Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: March 2014
PDL Classes: GI – Digestive Enzymes

Date of Last Review: November 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: CREON®, LIPASE/PROTEASE/AMYLASE
- Nonpreferred Agents: PANCREZE®, PERTZYE®, PANCRELIPASE®, ULTRESA®, VIOKASE®, ZENPEP®

Previous Conclusions and Recommendations:

- 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%).4,5
- 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.
- 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.

Conclusions and Recommendations:

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

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCT's) comparing PEP's to placebo or other products was conducted with limits for humans and English. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

None

Guidelines:
None

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 1):
A total of 43 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

A 51-week, open-label extension clinical trial in India assessed the efficacy and safety of pancreatin (Creon) 40000 in patients with pancreatic exocrine insufficiency due to chronic pancreatitis.[1] Compared to placebo, statistically significant improvements from baseline to end of the extension in mean coefficient of fat absorption, coefficient of nitrogen absorption, stool fat, stool nitrogen, and stool weight were observed. Significant improvements in both mean body weight and BMI were also observed. [1]

A 1 week, double-blind, randomized, placebo-controlled study compared Creon 25000 minimicrospheres to placebo in treating pancreatic exocrine insufficiency after pancreatic resection.[2] The primary efficacy measure was change in coefficient of fat absorption. The change in the Creon group increased and decreased in the placebo group, with a statistically significant treatment difference of 32.6% (95% CI 19.9-45.4; $p<0.001$). Stool frequency decreased by 0.9 stools/day in the Creon group and increased by 0.5 stools/day in the placebo group. Statistically significant improvements from baseline were also seen in body weight and body mass index. Adverse events occurred more in the treatment group than placebo (37.5% vs. 26.9%) and flatulence was the most common. There were no adverse events leading to discontinuations.

References:

1. Ramesh H, Reddy N, Bhatia S, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. *Pancreatology*. 2013;13(2):133–139. doi:10.1016/j.pan.2013.01.009.

2. Seiler CM, Izbicki J, Varga-Szabó L, et al. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. *Aliment Pharmacol Ther*. 2013;37(7):691–702. doi:10.1111/apt.12236.

Date: March 2014

Appendix 1: Abstracts of RCTs:

1. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013 Mar-Apr;13(2):133-9

BACKGROUND/OBJECTIVES:
To assess the efficacy and safety of pancreatin (pancrelipase) enteric-coated minimicrospheres (MMS) over a one-year period in patients with pancreatic exocrine insufficiency (PEI) due to chronic pancreatitis (CP).
METHODS:
This was a 51-week, open-label extension (OLE) of a one-week, multicenter, double-blind, randomized, placebo-controlled trial in India that enrolled patients ≥18 years of age with confirmed PEI due to CP. Patients received pancreatin (Creon(®) 40000 MMS™) at a dose of 80,000 Ph. Eur. lipase units with each of three main meals/day and 40,000 with each of up to three snacks/day.
RESULTS:
Of 61 patients entering the OLE, 48 completed treatment (nine were lost to follow up, two withdrew consent, one discontinued due to adverse event [acute exacerbation of CP], one protocol violation). There were significant improvements from baseline to end of OLE in mean ± SD coefficient of fat absorption (CFA: 22.7 ± 12.2%), coefficient of nitrogen absorption (CNA: 6.5 ± 7.9%), body weight (4.9 ± 4.9 kg), BMI (1.9 ± 1.9 kg/m(2)), and most nutritional laboratory parameters tested ($p \leq 0.001$). Mean daily stool frequency was reduced from 2.8 to 1.6 ($p < 0.001$). Improvements in clinical symptoms, clinical global impression of disease symptoms, and quality of life were also observed. Treatment-emergent adverse events (TEAEs) were observed in 64% of patients overall. Only 13% of patients experienced TEAEs judged treatment related.
CONCLUSIONS:
In patients with PEI due to CP, treatment with pancreatin for one year was associated with significant improvements in fat absorption, nitrogen absorption, and nutritional parameters, improvements in clinical symptoms, and a favorable safety and tolerability profile.

2. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. Aliment Pharmacol Ther. 2013 Apr;37(7):691-702

BACKGROUND:
Pancreatic exocrine insufficiency (PEI) often occurs following pancreatic surgery.
AIM:
To demonstrate the superior efficacy of pancreatin 25 000 minimicrospheres (Creon 25000 MMS; 9-15 capsules/day) over placebo in treating PEI after pancreatic resection.
METHODS:
A 1-week, double-blind, randomised, placebo-controlled, parallel-group, multicentre study with a 1-year, open-label extension (OLE). Subjects ≥18 years old with PEI after pancreatic resection, defined as baseline coefficient of fat absorption (CFA) <80%, were randomised to oral pancreatin or placebo (9-15 capsules/day: 3 with main meals, 2 with snacks). In the OLE, all subjects received pancreatin. The primary efficacy measure was least squares mean CFA change from baseline to end of double-blind treatment (ancova).
RESULTS:
All 58 subjects randomised (32 pancreatin, 26 placebo) completed double-blind treatment and entered the OLE; 51 completed the OLE. The least squares mean CFA change in the double-blind phase was significantly greater with pancreatin vs. placebo: 21.4% (95% CI: 13.7, 29.2) vs. -4.2% (-12.8, 4.5); difference 25.6% (13.9, 37.3), $P < 0.001$. The mean ± s.d. CFA increased from 53.6 ± 20.6% at baseline to 78.4 ± 20.7% at OLE end ($P < 0.001$). Treatment-emergent adverse events occurred in 37.5% subjects on pancreatin and 26.9% on placebo during double-blind treatment, with flatulence being the most common (pancreatin 12.5%, placebo 7.7%). Only two subjects discontinued due to treatment-emergent adverse events, both during the OLE.
CONCLUSIONS:
This study demonstrates superior efficacy of pancreatin 25 000 over placebo in patients with PEI after pancreatic surgery, measured by change in CFA. Pancreatin was generally well tolerated at the high dose administered

Date: March 2014