

Drug Class Literature Scan: Pancreatic Enzymes

Date of Review: September 2017

Date of Last Review: March 2014

Literature Search: 03/01/14 – 05/12/17

Current Status of PDL Class:

See **Appendix 1**.

Conclusions:

- This class scan identified 1 systematic review from the Cochrane Collaboration, 1 new randomized controlled trial, 1 guideline update, and 1 new FDA safety alert.
- There is insufficient comparative evidence between pancreatic enzyme preparations. There is insufficient evidence to support a difference in safety or efficacy of pancreatic enzyme preparations among cystic fibrosis patients or subgroups.

Recommendations:

- No further review or research needed.
- Evaluate comparative costs in executive session.

Previous Conclusions:

- Overall, there is a lack of large, high-quality trial data and no comparative studies are available. All trials are relatively small ranging from 17 to 54 subjects. Therefore, there is insufficient evidence to determine any differences in efficacy or safety between the agents. Efficacy endpoints are highly dependent on nutritional consults and accurate food diaries of study subjects.
- The included trials favored the studied pancreatic enzyme replacement products (PEPs) in the primary efficacy endpoints, improved coefficient of fat absorption (CFA), either change in CFA or overall CFA, from baseline to the end of the study compared to placebo. Mean CFAs for treatment groups ranged from 82.8-88.6%, which was statistically significantly larger than the mean CFA found in patients treated with placebo (47.4-49.6%).
- In clinical trials, patient diets were developed by nutritionists and tightly controlled, thus, trials did not account for inter-patient variability in diet, which can potentially affect efficacy of PEP products.
- Adverse effects for all available products are similar to placebo, with the most common side effects being various measures of abdominal discomfort. Other side effects include headache, weight loss, rash, flatulence and nasopharyngitis.
- The most important factor to consider in the treatment of EPI is administering the appropriate amount of lipase units to each individual patient based on diet.

Previous Recommendations:

- Due to no apparent differences in efficacy or safety, continue to recommend inclusion of at least one agent in this class in accordance with FDA recommendations and administration concerns.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:*Cochrane: Pancreatic Enzyme Replacement Therapy for People with Cystic Fibrosis*

A 2016 Cochrane systematic review evaluated the efficacy and safety of various formulations of pancreatic enzyme replacement therapies (PERT) for cystic fibrosis patients.¹ Thirteen studies included children and adults of different age groups (n=512).¹ Eight of the trials involved children ages 1-17 years, four trials studied adults ages 21-24 years, and one study included ages 12 and older.¹ All studies were of 4 weeks duration. Seven studies compared enteric coated microspheres (ECM) with other enteric-coated preparations, four compared ECM versus another ECM, and two compared various doses of PERT.¹ Primary outcomes assessed were changes in weight, height, and body mass index (BMI).¹ Study quality was mixed as all 13 trials lacked details of randomization and allocation concealment methods, 6 of the 13 studies gave no details of blinding methods, and several studies had a high risk of attrition and reporting bias due to incomplete outcome data and selective reporting.¹ Due to heterogeneous trial data, small sample sizes, and unclear to high risk of bias in a majority of the trials, the evidence was insufficient to quantify treatment effect size of the different pancreatic enzyme formulations on the nutritional status of cystic fibrosis patients.¹

New Guidelines:*Cystic Fibrosis Foundation*

The Cystic Fibrosis Foundation published a clinical practice guideline to address nutritional care of preschool children ages 2 to 5 years old with cystic fibrosis (CF).² The guideline committee consisted of 16 CF pediatric experts and parents; however, non-specialists or experts in methodology were not included on the guideline committee. Overall, there are very little data in children ages 2 to 5 years old and therefore the recommendations included in the guideline are based on expert opinion and are likely to change based on additional research. Consensus recommendations included in the guideline were based on extrapolation from other CF Foundation or general pediatrics guidelines due to the small pool of subjects and gaps in evidence. An 80% agreement threshold was decided a priori for recommendations. The consensus recommendations for children of preschool-aged children with CF and pancreatic insufficiency suggests PERT be

adjusted to a dose of no greater than 2500 lipase units per kilogram per meal with a maximum daily dose of 10,000 lipase units per kilogram. These recommendations are clearly consensus statements and are not systematically developed from a thorough evidence review and evaluation.

New Formulations:

No new formulations were identified.

New FDA Safety Alerts:

Updated Questions and Answers for Healthcare Professionals and the Public: Use an Approved Pancreatic Enzyme Product (PEP)

The FDA updated questions and answers directed to healthcare professionals and the public about the safe use of approved PEPs.³ The original text was posted on April 12, 2010 with the most recent version dated October 20, 2016.³ Each question addressed a particular area of product concern. The post included information on the most current PEP products available and their FDA-approved uses, as well as important details regarding safe administration, availability, and key points for patients and prescribers.³ Key points included:

1. Creon, Zenpep, Pancreaze, Viokace, and Pertzye are currently the only FDA-approved PEPs that are marketed in the United States.
2. PEPs are not interchangeable at the pharmacy. Patients currently taking an unapproved PEP will require a new prescription for Creon, Zenpep, Pancreaze, Viokace, or Pertzye.
3. When switching a patient to another PEP, consider starting with a similar amount of lipase enzyme, then adjust the dose based on the patient's response.
4. Recognize that the labeled contents of FDA-approved PEPs reflect the actual enzyme content of the product, whereas the labeled contents of unapproved PEPs underestimate the actual lipase content.
5. Recognize that it may take 1-2 weeks for a patient to adjust their dose of the new PEP. Individual patient response should be monitored when switching from an unapproved PEP to an approved one.

References:

1. Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2016. <http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD008227.pub3/abstract>.
2. Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. *Pediatrics*. 2016;137(4):e20151784. doi:10.1542/peds.2015-1784.
3. The Food and Drug Administration. CDER Postmarket Drug Safety Information for Patients and Providers - Updated Questions and Answers for Healthcare Professionals and the Public: Use an Approved Pancreatic Enzyme Product (PEP). <https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm204745.htm>. Accessed June 21, 2017.
4. Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. *Journal of Cystic Fibrosis*. 2016;15(5):675-680. doi:10.1016/j.jcf.2016.02.010.

Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL
CAPSULE DR	CREON	LIPASE/PROTEASE/AMYLASE	Y
CAPSULE DR	PANCREAZE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	PERTZYE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 12	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 18	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 20	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 6	LIPASE/PROTEASE/AMYLASE	N
TABLET	VIKACE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ZENPEP	LIPASE/PROTEASE/AMYLASE	N

Appendix 2: New Comparative Clinical Trials

A total of 9 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Taylor et al. ⁴ 2015 RCT, DB, Crossover, Noninferiority study, Multicenter	Group A: Zenpep [®] followed by Creon [®] Group B: Creon [®] followed by Zenpep [®] ; 28 days per treatment arm Dosing: patients began assigned treatment at a dose as close as possible to their established PEP treatment (maximum of 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day, not to exceed a dose of 10,000 lipase units/kg of body weight per day)	One clinical feature of CF and 2 disease causing mutations in genotype or sweat chloride concentration >60 mmol/L	CFA over 72 hours calculated from dietary fat intake and stools collected during the last 3 days (72 consecutive hours) of each treatment period	No difference: Noninferiority established; LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Creon, 85.3% [SE 1.1]; p = 0.297

Abbreviations: RCT = randomized clinical trial; DB = double blind; CF = cystic fibrosis; CFA = Coefficient of Fat Absorption; MD = mean difference; LS = least squares; SE = standard error

Appendix 3: Abstracts of Comparative Clinical Trials

Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. *Journal of Cystic Fibrosis*. 2016;15(5):675-680. doi:10.1016/j.jcf.2016.02.010.

Background:

Zenpep (APT-1008) is a pancreatic enzyme product for the treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF).

Methods:

Zenpep and Creon, both containing 25,000 lipase units, were compared in a randomized, double-blind, crossover, non-inferiority study for CF-associated EPI in patients aged ≥ 12 years. Patients on a standardized diet and stabilized treatment were randomized to two treatment sequences: Zenpep/Creon or Creon/Zenpep. The primary efficacy endpoint was the coefficient of fat absorption over 72 h (CFA-72 h).

Results:

96 patients (mean age 19.2 years, 60.4% males) were randomised with 83 completers of both sequences comprising the efficacy population. Zenpep demonstrated non-inferiority and equivalence to Creon in fat absorption (LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Creon, 85.3% [SE 1.1]; $p = 0.297$). Safety and tolerability were similar.

Conclusions:

Zenpep is comparable with Creon in efficacy and safety for the treatment of adolescents and adults with CF-associated EPI. (NCT01641393)

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 2 2017

1 Viokase.mp.4

2 Pertzye.mp. 2

3 Pancreaze.mp. 5

4 Zenpep.mp. 9

5 Creon.mp. 59

6 Ultresa.mp. 2

7 Pancrelipase/ or pancreaticlipase.mp. 207

8 lipase.mp. or Lipase/ 21068

9 protease.mp. 83937

10 amylase.mp. 11735

11 8 and 9 and 10 220

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 11 450

13 limit 12 to (humans and english and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews) and last 3 years) 9