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Pancreatic Enzyme Products Update
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Introduction: Pancreatic enzyme products (PEPs) contain pancrelipase, a mixture of porcine-derived enzymes including lipase, amylase, and protease, as an active ingredient.[1,2] Historically, these medications which were available as enteric-coated and nonenteric-coated formulations were developed decades ago as digestive aids to improve nutrient absorption in patients with pancreatic insufficiency. The nonenteric-coated PEPs could be administered to enterally-fed patients and were also used in combination with sodium bicarbonate to unclog feeding tube obstructions.[3-5] Currently, nonenteric-coated along with certain previously marketed enteric-coated PEPs are not being manufactured. Recent action by the Food and Drug Administration (FDA) has led to product availability issues and the need to provide patients with therapeutic alternatives for their usual PEP therapy.

FDA Action Regarding PEPs: The majority of PEP products were initially marketed prior to the enactment of the Federal Food, Drug and Cosmetic Act of 1938 which required all new drugs to undergo a new drug application (NDA) process for approval.[1,2] Several years ago, the FDA became aware that some commercially available PEPs did not contain the exact amounts of therapeutic enzymes listed in their product labeling. In many cases, there was significant ingredient variability. Products containing lower amounts of pancreatic enzymes produced suboptimal clinical effects, while those containing higher amounts were associated with an increased risk of adverse events. Furthermore, it was discovered that in order to preserve product shelf-life, some PEP manufacturers intentionally overfilled capsules to account for future enzyme degradation. Ingestion of these overfilled PEPs increased the risk of fibrosing colonopathy, a complication involving submucosal intestinal fibrosis related to high-dose pancreatic enzyme therapy.[1,6] In response to these concerns, the FDA announced in July 1991 that manufacturers would need to submit an NDA for current and new PEPs.[1,2,7] However it was not until 2004 that the FDA actually issued a mandate requiring PEP manufacturers to apply for FDA approval through the NDA process. In 2006, the FDA issued a guidance specifying certain manufacturing requirements which would need to be followed to ensure that a PEP would meet FDA quality standards. Afterwards, the FDA extended the approval deadline to April 28, 2010, to allow time for manufacturers to overcome any reformulating issues. After that deadline, the production of unapproved PEPs was not permitted. However, pharmacists were allowed to dispense unapproved PEPs until their supply was depleted.

Selection of an FDA-Approved PEP: Patients who are receiving unapproved PEPs should be switched to an FDA-approved formulation. The FDA-approved PEPs which are currently commercially available include Creon®, Pancreaze®, Zenpep®, and Pancrelipase™, an authorized generic of Zenpep®; these products are all enteric-coated formulations.[2,7] A new prescription must be written since current FDA-approved PEPs are not AB-rated (i.e., deemed to be therapeutically equivalent) to each other and to unapproved PEPs. One exception is that X-Gen Pharmaceutical's authorized generic Pancrelipase™ may be interchanged for Zenpep® since these products are identical.[8,9] All FDA-approved PEPs are marketed with a Risk Evaluation and Mitigation Strategy (REMS) requiring retail pharmacies to distribute Medication Guides which explain to patients the risks versus the benefits of therapy. The FDA-approved PEPs are labeled with their actual enzyme content. In contrast, the product labeling of non-FDA-approved PEPs may underestimate their actual enzyme content which may make it difficult to determine an accurate dose conversion to an FDA-approved product.[2] The enzyme components listed in the product labeling of various FDA-approved and unapproved PEPs are included in a table on this website: http://www.ashp.org/DocLibrary/Policy/DrugShortages/DS-Pancreatic-Enzyme-1-031110.aspx. There are no formal recommendations for switching patients to PEPs made by different manufacturers. When a clinician writes a prescription for a new PEP, a product with similar amounts of lipase enzyme should be selected initially and the dose should be adjusted based on the patient's response. Dosages should be individualized based on the patient's clinical symptoms (e.g., severity of steatorrhea) and the fat content of the diet.[8-11] It may take 1 to 2 weeks to adjust the dose of the new PEP. The preferred PEP on the Cleveland Clinic Formulary is Creon® delayed-release, enteric-coated microspheres. Cleveland Clinic Formulary Guidelines for dose conversion based on the amount of lipase ordered are shown in Table 1. Viokase®, a nonenteric-coated PEP, is also on the Cleveland Clinic Formulary; however, it is currently not commercially available pending FDA approval.

Therapeutic Use of PEPs Via Feeding Tubes: Enterally-fed patients with pancreatic insufficiency may require administration of pancreatic enzymes through a feeding tube.[12] Medications administered through feeding tubes must be in liquid form. Certain tablet formulations can be crushed to a fine powder and diluted with water to form a mixture which may be given through a large bore feeding tube; the contents of some capsules may also be prepared and given in a similar manner. In general, it is recommended that enteric-coated medications should not be given through feeding tubes, since crushing these products may reduce their therapeutic efficacy and/or increase their potential for adverse effects. Furthermore, enteric-coated formulations do not crush well and often break into small particles which could clog a feeding tube. This is problematic for enterally-fed patients with pancreatic insufficiency since the current FDA-approved PEPs are all enteric-coated. According to the FDA, the manufacturers of the FDA-approved PEPs are conducting studies to evaluate the feasibility of administering their respective products through a feeding tube. Eurand Pharmaceutical has developed two procedures for administering Zenpep® through a feeding tube which are currently being reviewed by the FDA.[13,14] These procedures are mainly suitable for outpatient situations. One method involves administering a mixture containing the contents of one Zenpep® 5000 unit capsule with regular applesauce through a large bore (14 French or greater) gastrostomy tube; in this case, the enteric-coated beads should not be crushed. For patients with smaller gauge gastrostomy, nasogastric, or jejunal tubes, the manufacturer recommends placing the contents Zenpep® capsules in a household blender along with the prescribed enteral formula. The enteric-coated beads of Zenpep® should be blended with the formula until no bead fragments are noticeable; afterwards, the preparation should be given immediately. Any of the Zenpep® strengths (5000-, 10,000-,15,000- and 20,000 units) may be utilized for this purpose along with a commercial nonelemental formula. Currently, there are no available data concerning enteral administration of Pancreaze® or Creon®. Since Creon® is the Cleveland Clinic's Formulary PEP, inpatients with feeding tubes who have pancreatic insufficiency may receive an elemental enteral formula which does not require significant pancreatic enzyme break-down.

PEPs and Feeding Tube Occlusions: Enteral feeding tube occlusions may occur due to high protein or viscous feeding formulas, slow administration with development of sediments, improper drug administration, inadequate flushing techniques, small lumen opening, or a combination of these factors.[15] Generally, periodic tube flushes of 15 to 30 mL of tepid water is the preferred method to avoid tube obstruction. In cases where the obstruction cannot be prevented, instilling a solution composed of one crushed tablet of Viokase® and one crushed tablet of sodium bicarbonate in tepid water has been shown to be effective in unclogging feeding tubes.[3] However Viokase® is not currently on the market and commercially available enteric-coated PEPs are not suitable for unclogging feeding tubes. Therefore, alternative methods to break-up feeding tube obstructions outlined in the Cleveland Clinic Nursing Protocols entitled "Nasogastric (NG)/Orogastric (OG) Tubes: Feeding or Decompression" and "Feeding Tubes: Care of the Patient with Gastric or Jejunal Tubes" should be utilized.[4,5] These protocols are located on this website: http://intranet.ccf.org/nursing/guidelines/clinPractice.asp. The first recommended method to unclog an obstructed feeding tube is to instill 50 mL of tepid water from a 60 mL syringe into the feeding tube. The syringe should be gently pulled back and forth applying mild pressure to help dislodge the clog. This may be repeated multiple times. During this process, it is recommended not to pull back on the feeding tube itself. Meat tenderizer, cranberry juice or ginger ale should not be used to unclog a feeding tube; these products have either been found

to be ineffective or may actually exacerbate the clog. Another alternative is Clog Zapper™, which contains a patented food-grade powder designed to break-up formula feeding tube clogs.[16] It is available from the Cleveland Clinic Main Storeroom (item #155280) as a kit which includes a 10 mL syringe with declogging powder, 6 mL syringe, 12 inch applicator, and two 4 inch by 4 inch gauze pads. The instructions for use of Clog Zapper™ are included in Table 2.

Conclusion: Pancreatic enzyme products are used as digestive aids in patients with pancreatic insufficiency. These products were marketed long before the FDA's NDA requirements were enacted. In recent years, the FDA discovered that PEPs lacked uniform content which could affect both product safety and efficacy. As a result, the FDA required manufacturers to submit an NDA for all new and existing PEPs. Pancreatic enzyme products which did not receive FDA approval by the end of April 2010 will no longer be manufactured. Only enteric-coated PEPs including Zenpep®, Pancrelipase™ (an authorized generic version of Zenpep®), Pancreaze® and Creon® are FDA-approved and currently commercially available. In most cases, supplies of unapproved PEPs have been exhausted requiring clinicians to write prescriptions for FDA-approved PEP brands. An FDA-approved PEP with a similar lipase content as the patient's previously prescribed unapproved product should be selected and the patient's dose should be adjusted per clinical response. Since nonenteric-coated Viokase® tablets are still not available, elemental enteral formulas can be given to patients with pancreatic insufficiency who require tube feedings. Furthermore, Clog Zapper™ can be used in lieu of Viokase® and bicarbonate solution to break up feeding tube clogs that cannot be removed by irrigation with water.

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Table 1. Cleveland Clinic Dose Conversions for Enteric-Coated Pancreatic Enzymes*

Orders for the Following Lipase Unit Range:	Will be Automatically Therapeutically Interchanged to:
4000-8000 lipase units	Creon® 6000 lipase units
10,000-16,000 lipase units	Creon® 12,000 lipase units
18,000-24,000 lipase units	Creon® 24,000 lipase units

*Note: Creon® 5, 10, and 20 products labeled as containing 5000-, 10,000-, and 20,000-units of lipase, respectively, are currently being phased off the market being replaced with corresponding FDA-approved Creon® products containing 6000-, 12,000- and 24,000–units of lipase. Although the labeled amounts of lipase are higher in the FDA-approved products, their activity is considered similar to their respective predecessors since the original labeling did not take overfill into account. The FDA has mandated that current labeling must list the actual amount of lipase contained in each capsule.

Table 2. Clog Zapper™ Instructions for Use in Nasogastric and Jejunosteomy Tubes [16]*†

1. Turn feeding pump OFF and close roller clamp on administration set.
2. Insert Clog Zapper™ applicator tubing into feeding tube. Note: It may not be possible to place the applicator all the way into the feeding tube, the distal end of the applicator may be pressing against the clog. If this is the case, take out the applicator and trim the applicator tubing to the appropriate length. Do not try to break up the clog with the distal end of the applicator.
3. Fill the Clog Zapper™ syringe to 10 mL mark with water.
4. Shake syringe to remove lumps.
5. Gently fill tube with recommended dosage of 2-5 mL of Clog Zapper™solution.
6. Remove applicator from tube. Plug the tube. Keep applicator and syringe together with patient if procedure must be repeated.
7. Keep solution in tubing for 60 minutes.
8. Fill oral syringe with 6 mL of water.
9. Flush tubing with 6 mL of water.
10. If tubing cannot be flushed, repeat steps #4-9. Check with physician to determine how many times the procedure needs to be repeated.
11. After tube clears, resume feeding.

*Manufacturer recommends use of protective eyewear since Clog Zapper™ can cause irritation if it gets in the eyes.
†Once reconstituted Clog Zapper™ may be kept under refrigeration for 24 hours.

Formulary Update

The CCHS Medical Staff P&T Committee met in November 2010, and the CC Local P&T Committee met in December 2010, the following decisions were made:

Additions:

1. **Hexaminolevulinate (Cysview®):** It is an optical imaging agent for the use in cystoscopic detection of non-muscle invasive papillary cancer of the bladder in patients known or suspected to have lesion(s) on the basis of prior cystoscopy. Its use is **restricted** to the outpatient setting only. This drug will be used by the Glickman Urological Institute.
2. **Nelarabine (Arranon®):** It is FDA-approved for the treatment of T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Its use is **restricted** to the Department of Hematology and Oncology.
3. **Dabigatran (Pradaxa®):** It is an FDA-approved oral direct thrombin inhibitor for the prevention of stroke in patients with non-valvular atrial fibrillation. The dose of dabigatran is 150 mg twice a day. The capsule must be swallowed whole, as breaking or opening the capsules significantly increases the exposure to dabigatran and may increase the risk of adverse events. Appropriate renal dose adjustments are needed and renal function needs to be monitored. If a patient's creatinine clearance is 15 to 30 mL/min, the dose should be decreased to 75 mg twice a day.
4. **Nebivolol (Bystolic®):** It is an FDA-approved $beta_1$-selective beta-blocker that also increases nitric oxide and thereby induces peripheral vasodilatation. There are no clinical advantages to other beta-blockers. Therefore, its use is **restricted** for continuation of therapy from home only (i.e., no initiation of therapy in the hospital).
5. **Testosterone pellets (Testopel®):** This is a different dosage form of testosterone. The number of pellets implanted depends on the minimal daily requirements of testosterone propionate. Its use is **restricted** to the Departments of Urology and Endocrinology for outpatient use only.

Not Added to Formulary:

1. **Tetrastarch (Voluven®):** It will not be ordered, stocked, or dispensed.
2. **Tolvaptan (Samsca®):** It will not be ordered, stocked, or dispensed.