrelipase) Capsules** and anticipates approval in 2008. This NDA was submitted in response to the new guidelines issued by the Food and Drug Administration (FDA) (drafted in April 2004 and finalized in April 2006), declaring 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 an NDA. These applications were required to include studies proving the safety and efficacy of such products. The FDA has already granted ULTRASE Fast Track designation and upon filing received priority review status.

ULTRASE Capsules are orally administered capsules containing enteric-coated microspheres or minitablets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. Pancreatic extract drug products such as ULTRASE are indicated as replacement therapy to treat conditions associated with exocrine pancreatic insufficiency, including chronic pancreatitis, pancreatic tumors, pancreatectomy, Cystic Fibrosis (CF) and Schwachman's Syndrome. Dosing of these enzymes must be individualized to meet the needs of each patient. In order for patients to receive an appropriate dosage of the prescribed pancreatic enzyme they must rely upon the consistency of a known dose of a specific pancreatic enzyme; however, variations between capsules or batches of similar products or brands have been known to lead to an inconsistent absorption of essential nutrients in persons with pancreatic insufficiency. The FDA's requirement for companies to submit NDAs was based upon *in vitro* and *in vivo* studies demonstrating variations in bioactivity among pancreatic extract drug products that were labeled as containing the same enzyme activity. As ULTRASE does not require overfill, it will be filled at 100 percent of label claim.

James H. Grendell, MD, Chief of Gastroenterology at Winthrop University Hospital and Professor of Medicine at State University of New York at Stony Brook School of Medicine (Stony Brook, NY), notes that "Ultrase is an excellent enteric coated pancreatic enzyme supplement that we ought to be using to treat pancreatic insufficiency. There are a few other products made by established manufacturers that meet the same high standards as ULTRASE. These products have undergone appropriate testing to demonstrate that they work effectively in patients. This is particularly important with pancreatic enzymes because they are biologically derived products with a mixture of enzymes." Dr. Grendell continues, "There are, however, a number of companies with so-called 'generic' products on the market that have not undergone rigorous clinical testing. This clinical testing is critical." Dr. Grendell points that "often times a third-party payor will impose one of these off-brand products on a patient. This type of substitution is simply not appropriate because there are no true generics for pancreatic enzyme supplements." Dr. Grendell notes that this is often done without the physician's knowledge—and sometimes without the patient's knowledge. "This is a big problem when treating patients with pancreatic insufficiency. The formulation or ratio of the various enzymes could be quite different. The good news is that this is all going to end now with the FDA's new rules."

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>
> **James H. Grendell, MD**

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

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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.[1]

Ultrase and Ultrase MT are trademarks of Axcan Pharma US, Inc. Ultrase and Ultrase MT are manufactured by Eurand International, Milan, Italy, using its DIFFUCAPS® or EURAND MINITABS® technology for Axcan Pharma US, Inc.

Ultrase and Ultrase MT Safety Overview

Ultrase and 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: chronic pancreatitis, pancreatic tumors, pancreatectomy, cystic fibrosis, 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.

PYLERA™: The Only 3-in-1 Capsule

A First-Line Option to Eradicate H. pylori

In September 2006 the FDA approved **Pylera,™** a patented 3-in-1 capsule for the eradication of *Helicobacter pylori* (*H. pylori)* infection. Pylera, developed by **Axcan Pharma Inc. (Mont Saint-Hilaire, Quebec)**, combines the strength of three ingredients in one capsule: bismuth subcitrate potassium (140 mg), metronidazole (125 mg) and tetracycline hydrochloride (125 mg). With a separate prescription for omeprazole, Pylera re-invents the quadruple-based or OBMT (omeprazole or H_2 blocker plus a combination of bismuth, metronidazole, and tetracycline HCL) therapy regimen. Pylera is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within 5 years). Pylera, compared to other available quadruple or OBMT therapies, provides a shorter duration of therapy (10 days vs. 14 days) and a more simplified dosing regimen (reduced pill burden 140 vs. 252). Clinical studies have confirmed that Pylera can be used in a wide range of patients and is not only as safe and effective as other therapies for the eradication of *H. pylori*, but is generally as well-tolerated.[2]

The August 2007 issue of *The American Journal of Gastroenterology* published the updated guideline of The American College of Gastroenterology (ACG) regarding management of *H. pylori.* Armed with new information, the ACG set forth its latest recommendation regarding primary therapies in the United States for *H. pylori* eradication.[2] This recommendation includes the use of a bismuth-based quadruple therapy similar to that used in Plyera, and states that the combination of a PPI (or H2RA), bismuth subcitrate potassium, metronidazole, and tetracycline, taken for 10–14 days is one of two preferred first-line treatments of *H. pylori*.[2*] Studies have shown this course of therapy to be one of the treatments with the greatest likelihood of eradicating *H. pylori* infection.[3]

Careful consideration must be given to antibiotic resistance when selecting from the various treatment regimens.[2] Recent studies have suggested that eradication rates of *H. plylori* with the widely used first-line OAC triple therapy (20 mg of omeprazole, 1 g of amoxicillin and 500 mg of clarithromycin, all given twice a day), have decreased to 70 to 85 percent, which can be attributed to increasing clarithromycin resistance.[2] A recent multicenter U.S. study collected data from 1993 to 1999 and reported antibiotic resistance rates for *H. pylori* strains, of 10% for clarithromycin, and 1.4% for amoxicillin.[4] Additional data collected from 1998 to 2002 showed resistance rates of 13% for clarithromycin and 0.9% for amoxicillin.[5] While a direct comparison of these two data groups is difficult, it appears that while clarithromycin resistance has increased, resistance rates for amoxicillin has remained somewhat steady.[2] Additional studies have shown quite clearly that clarithromycin resistance is associated with a high rate of treatment failure when clarithromycin-containing regimens are employed.[6,7,8]

H. pylori continues to be a widespread chronic infection infecting people worldwide,[2] although the incidence of infection appears to be on the decline in many parts of the world. It has been estimated that approximately 30 to 40 percent of the US adult population is infected.[9] Current research indicates that *H. pylori* may be an important factor linked to the development of a wide spectrum of diseases including peptic ulcer, gastritis, dyspepsia, gastric cancer, gastric MALT lymphoma and dyspeptic symptoms.[2]

**Recommended primary therapies for* H. pylori *infection also include: a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days.*

To Learn More

For more information about Pylera,™ ULTRASE® or other Axcan Pharma™ products, please call 1-800-950-8085; or visit the Web site at www.axcan.com.

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