Clinical Policy Title: Digestive enzyme cartridge

Clinical Policy Number: CCP.1336

Effective Date: October 1, 2017
Initial Review Date: September 21, 2017
Most Recent Review Date: October 2, 2018
Next Review Date: October 2019

Related policies:

CCP.1052 Nutritional support

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of a digestive enzyme cartridge (RELiZORB®, Alcresta™ Therapeutics Inc., Newton, Massachusetts) to be investigational and, therefore, not medically necessary (Freedman, 2018; Schwarzenberg, 2016; Borowitz, 1995, updated online 2016).

A digestive enzyme cartridge may be considered on a case-by-case basis for members ages 5 years and older with exocrine pancreatic insufficiency who are partially or completely unable to hydrolyze fats in enteral formula.

Limitations:

All uses of a digestive enzyme cartridge are considered experimental and will be reviewed on a case-by-case basis.

Alternative covered services:

• Pancreatic enzyme replacement therapy.
• Enteral nutrition.
• Nutritional counseling.

Background

The acinar cells of the exocrine pancreas produce amylase, protease, and lipase, which aid in digestion of carbohydrates, proteins, and fats, respectively (Alkaade, 2017). A deficiency of these enzymes characterizes exocrine pancreatic insufficiency, resulting in the inability to properly digest essential nutrients, particularly fats. Lipase deficiency can result in inadequately hydrolyzed fats and clinically significant fat malabsorption with consequences to lipid homeostasis, vascular function, and cellular function, growth, and immunity.

Diagnosis of exocrine pancreatic insufficiency is largely clinical, and etiology can be relevant to the clinical presentation and symptoms (Alkaade, 2017). Common pancreatic etiologies of exocrine pancreatic insufficiency are chronic pancreatitis (the most common overall), cystic fibrosis (the most common among children), pancreatic duct obstruction, pancreatic surgery, and the rare Shwachman-Diamond syndrome; non-pancreatic causes include celiac disease, Crohn’s disease, Zollinger-Ellison syndrome, and motility disorders (Fieker, 2011).

Common clinical indicators of fat malabsorption are steatorrhea and continued weight loss, abdominal discomfort, abdominal bloating, loss of appetite, and low circulating levels of micronutrients, lipoproteins, and fat-soluble vitamins. The fecal fat quantification test and \[^{13}\text{C}\text{-mixed triglycerides breath test}\] are considered among the most accurate tests for diagnosing exocrine pancreatic insufficiency, but macro- or micronutrient deficiencies in blood tests, imaging, fecal elastase 1 assay, and direct pancreatic function tests may also be used (Lindkvist, 2013).

Treatment of nutritional deficiency in exocrine pancreatic insufficiency:

Persons with exocrine pancreatic insufficiency often need pancreatic enzyme replacement therapy or enteral nutrition to reach the nutritional goals not achieved with dietary intake (Freedman, 2017a). Among the more than 30,000 persons living with cystic fibrosis in the United States, approximately 87 percent require pancreatic enzyme replacement therapy and 12 percent rely on supplemental tube feedings (Cystic Fibrosis Foundation, 2015).

Pancreatic enzyme replacement therapy products are porcine-derived pancreatic digestive enzymes indicated for oral administration. The U.S. Food and Drug Administration (2016) has approved several pancreatic enzyme replacement therapy products for treatment of exocrine pancreatic insufficiency.

Current enteral nutrition formulas address the malabsorption of lipid-soluble vitamins (A, D, E, and K) and macronutrients, but they also contain complex long-chain triglycerides (fats) that require lipase for fat hydrolysis. The U.S. Food and Drug Administration has not approved mixing oral pancreatic enzyme
replacement therapy products in enteral formula, although a small number of patients may receive it through this route of delivery (Freedman, 2017a).

**RELiZORB:**

RELiZORB is a cartridge filled with immobilized lipase enzyme covalently bound to polymeric beads that fits between the infusion pump and the implanted feeding tube. RELiZORB is intended to mimic the function of lipase in patients with exocrine pancreatic insufficiency and address the unmet need for pancreatic enzyme replacement therapy in patients receiving enteral nutrition.

In 2015, U.S. Food and Drug Administration granted a *de novo* classification for RELiZORB as an Enzyme Packed Cartridge (product code PLQ; new regulation number 876.5985) and subsequently issued a Class II designation with 510(k) marketing approval (U.S. Food and Drug Administration, 2015). The U.S. Food and Drug Administration first approved RELiZORB for adults who are partially or completely unable to hydrolyze fats in enteral formula, and recently expanded approval to include children ages 5 years and older (U.S. Food and Drug Administration, 2017). RELiZORB is a single-use device with a six-month shelf life.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on August 13, 2018. Search terms were: “Cystic Fibrosis (MeSH),” “Enteral Nutrition (MeSH),” “Pancreas, Exocrine/abnormalities (MeSH),” and free text terms “relizorb,” “lipase,” and “immobilized lipase.”

We included:

- **Systematic reviews,** which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses,** such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**
We identified one completed study with results (Freedman, 2017b), one completed open-label study with no published results (Absorption and Safety with Sustained Use of RELiZORB Evaluation [ASSURE] study; Clinicaltrials.gov identifier: NCT02750501), and two related guidelines from the Cystic Fibrosis Foundation (Schwarzenberg, 2016; Borowitz, 1995, updated online 2016). The evidence for the safety and efficacy of RELiZORB consists of a single crossover study of 33 adult and pediatric patients in stable health with cystic fibrosis and confirmed exocrine pancreatic insufficiency who receive ongoing enteral nutrition and pancreatic enzyme replacement therapy (Freedman, 2017b). The study duration was 27 days. Fat absorption was measured by total plasma docosahexaenoic acid + eicosapentaenoic acid concentrations.

Despite long-term use of enteral nutrition (mean of 6.6 years) at a mean volume of approximately 800 mL, baseline total plasma docosahexaenoic acid + eicosapentaenoic acid levels were 60 percent of normal mean plasma levels, and, among children (ages 5 to 12 years) and adolescents (ages 13 to 18 years), the body mass index (body mass index) percentiles were 41.3 percent and 25.8 percent, respectively. Compared with placebo, RELiZORB use resulted in a statistically significant 2.8-fold increase in total fat absorption. RELiZORB was associated with no adverse events, a decrease in the frequency and severity of most symptoms of malabsorption, and increased preservation of appetite and breakfast consumption compared with pre-study regimens. Gains in body mass index in children and adolescents were not reported, and long-term outcomes have not been determined.

The open-label ASSURE Study (Clinicaltrials.gov identifier: NCT02750501) examined extended RELiZORB use over 90 days, and results are pending. The Cystic Fibrosis Foundation acknowledges the limitations in the literature to define the optimal delivery of pancreatic enzymes in enteral feedings and the potential, but as yet undefined role, of RELiZORB (Schwarzenberg, 2016; Borowitz, 1995, updated online 2016).

**Policy updates:**

In 2018, we added the 90-day results of the ASSURE study (Freedman, 2018). This study demonstrated favorable safety and efficacy of RELiZORB supplementation over a longer-duration, but small sample size is the main limitation of the evidence. The results do not warrant a policy change at this time.

Policy ID changed from CP# 08.02.09 to CCP.1336.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedman (2018)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Absorption and safety with sustained use of RELiZORB</td>
<td>• A multicenter, 90-day open label, single-arm study of 44 enrolled subjects (36 completed the study) with cystic fibrosis (mean age of 13.6 years, body mass index of</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| Freedman (2017b) | **Increased fat absorption from enteral formula through an in-line digestive cartridge in patients with cystic fibrosis**  
Clinicaltrials.gov identifier: NCT02598128 |

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| Freedman (2017b) | 17.7 kg/m² who had received enteral nutrition for an average of 6.2 years. One cartridge of RELiZORB was added to overnight enteral nutrition.  
- The omega-3 index increased from a baseline value of 4.4% to 9.4% at 90 days ($P < .001$ for each increase from baseline to 60 and 90 days) The magnitude and significance of these increases were similar in groups ≤ 12 years and 13–18 years, but were not statistically significant in adults ≥ 19 years at day 60 ($P = .051$), likely because of the small sample size ($n = 5$).  
- Secondary efficacy outcomes of changes in plasma and erythrocyte membrane composition of total eicosapentaenoic acid, total docosahexaenoic acid, and omega-6 to omega-3 fatty acids also improved over the 90-day period.  
- RELiZORB use was not associated with any unanticipated adverse events.  
- The impact of the improvement in omega-3 levels pulmonary and inflammatory status and anthropometric parameters requires further study. |

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| Freedman (2017b) | **Key points:**  
- Multicenter, randomized, double-blind, crossover trial with 33 enrollees with cystic fibrosis and confirmed exocrine pancreatic insufficiency, ages 4 to 45 years, receiving enteral nutrition at least four times per week, using pancreatic enzyme replacement therapy, and stable with no significant changes in health status within 14 days before baseline evaluation.  
  - Run-in period (seven days): Peptamen, 1.5 enteral feedings at home.  
  - Crossover period (11 days): randomized either to RELiZORB then placebo, or placebo then RELiZORB. All received Impact Peptide 1.5 on days one and nine, and Peptamen 1.5 during the eight-day washout period between days one and nine.  
  - During the open label period (nine days), RELiZORB was used during nocturnal enteral feedings with Impact Peptide 1.5.  
- Safety endpoints: frequency and severity of anticipated or unanticipated adverse events.  
- Efficacy endpoints: sum total plasma docosahexaenoic acid + eicosapentaenoic acid measured by Δ peak plasma for 24 hours (Cmax) and area under the curve for plasma concentrations for 24 hours (AUC0–24).  
- At baseline:  
  - Characteristics 81.8% ≤ 18 years, 60.6% male, 94% white.  
  - History of enteral nutrition (mean of 6.6 years) at a mean volume of approximately 800 mL.  
  - Mean (standard deviation [SD]) plasma concentration for total plasma docosahexaenoic acid + eicosapentaenoic acid 49.0 (25.7) mg/mL, ~ 60% of normal.  
- Compared with placebo, digestive cartridge use:  
  - Resulted in a 2.8-fold increase in mean total plasma docosahexaenoic acid + eicosapentaenoic acid AUC0–24 (SD) (537.0 [400.5] μg x h/mL vs 192.2 [198.7] μg x h/mL, respectively; $P < 0.001$), and a 2.2-fold increase in mean total plasma docosahexaenoic acid + eicosapentaenoic acid Cmax (SD) (42.8 [22.9] μg/mL vs. 20.1 [13.5] μg/mL; $P < 0.001$).  
  - Provided plasma concentrations of total plasma docosahexaenoic acid + eicosapentaenoic acid from seven to 24 hours consistent with concentrations found in healthy humans. |
Digestive cartridge use decreased the frequency and severity of several gastrointestinal events reported during the open-label safety period vs. run-in period, despite using a formula with increased fat content and a higher percentage of long-chain triglycerides.

Key points:
The optimal way to deliver pancreatic enzymes with tube feedings remains unanswered in the literature.

Key points:
- The best way to administer pancreatic enzyme replacement therapy with continuous overnight enteral feedings is unclear.
- Foundation mentions but does not specifically recommend for or against RELiZORB.

References

**Professional society guidelines/other:**


**Peer-reviewed references:**


Centers for Medicare & Medicaid Services National Coverage Determinations:

No National Coverage Determinations identified as of the writing of this policy.

Local Coverage Determinations:
No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>E16.4</td>
<td>Zollinger-Ellison syndrome</td>
<td></td>
</tr>
<tr>
<td>E84.1-E84.9</td>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>K86.1</td>
<td>Other chronic pancreatitis</td>
<td></td>
</tr>
<tr>
<td>K86.81</td>
<td>Exocrine pancreatic insufficiency</td>
<td></td>
</tr>
<tr>
<td>K50.00</td>
<td>Crohn’s disease of small intestine without complications</td>
<td></td>
</tr>
<tr>
<td>K90.0</td>
<td>Celiac disease</td>
<td></td>
</tr>
<tr>
<td>Q45.3</td>
<td>Other congenital malformations of pancreas and pancreatic duct</td>
<td></td>
</tr>
</tbody>
</table>