Digestive enzyme cartridge

Clinical Policy ID: CCP.1336

Recent review date: 9/2026

Next review date: 1/2028

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

First Choice Next has developed clinical policies to assist with making coverage determinations. First Choice Next'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, on a case by case basis, by First Choice Next 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. First Choice Next'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. First Choice Next's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, First Choice Next will update its clinical policies as necessary. First Choice Next'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 adult and pediatric members, including neonates and infants in stable health 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

Evidence from guidelines, randomized clinical trials, and observational studies demonstrates that in-line immobilized lipase cartridges designed to work with enteral nutrition systems safely and effectively improve fat absorption, gastrointestinal tolerance, and anthropometric measures in people with cystic fibrosis who are unable to meet nutritional goals with dietary intake alone. While enzymatic cartridge technology is a relatively recent

development in enteral feeding for cystic fibrosis, the available evidence indicates clinically meaningful improvements in plasma omega-3 fatty acid concentrations, body mass index, height and weight z-scores, and symptom burden. International guidelines acknowledge these benefits while noting the importance of individualized decision-making and the need for protease and amylase supplementation alongside cartridge use. The evidence base comprises high-quality randomized trials and multiple observational studies with generally consistent findings, though continued research is warranted to optimize use and explore broader applications across age groups.

Guidelines

The Cystic Fibrosis Foundation established that approximately 85% of people with cystic fibrosis have pancreatic insufficiency, and over 10% use supplemental enteral nutrition (Leonard, 2023). The foundation's multidisciplinary committee acknowledged that prior guideline recommendations regarding pancreatic enzyme replacement therapy with enteral feeding were absent due to lack of clinical trial data. However, Leonard (2023) explicitly stated that inline enzymatic cartridges are safe and effective for digesting nutrients and promoting weight gain in people with cystic fibrosis receiving enteral tube feeds, marking a significant evolution in recommendations since the 2016 Cystic Fibrosis Foundation Enteral Feeding Guidelines.

European guidelines developed through systematic literature review and Delphi consensus methods offered more cautious positions. The European guidelines on pancreatic exocrine insufficiency (Dominguez-Munoz, 2024) indicated that pancreatic enzyme replacement therapy can be added to enteral nutrition if required, but efficacy has not yet been proven (Level of Evidence 4; 94.0% agreement). This assessment noted that while lipase-containing cartridges designed to connect to enteral nutrition systems have been developed, comparative studies on adding pancreatic enzyme replacement therapy to food remain lacking. Notably, Dominguez-Munoz (2024) also recommended that for participants with pancreatic exocrine insufficiency receiving enteral nutrition, peptide- and medium-chain triglyceride-based formulas may be worth considering for those intolerant to standard polymeric feeds (Level of Evidence 5; 91.6% agreement).

The most recent multidisciplinary guideline update (Wilschanski, 2024) recommended that pancreatic enzymes can be administered orally at the start of enteral nutrition and during the night if the participant is awake, with enzymes in non-enteric or powder form potentially mixed into the feed if oral intake of enzymes is not feasible (Grade Good Practice Point, 91% agreement). Wilschanski (2024) acknowledged limited evidence that the new inline cartridge available in the United States improves nutrient, particularly lipid, absorption. Importantly, this guideline emphasized that for most people with cystic fibrosis on tube feeding, pancreatic enzyme replacement therapy alone supports good outcomes, and consideration of the inline cartridge should be individualized based on factors such as inadequate response to usual enzyme therapy dosing or persistent gastrointestinal issues. Wilschanski (2024) also clarified that the inline cartridge contains only lipase, necessitating supplemental protease and amylase through additional pancreatic enzyme replacement therapy. The guideline noted that these supportive enteral feeds are not available in Europe and cost considerations must factor into decision-making.

Clinical Trials

Two multicenter prospective clinical trials evaluated enzymatic cartridge efficacy in people with cystic fibrosis receiving enteral nutrition: a randomized, double-blind, crossover trial with open-label safety period (N = 33 participants; Freedman, 2017) and a 90-day open-label prospective study (N = 36 participants; Stevens, 2018). Both enrolled participants with similar demographic profiles (mean ages 14.5 years, standard deviation [SD] 6.2 and 13.8 years, SD 5.4, respectively) who had been receiving enteral nutrition for an average of over 6 years, and both demonstrated that enzymatic cartridge use substantially improved fat absorption markers.

Fat absorption, measured through plasma omega-3 fatty acid concentrations, improved significantly in both trials. Freedman (2017) demonstrated a 2.8-fold increase in area under the curve for omega-3 fatty acids with cartridge

use compared with placebo (537.0 micrograms x hours/mL, SD 400.5 versus 192.2 micrograms x hours/mL, SD 198.7; p < 0.001), with peak omega-3 concentration 2.2-fold higher (42.8 micrograms/mL, SD 22.9 versus 20.1 micrograms/mL, SD 13.5; p < 0.001). These findings were noteworthy given that baseline omega-3 plasma concentrations were only 60% of levels found in normal healthy subjects. Stevens (2018) extended these absorption findings over a longer duration, showing the omega-3 index increased from a below-target baseline of 4.4% to 8.4% at 60 days and 9.4% at 90 days (p < 0.001 for each timepoint), reaching the target range by day 60. Plasma docosahexaenoic acid plus eicosapentaenoic acid concentrations increased from baseline 72.73 micrograms/mL (SD 52.1) to 166.46 micrograms/mL (SD 73.7) at 90 days, and the omega-6 to omega-3 ratio decreased from 11.52 (SD 4.3) to 5.23 (SD 3.1), representing a meaningful shift toward more favorable lipid metabolism.

Both trials also found consistent improvements in gastrointestinal tolerance. In the crossover trial, Freedman (2017) reported decreases in the frequency and severity of most malabsorption symptoms during cartridge use, with the proportion of participants missing breakfast decreasing from 50% to 33.3% and those reporting reduced appetite decreasing from 46.9% to 30.3%. Notably, 42.4% of participants (14 of 33) stopped self-administering oral pancreatic enzyme replacement therapy with enteral nutrition despite instructions, yet still experienced fewer gastrointestinal events. In the 90-day study, Stevens (2018) found the proportion of participants reporting any gastrointestinal symptom decreased progressively from 59.0% at baseline observation to 30.8% at day 90, while 61% of participants demonstrated improvements in weight z-scores and percentiles.

Safety was excellent across both trials. Freedman (2017) reported no adverse experiences associated with cartridge use, and Stevens (2018) identified only 1 adverse event (constipation) judged as possibly device-related.

Retrospective and Observational Studies

Four retrospective or observational studies, ranging from single-center case reviews (n = 18 participants, Hendrix, 2022; (n = 29) participants, Shrivastava, 2024) to multicenter evaluations (n = 100 participants in efficacy analysis, Sathe, 2020; (n= 143) participants in efficacy analysis, Freeman, 2026), provide real-world evidence of enzymatic cartridge use across diverse settings and age groups.

Weight and body mass index improvements were a consistent finding across all four studies, though the magnitude varied with age and baseline nutritional status. Among older children and adolescents, Sathe (2020) reported weight z-score improvements of 0.20 (standard error [SE] 0.079; p = 0.014) at 6 months in 93 participants ages 2-18 years across 15 centers, while Shrivastava (2024) found weight z-score improvements nearing significance at 12 months post-cartridge (adjusted mean difference 0.2816; 95% confidence interval [CI] -0.0003 to 0.5634; p = 0.0502) when excluding 7 participants with advanced lung disease (forced expiratory volume in 1 second less than 40%). In the youngest population studied, Freeman (2026) reported the largest weight z-score improvement of 0.63 (p < 0.001) from baseline to 12 months in 143 participants ages 1-4 years across 90 clinics, suggesting that younger children with greater growth potential may derive the most benefit. Hendrix (2022) similarly found significant body mass index improvements in both adult participants (from baseline 16.46 kg/m2, SD 1.443 to 19.10 kg/m2, SD 1.781, at month 9; p = 0.031) and pediatric participants (body mass index z-scores improved from -0.91 to -0.26 at month 3; p = 0.022).

Height and linear growth improvements, while present across studies, were more variable. Sathe (2020) demonstrated significant height z-score improvement of 0.17 (SE 0.058; p = 0.005) at 6 months, and comparison with 1,868 historical controls from the Cystic Fibrosis Foundation Patient Registry (2014) showed cartridge participants had significantly greater increases in height z-scores (mean treatment difference 0.20; p = 0.001). Shrivastava (2024) reported statistically significant height z-score improvements from 6 months pre-cartridge to 6 months post-cartridge (adjusted mean difference 0.2540; 95% CI 0.0487 to 0.4592; p = 0.0153) and to 12 months post-cartridge (adjusted mean difference 0.2684; 95% CI 0.0203 to 0.5166; p = 0.0340), with even

greater improvement in participants without advanced lung disease (adjusted mean difference 0.3402; 95% CI 0.0846 to 0.5957; p = 0.0091). Hendrix (2022) found length or stature-for-age z-scores improved from -1.23 to -0.98 at month 9 (p = 0.041). In contrast, Freeman (2026) did not observe statistically significant height improvements, which the authors attributed to the younger age of their cohort and the well-documented pattern in which weight increases precede height gains in undernourished children with cystic fibrosis.

Progress toward the Cystic Fibrosis Foundation nutritional target of body mass index at or above the 50th percentile was documented across the two largest studies. Sathe (2020) found the proportion of participants reaching this target increased from 37.1% at baseline to 50.0% at 12 months. Freeman (2026) reported that among people with cystic fibrosis initiating cartridge use at ages 2-4 years, body mass index at or above the 50th percentile increased from 22% at baseline to 43% at 12 months (p = 0.021), and in 1-year-old people with cystic fibrosis, weight-for-length at or above the 50th percentile increased from 33% to 65% at 12 months (p = 0.020).

Gastrointestinal tolerance was a notable benefit in the study that specifically evaluated it. Hendrix (2022) reported that 77.8% of participants had gastrointestinal complaints before cartridge initiation compared with only 27.8% after use began (mean cartridge use duration 17.8 months, SD 9.9). Specific symptom improvements included reduction in nausea or vomiting from 33.3% to 11.1% and reduction in abdominal pain from 16.7% to 11.1%. No serious injuries or unexpected safety risks were identified in post-market surveillance across any of the observational studies (Freeman, 2026).

In 2026, we reorganized the findings section and incorporated three newly identified sources: two international clinical practice guidelines addressing pancreatic enzyme replacement therapy with enteral nutrition (Dominguez-Munoz, 2024; Wilschanski, 2024) and one multicenter retrospective observational study reporting real-world growth outcomes in children ages one to five years receiving enteral formula through an immobilized lipase cartridge (Freeman, 2026). We also clarified coverage criteria to not adults and pediatric populations, including nenonates were eligible for coverage.

References

On June 6, 2026, 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.

3/2025: Policy references updated. Coverage modified.

3/2026: Policy references updated.

7/2026: Policy references updated. Coverage modified.

9/2026: Policy references updated. Coverage modified.

Related Codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1336. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code Description
B4149	Blenderized natural foods with intact nutrients, 100 cal = 1 unit
B4150	Nutritionally complete with intact nutrients, 100 cal = 1 unit
B4152	Nutritionally complete, calorically dense (≥1.5 kcal/mL), 100 cal = 1 unit
B4153	Hydrolyzed proteins (amino acids/peptide chain), 100 cal = 1 unit
B4154	Special metabolic needs (excludes inherited diseases), 100 cal = 1 unit
B4155	Nutritionally incomplete/modular nutrients, 100 cal = 1 unit
B4157	Special metabolic needs for inherited disease of metabolism, 100 cal = 1 unit
B4158–B4162	Pediatric-specific enteral formulas (various types), 100 cal = 1 unit