Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

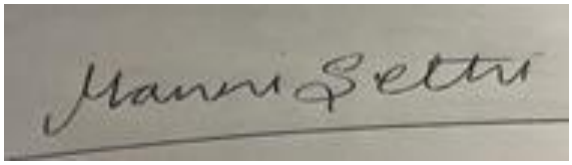
Plan: AmeriHealth Caritas Pennsylvania & Keystone First	Submission Date: 3/1/2025
Policy Number: CCP.1336	Effective Date: 10/2017 Revision Date: 3/1/2025
Policy Name: Digestive enzyme cartridge	

Type of Submission:

☐ New Policy	☒ Prior Authorization Policy
☒ Revised Policy*	☐ Base Policy
☐ Annual Review- no revisions	☐ Experimental/Investigational Policy
	☐ Statewide PDL
	☐ Other:

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 

Digestive enzyme cartridge

Clinical Policy ID: CCP.1336

Recent review date: 3/2025
Next review date: 7/2026
Policy contains: Cystic fibrosis; exocrine pancreatic insufficiency; pancreatic enzyme replacement therapy.

Keystone First- CHIP has developed clinical policies to assist with making coverage determinations. Keystone First- CHIP'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 Keystone First- CHIP, on a case by case basis, 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. Keystone First- CHIP'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. Keystone First- CHIP's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First- CHIP will update its clinical policies as necessary. Keystone First- CHIP's clinical policies are not guarantees of payment.

Coverage policy

An in-line digestive enzyme cartridge (RELiZORB®, Alcresta™ Therapeutics Inc., Newton, Massachusetts) is clinically proven and, therefore, may be medically necessary for members aged one year 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 (Hendrix, 2022; Leonard, 2023; Sathe, 2021; U.S. Food and Drug Administration, 2025).

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 six single-use cartridges per 24-hour period (Alcresta Therapeutics Inc., 2025) for up to 90 days. Reauthorization every six months (180 days) thereafter is conditioned on evidence of continued weight gain and gastrointestinal symptom resolution.

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. 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 (Alkaade, 2017)
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. RELiZORB is indicated for use with children aged one year and older and adults to hydrolyze fats in enteral formula. The expanded indication is based on a retrospective review of real world data suggesting no additional safety concerns in patients aged one to two years old who used RELiZORB in enteral formula as part of their nutrition routine (U.S. Food and Drug Administration, 2025).

Findings

Guidelines

A consensus statement from the Cystic Fibrosis Foundation acknowledges that in-line digestive enzyme cartridges are safe and effective for digesting nutrients and promoting weight gain for people with cystic fibrosis using enteral tube feeds (Leonard, 2023).

Evidence review

We identified one completed study with results (clinicaltrials.gov identifier: NCT02598128; Freedman, 2017a) and one completed open-label study (Absorption and Safety with Sustained Use of RELiZORB Evaluation [ASSURE] study; clinicaltrials.gov identifier: NCT02750501). 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. The study enrolled 100 participants ages birth to 45 years, of which 18 were between the ages of two to five years. During 12 months of use in participants ages two years and older (n=93), use of an in-line lipase cartridge results in significant improvements in height and weight z-scores with a trending improvement in body mass index. The frequency of achieving the 50th percentile increased steadily for weight and body mass index from baseline to 12 months but not for height.
In 2022, we added a case series of 18 participants (13 of whom were children, and four who were ages birth to five years), who used a digestive enzyme cartridge with enteral nutrition for three to 27 months. Authors reported an immediate reduction in gastrointestinal symptoms and improvements in anthropometrics after one year to undernourished patients receiving supplemental enteral nutrition (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 require further study (Shrivastava, 2024).
In 2025, we added regulatory information approving RELiZORB for children ages one year and older and new guidance from the Cystic Fibrosis Foundation. The coverage was modified to align with these changes.

References

On March 4, 2025, 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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U.S. Food and Drug Administration. Device classification under Section 513(f)(2)(de novo) database. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm?ID=DEN150001. Published November 20, 2015.

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.
3/2025: Policy references updated. Coverage modified.