Digestive enzyme cartridge

Clinical Policy ID: CCP.1336

Recent review date: 11/2024

Next review date: 3/2026

Policy contains: Cystic fibrosis; exocrine pancreatic insufficiency; pancreatic enzyme replacement therapy.

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Coverage policy

An inline digestive enzyme cartridge (RELiZORB®, Alcresta™ Therapeutics Inc., Newton, Massachusetts) is clinically proven and, therefore, may be medically necessary for members age five years and older in stable health who have cystic fibrosis and confirmed exocrine pancreatic insufficiency and are receiving ongoing enteral nutrition and pancreatic enzyme replacement therapy (Cystic Fibrosis Foundation, 2021; Schwarzenberg, 2016; Stevens, 2018).

Limitations

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

Initial authorization for RELiZORB is for up to two single-use cartridges per 24-hour period (Alcresta Therapeutics Inc., 2024) for up to 90 days. Reauthorization every six months (180 days) thereafter is conditioned on evidence of continued weight gain and gastrointestinal symptom resolution.

Enteral formulas containing insoluble fiber should **not** be used with RELiZORB, as insoluble fiber may clog the RELiZORB cartridge (Alcresta Therapeutics Inc., 2024).

RELiZORB is designed for use with enteral nutrition pump systems with low-flow or no-flow alarms and is not for use with gravity feed systems (Alcresta Therapeutics Inc., 2024).

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}C-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).

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, 2017b). Pancreatic enzyme replacement therapy products are porcine-derived pancreatic digestive enzymes indicated for oral administration. The U.S. Food and Drug Administration has approved several pancreatic enzyme replacement therapy products for treatment of exocrine pancreatic insufficiency (Medical News Today, 2022).

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, 2017b).

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.

The U.S. Food and Drug Administration (2015) 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. It first approved RELiZORB for adults who are partially or completely unable to hydrolyze fats in enteral formula, and recently expanded approval to include children five years and

older (U.S. Food and Drug Administration, 2017, 2019). RELiZORB is a single-use device with a six-month shelf life. It is the only enzyme product to break down fats in enteral formula approved by the Food and Drug Administration.

Findings

Guidelines

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 (Borowitz, 1995, updated online Cystic Fibrosis Foundation, 2016; Schwarzenberg, 2016).

Evidence review

We identified one completed study with results (clinicaltrials.gov identifier: NCT02598128; Freedman, 2017a), one completed open-label study (Absorption and Safety with Sustained Use of RELiZORB Evaluation [ASSURE] study; clinicaltrials.gov identifier: NCT02750501), and two related guidelines from the Cystic Fibrosis Foundation (Borowitz, 1995, updated online 2016; Schwarzenberg, 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, 2017a). 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% of normal mean plasma levels, and, among children (ages 5 to 12 years) and adolescents (ages 13 to 18 years), the body mass index percentiles were 41.3% and 25.8%, respectively (Freedman, 2017a). 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.

In 2018, we added the 90-day results of the ASSURE study (Stevens, 2018). 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 old and 13 years old to 18 years old, but were not statistically significant in adults ≥ 19 years old at day 60 ($P = 0.051$), 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. The impact of these improvements requires further study.

This study demonstrated favorable safety and efficacy of RELiZORB supplementation over a longer duration, but significant limitations and uncertainty in the evidence remain. In addition to small sample size, the investigators used an invalidated recall (diary) method to track changes in symptoms. Variation in the number of cartridges used per participant and normal diet consumption further adds to the uncertainty in the findings. The results did not warrant a policy change at that time. The policy ID was changed from CP# 08.02.09 to CCP.1336**.**

In 2019, we added new information on a 90-day, phase 4, open-labeled exploratory study of RELiZORB in children with short bowel syndrome who are dependent on enteral nutrition, representing an off-label use (clinicaltrials.gov identifier: NCT03530852). The primary completion date is slated for September 30, 2021.

We reconsidered the coverage status based on increasing positive clinical experience among pediatricians with RELiZORB in children with cystic fibrosis. In consultation with associate pediatricians, we revised the policy from

investigational to medically necessary for members age five years and older in stable health with cystic fibrosis and confirmed exocrine pancreatic insufficiency who are receiving ongoing enteral nutrition and pancreatic enzyme replacement therapy.

In 2020, we identified no newly published, relevant literature to add to the policy. The U.S. Food and Drug Administration (2019) determined that minor design changes to RELiZORB were substantially equivalent to the original device and do not affect indications for use. No policy changes are warranted.

In 2021, we updated the references and added one new study (Sathe, 2021) with no policy changes required.

In 2022, we added a review of 18 participants (13 of whom were children) who used a digestive enzyme cartridge with enteral nutrition for 3 – 27 months; authors report an immediate reduction in reported gastrointestinal symptoms, and improvements in anthropometrics after one year (Hendrix, 2022).

In 2023, no studies were added, and no policy changes are warranted.

In 2024, we added one retrospective study of 29 participants with cystic fibrosis and exocrine pancreatic insufficiency who received supplemental tube feedings and an in-line lipase cartridge for a continuous 12-month period. The mean age of participants was 8.41 years at the time the cartridge was initiated. Using multivariable longitudinal regression, height, weight, and body mass index z scores changed over time, but only changes in mean height z scores were statistically significant. Long-term positive effects on achieving linear growth and pulmonary function requires further study (Shrivastava, 2024). No policy changes are warranted.

References

On September 16, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “Cystic Fibrosis (MeSH),” “Enteral Nutrition (MeSH),” “Pancreas, Exocrine/abnormalities (MeSH),” “relizorb,” “ilipase,” and “immobilized lipase.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

9/2017: initial review date and clinical policy effective date: 10/2017

11/2018: Policy references updated. Policy ID changed.

11/2019: Policy references updated. Policy coverage changed.

11/2020: Policy references updated.

11/2021: Policy references updated.

11/2022: Policy references updated.

11/2023: Policy references updated.

11/2024: Policy references updated.