

Why Pancreatic Enzyme Preparations Are Not Interchangeable in the Treatment of Pancreatic Insufficiency of Cystic Fibrosis

Cystic fibrosis (CF) is a progressive fatal genetic disease affecting about 30,000 Americans. While the major cause of morbidity and eventual death among individuals with CF is from pulmonary disease, ninety percent of this population also have pancreatic insufficiency. Malabsorption of fat and protein leads to wasting and growth retardation, which at one time was a leading cause of death during the first few years of life. Pancreatic enzyme replacement therapy facilitates improved nutrition by decreasing the malabsorption of fat and protein and permitting weight gain and growth at a more normal rate. Addressing the problem of malabsorption and aggressively treating the lung disease associated with CF have resulted in the extension of the median survival of CF patients from 14 years in 1970 to over 30 years in 2000.

Status of Pancreatic Enzyme Products

Since pancreatic enzyme preparations, like a number of other medications on the United States market, antedate regulations by the Food and Drug Administration (FDA), they never underwent review by the FDA as new drugs. FDA allows these medications to remain on the market as “grandfathered” products in the absence of specific concerns about them. The agency has begun a review of the “grandfathered” pancreatic enzyme products. In 1995, it declared that over-the-counter (OTC) pancreatic enzymes are not generally recognized as safe and effective and required that they be withdrawn from the market. At the same time, FDA signaled its intention to require new drug applications (NDAs) for the pancreatic enzyme products that are marketed on a prescription basis. However, due to lifesaving impact of these products for people with CF, FDA has allowed the continued use of these products while it is identifying requirements for NDAs.

Effectiveness of Pancreatic Enzyme Products

Pancreatic enzymes were only modestly effective in the form they were initially marketed. The enzymes in older formulations were largely inactivated by gastric acidity, with less than 10 percent of the lipolytic and 20 percent of the tryptic activity reaching the ligament of Treitz in the duodenum.^{1,2} The introduction of pH dependent enteric coatings on enzyme preparations just over 20 years ago has improved the effectiveness of pancreatic enzyme products. Use of a pH dependent polymer coating that resists dissolution of the preparation in the stomach but releases the enzyme in the more alkaline duodenum substantially increases fat absorption with utilization of fewer capsules than required with uncoated pancreatic enzymes.³

¹Graham DY. Enzyme replacement therapy of exocrine pancreatic insufficiency in man. Relations between *in vitro* enzyme activities and *in vivo* potency in commercial pancreatic extracts. N Eng. J Med 1977;296:1314-7.

²DiMugno EP, Malagelada JR, Go VLW, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency. Comparison of two dosage schedules. N Eng J Med 1977;296:1318-22.

³Nassif EG, Younoszai MK, Weinberger MM, Nassif EM. Comparative effects of antacids, enteric coating, and bile salts on the efficacy of oral pancreatic enzyme therapy in cystic fibrosis. J Pediatr 1981;98:320-3.



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Since the introduction of Pancrease, the first pancreatic enzyme preparation with a pH dependent enteric coating, two other major brands have been marketed, Creon and Ultrase. While the major brands have been associated with generally acceptable clinical utility with at least some clinical documentation from controlled clinical trials,^{3,4} differences among products in release characteristics have been reported.^{5,6} Differences in clinical effect have been reported to be associated with those variations in release characteristics.⁷ In an in-vitro study of all of the microencapsulated formulations available in 1994 in the US, Kraisinger and colleagues found that various products released enzymes at different pHs and differed in their ability to prevent inactivation by acid as would occur in the stomach.⁸ Potentially important clinical differences in effectiveness for improving absorption of fat and protein have been reported even for major brand name pancreatic enzyme preparations.⁹ Gross clinical treatment failure has been reported for at least one generic formulation.¹⁰

Substitution of Pancreatic Enzymes

When FDA published its findings regarding pancreatic enzymes, including a recommendation that OTC products be removed from the market, it raised concerns about all pancreatic enzyme products, both OTC and prescription. In its 1995 rule, the FDA stated, "[Some of these] products have shown significant differences in bioavailability. The agency finds that these differences raise a potential for serious risk to patients using these products."¹¹ Therefore, physicians who provide care to individuals with CF must make decisions regarding the most appropriate pancreatic enzymes for their patients based on the available data and their clinical experience.

⁴Stern RC, Eisenberg JD, Wagener JS, Ahrens R, Rock M, doPico G, Orenstein DM. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. *Am J Gastroenterol* 2000;95:1932-8.

⁵Littlewood JM, Kelleher J, Walters MP, Johnson AW. *In vivo* and *in vitro* studies of microsphere pancreatic supplements. *J Pediatr Gastroenterol Nutr* 1988;7, Suppl 1:S22-9.

⁶Walters MP, Littlewood JM. Pancreatin preparations used in the treatment of cystic fibrosis – lipase content and *in vitro* release. *Aliment Pharmacol Ther* 1996;10:433-40.

⁷Elliot RB, Excobar LC, Lees HR, Akroyd RM, Reilly HC. A comparison of two pancreatin microsphere preparations in cystic fibrosis. *N Z Med J* 1992;105:107-8.

⁸Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and *in vitro* performance of microencapsulated formulations. *J Clin Pharmacol* 1994;34:158-66.

⁹Beverley DW, Kelleher J, MacDonald A, Littlewood JM, Robinson T, Walters MP. Comparison of four pancreatic extracts in cystic fibrosis. *Arch Dis Child* 1987;62:564-8.

¹⁰Hendeles L, Dorf A, Stecenko A, Weinberger M. Treatment failure after substitution of generic pancrelipase capsules. Correlation with *in vitro* lipase activity. *JAMA* 1990;263:2459-61.

¹¹FDA. Exocrine Pancreatic Insufficiency Drug Products for Over-The-Counter Human Use. *Fed Register* 1995;60:20164.



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As a general matter, FDA has developed standards for generic drug substitution of products which are included in the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). Only those products indicated as “Equivalent” should be considered for generic substitution. However, these standards are not applicable to pancreatic enzyme products, because these are unapproved, “grandfathered” drugs that are not listed in the Orange Book. Also, currently available products were not developed as “generic” versions of a previously approved drug that is referenced in the Orange Book. Each drug was independently developed by a different manufacturer without direct reference to approval data regarding quality, safety, and efficacy from any manufacturer.

Decisions about the use of these medications, which are essential to the health and well-being of patients with CF, must be made by physicians on the basis of the available clinical data and the individual’s response to currently marketed products. Substituting one preparation for another must be done only with medical supervision and assessment, ideally using products for which the better quantum of clinical data is available. Substitution or “switchability” of pancreatic enzymes based on a lesser standard is therefore a deviation from good clinical and pharmacy practice. A third party payer insisting on “generic substitution” of pancreatic enzymes for a patient with CF misunderstands the current marketing paradigm under which these products operate and erroneously concludes these products are equivalent. This inappropriate substitution of pancreatic enzyme products endangers the health and well-being of patients with CF by contributing to potential medical complications. This is neither in the patient’s nor the insurer’s best interest.

For more information about cystic fibrosis and pancreatic enzymes, please contact:

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