

01.02.01 Enteral Nutrition Therapy and Oral Formula

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Related Policies:

- [10.01.15 Medical Foods and Specialized Formula for Inborn Errors of Metabolism](#)

Summary

Description

Note: For the purposes of this policy, the term "enteral nutrition therapy" will refer to nutrients administered into the alimentary canal through a tube, such as percutaneous endoscopic gastrostomy (PEG) tube, jejunostomy (J-tube) tube, percutaneous endoscopic jejunostomy (PEJ) tube, nasogastric (NG) tube. Refer to the member's benefit document to determine coverage.

The most optimal route of enteral intake is swallowing by mouth. Oral enteral formulas for nutritional support are given to replace or supplement dietary intake in individuals at risk of or experiencing malnutrition. When oral intake is not possible, a tube may be placed to facilitate transport of nutrition to

the digestive/absorptive sites of the gastrointestinal (GI) tract to provide enteral nutrition therapy in an effort to provide adequate nutritional support.

- Enteral nutrition therapy may be utilized in the management of multiple conditions including, but not limited to pancreatic insufficiency (i.e., exocrine pancreatic insufficiency [EPI]) due to complications caused by cystic fibrosis (CF), pancreatitis, and short bowel syndrome.
- Oral enteral formula nutrition therapy may be utilized in the management of conditions including, but not limited to permanent inborn errors of metabolism such as PKU, intolerable foods, lactose intolerance, to supplement a deficient diet or to provide alternative nutrition in the presence of the following conditions allergies, gastrointestinal disorders, hypoglycemia and obesity. *See also medical policy [10.01.15 Medical Foods and Specialized Formula for Inborn Errors of Metabolism](#).*

OBJECTIVE

The first objective of this medical policy is to determine whether the use of digestive enzyme cartridges (e.g., RELiZORB®) improves the net health outcomes of individuals who have failed optimal pancreatic enzyme replacement therapy (PERT) requiring enteral nutrition therapy due to pancreatic insufficiency.

The second objective of this medical policy is to determine whether the use of oral enteral formula nutrition therapy to include regular store-bought formula and banked human breast milk regardless of whether these are prescribed by or authorized by a licensed healthcare practitioner would be considered medically necessary or non-covered as not a contract benefit, see [Policy](#).

Summary of Evidence

For individuals who have pancreatic insufficiency due to cystic fibrosis (CF) who are receiving digestive enzyme cartridges (e.g., RELiZORB®) with enteral nutrition therapy via nasogastric, gastrostomy or jejunostomy tube, the evidence includes randomized controlled trial (RCT) and observational studies. Relevant outcomes are overall survival, change in disease status, health status measures and quality of life (QOL). While the current evidence has shown inconsistent patient outcomes related to height, weight, BMI, and gastrointestinal (GI) symptoms from baseline to 12-month follow-up, the evidence has demonstrated the digestive enzyme cartridge (e.g., RELiZORB®) utilized for the emulsion of fat during enteral nutrition has resulted in increased levels of circulating absorbable fatty acids. Additional RCTs are still needed to include comparisons to placebo, sham or active treatments with longer follow-up to determine the efficacy and safety in individuals with pancreatic insufficiency due to CF. The evidence is insufficient to determine the technology results in improved net health outcomes. However, even though there is paucity in the peer-reviewed scientific evidence in showing consistent evidence regarding the effectiveness of RELiZORB® in individuals with CF with pancreatic insufficiency receiving enteral nutrition therapy via nasogastric, gastrostomy or jejunostomy tube, for certain carefully-selected individuals this treatment is considered generally accepted standard of medical practice in the United States and will be considered medical necessary when the criteria below is met, see [Policy](#).

For individuals who have pancreatic insufficiency caused by other conditions including, but not limited to pancreatitis and short bowel syndrome, the evidence includes systematic review regarding pediatric pancreatitis. Relevant outcomes are overall survival, change in disease status, health status measures and QOL. Based on the review of the peer reviewed evidence is limited regarding the use of RELiZORB® for the treatment of complications of complex disorders including but not limited to the following pancreatitis and short bowel syndrome who require enteral nutrition therapy. RCTs are needed to determine safety and efficacy and also, to determine how RELiZORB® is best administered and optimized

in these individuals compared to other methods of administration of PERT. The evidence is insufficient to determine the technology results in improved net health outcomes.

Additional Information

Not applicable.

PRIOR APPROVAL

Not applicable.

POLICY

Enteral Nutrition Therapy Via Tube

Benefits are available for enteral nutrition therapy **ONLY** when the prescribed feeding solution is issued or authorized by a *licensed healthcare practitioner and is administered through a feeding tube (e.g., nasogastric, gastrostomy, jejunostomy). *Refer to the member's benefit document to determine coverage.*

Note: *Blenderized baby food, food additives, and over the counter food administered with an enteral nutrition feeding system is considered a **non-covered benefit and NOT eligible for coverage**, see also medical policy [10.01.15 Medical Foods and Specialized Formula for Inborn Errors of Metabolism](#).*

Digestive Enzyme Cartridge

Digestive enzyme cartridges (e.g., RELiZORB®) may be considered **medically necessary** when **ALL** of the following are met:

- The individual has a diagnosis of cystic fibrosis (CF);
- The individual has a confirmed history of exocrine pancreatic insufficiency (EPI);
- The individual requires enteral tube nutrition through (e.g., nasogastric, gastrostomy or jejunostomy) for continuous durations of 6 hours or more;
- Individual has documented failure of pancreatic enzyme replacement therapy (PERT) (as evidence by insufficient weight gain or weight loss) from enteral formula, despite optimizing therapy with PERT in the form of oral tablets or capsules administered or via feeding tube.

Digestive enzyme cartridges (e.g., RELiZORB®) may be considered **medically necessary** for continuation of therapy when **ALL** of the following are met:

- The individual has evidence of stable or increased weight from use of RELiZORB®;
- The individual has a reduction of symptoms including diarrhea or morning bloating;
- The individual continues to require enteral tube nutrition (e.g., nasogastric, gastrostomy or jejunostomy) for continuous duration of 6 hours or more.

Note:

- *B4105 ≤ 6 months of age and no diagnosis criteria 2 UOS or 62 UOS per month.*
- *B4105 > 6 months of age and no diagnosis criteria 186 UOS which allows 6 units in a 31day period.*

Digestive enzyme cartridges (e.g., RELiZORB®) not meeting the above criteria is considered **investigational**, because the evidence is insufficient in determining the technology improves net health outcomes.

Oral Enteral Formula Nutrition Therapy

Oral enteral formula nutrition therapy is considered a **non-covered benefit, except** for permanent inborn errors of metabolism that interfere with the metabolism of specific nutrients when the product is a medical food for oral feeding, *see also medical policy [10.01.15 Medical Foods and Specialized Formula for Inborn Errors of Metabolism](#)*.

Specialized formulas to include regular store-bought formula, including but not limited to the following below, and banked human breast milk regardless of whether these are prescribed by or authorized by a *licensed healthcare practitioner when given orally or for enteral nutrition therapy given to replace intolerable foods, lactose intolerance, to supplement a deficient diet or to provide alternative nutrition in the presence of the following conditions allergies, gastrointestinal disorders, hypoglycemia and obesity are considered a **non-covered benefit and not eligible for coverage**:

- Alimentum®
- Elecare®
- Mongen®
- Neocate®
- Neosure®
- Nutramigen®
- Portagen®
- Progestimil®

POLICY GUIDELINES

*Covered Provider

Physician or licensed qualified non-physician practitioner (a licensed qualified non-physician may include the following: Nurse Practitioners, Physician Associates, or Clinical Nurse Specialist Practitioners).

Pancreatic Insufficiency:

Pancreatic insufficiency is characterized by the inability of the pancreas to produce or deliver sufficient enzymes required to break down and absorb nutrients. The most common causes of pancreatic insufficiency are cystic fibrosis and chronic pancreatitis. Some patients with pancreatic insufficiency may also receive enteral nutrition through feeding tube to supplement dietary needs.

Patients with pancreatic insufficiency most commonly present with gastrointestinal symptoms that may include the following:

- Gas
- Bloating
- Dyspepsia (indigestion)
- Abdominal pain
- Diarrhea

- Nausea
- Weight loss
- Steatorrhea (abnormally high fat content in feces)
- Other biochemical changes related to malabsorption and maldigestion.

Pancreatic Enzyme Replacement Therapy (PERT)

Pancreatic enzyme replacement therapy (PERT) generally contains a mixture of enzyme, including amylase, lipase, and protease.

When the individual is receiving enteral nutrition through feeding tube (nasogastric, gastrostomy or jejunostomy) and the individual has pancreatic insufficiency PERT may be taken orally or mixed with the enteral tube feeding formula.

FDA Approved Oral Pancreatic Enzyme Preparations

- Creon (oral delayed release capsule)
- Zenpep (oral delayed release capsule)
- Pancreaze (oral delayed release capsule)
- Ultresa (oral delayed release capsule)
- Viokace (non-enteric coated immediate release tablet)
- Pertyze (oral delayed release capsule with bicarbonate-buffered enteric-coated microspheres)

Pancreatic Enzyme Replacement Therapy (PERT) Response or Failure

Several factors determine the response to treatment including degree of residual pancreatic function, anatomy, and the size and fat content of meals. Differences in the remaining pancreatic secretion and gastric production of lipase therapy tailored to the individual patient, based on severity of symptoms and response to treatment. The response to pancreatic enzyme replacement therapy (PERT) should be gauged by improvement in symptoms including the following:

- Stool consistency
- Loss of visible fat or oily droplets in the stool
- Weight gain

Repeating fecal fat measurement can help gauge response. Of note, fecal elastase-1 measures will not be affected by PERT and should not be used to guide dose adjustments. Fat soluble vitamins should be periodically checked to ensure adequate supplementation.

The most common reason for failure is inadequate dose. Either the patient requires more enzyme, or the timing of delivery is off, resulting in inadequate mixing of enzymes with chyme in the duodenum. In patients taking the PERT correctly, the first step would be to double the dose of enzyme. The addition of acid suppression with proton pump inhibitors (PPI) or histamine 2 blockers (H2B) is a reasonable next step in patients with suboptimal response. On occasion, changing formulations may improve symptoms if dosage increases and acid suppression fails to improve symptoms.

Coding

See the [Codes table](#) for details.

BACKGROUND

Enteral Nutrition Therapy

Enteral nutritional therapy by tube is indicated in individuals who cannot maintain adequate oral intake of food or nutrition to meet their metabolic demands due to complications of certain conditions. Enteral nutrition therapy involves administering nutritional formulas directly into the GI tract and the daily amount of enteral nutritional formula required is specific to the individual's needs. The enteral nutrition therapy may be provided either through intermittent (i.e. overnight or bolus) or continuous (infused 24 hours per day) by use of an infusion pump. *Refer to the member's benefit document to determine coverage.*

Specialized Formula

The use of enteral nutrition preparations and specialized formula is frequently given orally for conditions including, but not limited to allergies, malnutrition, gastrointestinal reflux, eating disorders, and weight loss. Wellmark contracts exclude the use of enteral nutrition preparations when given orally including specialized and over the counter formula when given orally, except for permanent inborn errors of metabolism. See also medical policy [10.01.15 Medical Foods and Specialized Formula for Inborn Errors of Metabolism](#).

Digestive Enzyme Cartilages

Pancreatic insufficiency is characterized by the inability of the pancreas to produce or deliver sufficient enzymes required to break down and absorb nutrients. The most common cause of pancreatic insufficiency is CF. Individuals with pancreatic insufficiency experience an insufficient release of amylase, protease, and lipase into the duodenum of the small intestine. This results in inadequate digestion of carbohydrates, proteins, and fats. Up to 10% of individuals with CF use tube feedings to reach ideal calorie goals (Shrivastava et. al. 2024) and the overall prevalence of cystic fibrosis is estimated to be 40,000 in the United States and 105,000 across 94 countries (Cystic Fibrosis Foundation accessed May 2025).

Individuals with pancreatic insufficiency most commonly present with GI symptoms that include gas, bloating, dyspepsia (indigestion), abdominal pain, diarrhea, nausea, weight loss, steatorrhea (abnormally high fat content in feces), and other biochemical changes related to lipid malabsorption and maldigestion. This can lead to an impaired quality of life, changes in bone density, increased risk of mortality, and other sequelae of nutritional deficiencies.

The primary pharmacologic treatment for pancreatic insufficiency that cannot be controlled by dietary and lifestyle interventions alone is PERT. PERT generally contains a mixture of enzymes, including amylase, lipase, and protease, and is most commonly administered orally in conjunction with food. However, some patients with pancreatic insufficiency may also receive enteral nutrition. Enteral nutrition therapy is provided for a variety of indications in patients who are unable to obtain sufficient nutrition through conventional feeding. It involves administration of a specialized formula containing a mixture of carbohydrates, lipids, proteins, vitamins, and minerals to the stomach or small intestine via a feeding tube. Delivery can be via a nasogastric tube or a surgically implanted tube (e.g., gastrostomy or jejunostomy tube). Individuals with pancreatic insufficiency who receive enteral nutrition typically receive PERT orally, although some may mix PERT with enteral formula or utilize novel in-line enzyme cartridges (i.e., RELiZORB®).

Currently, RELiZORB® is the only single-use in-line immobilized lipase-coated cartridge marketed for hydrolysis of lipase in individuals receiving enteral nutrition therapy. The RELiZORB® system is designed to mimic the normal function of lipase release and contains the digestive enzyme lipase. As enteral formula flows through the cartridge, it makes contact with the lipase which hydrolyzes fats from the triglyceride from into fatty acids and monoglycerides to enable easier absorption and utilization by the body.

Regulatory Status

Relizorb®

Table 1. Relizorb™ FDA Approval Information

Device	510(k) Number or PMA Number	Notice Date	Indication
RELiZORB® (Alcresta Therapeutics Inc.)	K250499	April 17, 2025	Relizorb™ is indicated for use in pediatric patients (including neonates and infants) and adult patients to hydrolyze fats during enteral feeding
RELiZORB® (Alcresta Therapeutics Inc.)	K243284	January 15, 2025	Relizorb™ is indicated for use with pediatric patients (ages 1 years and above) and adult patients to hydrolyze fats in enteral formula.
RELiZORB® (Alcresta Therapeutics Inc.)	K232784	December 21, 2023	Relizorb™ is indicated for use with pediatric patients (ages 2 years and above) and adult patients to hydrolyze fats in enteral formula.
RELiZORB® (Alcresta Therapeutics Inc.)	K231156	August 30, 2023	Relizorb™ is indicated for use with pediatric patients (ages 2 years and above) and adult patients to hydrolyze fats in enteral formula.
RELiZORB® (Alcresta Therapeutics Inc.)	K163057	July 12, 2017	Relizorb™ is indicated for use in pediatric patients (age ≥5 years) and adult patients to hydrolyze fats in enteral formula.
RELiZORB® (Alcresta Therapeutics Inc.)	K161247	June 30, 2016	Relizorb™ is indicated for use in adults to hydrolyze fats in enteral formula.

Device	510(k) Number or PMA Number	Notice Date	Indication
RELiZORB® (Alcresta Therapeutics Inc.)	DEN150001	November 20, 2015	Relizorb™ is indicated for use in adults to hydrolyze fats in enteral formula.

RATIONALE

This evidence review was created in May 1995 and has been updated regularly with a search of the PubMed database. The most recent literature search was conducted through April 2026.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Relizorb®

Clinical Context and Therapy Purpose

RELiZORB® is a single-use digestive enzyme cartridge that connects in-line with existing enteral pump feed sets and pump extension sets for individuals having difficulty breaking down and absorbing fats despite optimal therapy with PERT. As the enteral tube feeding formula passes through the RELiZORB® cartridge contact is made with lipase and the fat in the formula is broken down to its absorbable form (fatty acids and monoglycerides) prior to ingestion to allow easier absorption and utilization by the body.

Populations

The relevant populations of interest are individuals with pancreatic insufficiency requiring enteral nutrition therapy via a feeding tube (e.g., nasogastric, gastrostomy, jejunostomy).

The most common cause of pancreatic insufficiency is CF.

Interventions

The therapy being considered is PERT with enteral formula utilizing single-use in-line enzyme cartridge system RELiZORB®.

The RELiZORB® cartridge contains the digestive enzyme lipase and as the enteral formula flows through the cartridge it makes contact with the lipase which hydrolyzes fats from the triglyceride form into fatty acids and monoglycerides to enable easier absorption and utilization by the body.

Comparators

The recommended first line therapy for pancreatic insufficiency is primary pharmacologic treatment using PERT orally, the pancrelipase medication contains lipases, proteases and amylases for fat conversion.

Outcomes

Failure to break down fats results in insufficient caloric intake, not being able to gain or maintain weight, weight loss, having lower levels of some vitamins, and getting enough of certain kinds of fats such as omega-3 fats, which are important for normal growth and development.

The key outcomes include improving gastrointestinal symptoms to improve caloric intake to assist the individual in maintaining or gaining weight by reducing fatty acid and vitamin deficiencies which are important for normal growth and development.

The general outcomes of interest are overall survival, change in disease status, health status measures and QOL.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Pancreatitis

Systematic Review

In 2018, the ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) Cystic Fibrosis/Pancreas Working Group and the NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) Pancreas Committee combined efforts in reviewing the evidence through August 2016 regarding pediatric pancreatitis (acute pancreatitis [AP], recurrent acute

pancreatitis [ARP] and chronic pancreatitis [CP]) with or without exocrine pancreatic insufficiency (EPI) and nutritional management in a position paper to assist in the development of recommendations based on the scientific evidence (Abu-E;-Haija et al). Determining the most optimal nutritional support is an essential part of managing pancreatitis, however, the authors reported most studies regarding the literature on nutrition in AP, ARP, and CP have been conducted in adults with limited evidence in children with few recommendations made. Gaps were noted in the knowledge relating to optimal nutrition for AP; the role of diet or dietary supplements on recurrent attacks of pancreatitis and pain episodes; monitoring practices to detect early growth and nutritional deficiencies in CP; and identifying risk factors that predispose children to these deficiencies. The authors indicated there was insufficient literature reporting on the benefit of pancreatic enzyme replacement therapy (PERT) in ACP, whether in pediatrics or adults. The authors reported “The recommendations made by the writing group received at least 75% support (5=strongly agree or 4=agree) and most recommendations were supported by a Grade 1C evidence: strong recommendation but low quality of evidence, and several recommendations are based on expert opinion due to the lack of medical literature. Early enteral nutrition with a return to a normal fat diet appears most optimal for children along the spectrum of AP, ARP, and CP. Special attention must be directed towards children with CP who are at risk of developing complications such as EPI and T3cDM that will further affect their nutritional status.” They noted that future research is needed to expand the evidence regarding specific nutritional interventions in children with pancreatic diseases.

Cystic Fibrosis

Systematic Review

Hayes Inc completed an Evolving Evidence Review (October, 2024) of RCTs, systematic reviews and observational studies that evaluated the digestive enzyme in-line cartridge, ReliZorb in individuals with cystic fibrosis-related pancreatic insufficiency. Reviewers searched PubMed, Embase and the manufacturer’s website and identified a fair-quality RCT (Freedman 2017) and observational studies (Shrivastava 2024, Stevens 2018 and Sathe 2021) summarized below, and an additional observational study (Hendrix 2022). No systematic reviews were identified. Hayes Inc. concluded the evidence demonstrated ReliZorb resulted in increased levels of absorbable fatty acids in individuals with cystic fibrosis-related pancreatic insufficiency, however, results were inconsistent from baseline (BL) through 12-months of follow-up related to height, weight, BMI and gastrointestinal (GI) symptoms. While some studies showed an improvement in height, weight, BMI and GI symptoms this was typically found within 90 days to 6 months of BL, and no differences were noted at 6 to 12-months in these outcome measures. Thus, Hayes Inc. concluded that the overall body of evidence suggests a “minimal” level of support for use of Relizorb for treatment of cystic fibrosis-related pancreatic insufficiency in patients receiving enteral nutrition due to limitations including a paucity of comparative data (i.e., 1 industry sponsored RCT Freedman 2017) with comparison to placebo only, studies with small sample sizes, short term follow-up and evidence considered fair to poor quality.

Randomized Controlled Study

In 2017, Freedman et al performed an industry sponsored (Alcresta Therapeutics, Inc, Newton, MA) multicenter, randomized, double-blind, crossover trial with an open-label safety period utilizing Relizorb single-use digestive enzyme cartridge that hydrolyzes fat in enteral formula which evaluated the safety, tolerability, and fat absorption in patients with cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI) receiving enteral nutrition (EN). Thirty-four screened patients were enrolled as participants in the study and 33 were randomized and completed the study. The study was comprised of 3 periods: a 7-day run-in period (Period A), a randomized, double-blind, placebo-controlled, cross-over period (Period B), and a 7-day open-label safety period (Period C). Period A was a run-in observation period and during this

7-day period, participants adapted to 500 to 1000 mL of a standardized enteral formula in place of their usual formula. Peptamen 1.5, which contains 9.8 g of fat per 250 mL (70% medium-chain triglycerides [MCTs] and 30% long-chain triglycerides [LCTs]), was chosen because it is a commonly used semi-elemental formula in patients with CF. This is similar to formula with a higher fat and LCT content used later in the study. Baseline GI symptoms were also recorded during period A. In Period B randomization occurred on the first day, a double-blind, randomized crossover period to evaluate fat absorption from enteral formula with and without digestive cartridge. Participants were randomized to first receive EN through either digestive cartridge or placebo cartridge. Placebo cartridges were identical to the blinded digestive cartridges in appearance and handling. After a 7-day washout period when participants received Peptamen 1.5 with their usual dose of PERT products but without digestive cartridge, participants crossed over and received EN through the opposite cartridge (placebo or digestive cartridge). For 3 days before each in-clinic feeding, participants were asked to discontinue any motility agents and were counseled to avoid dietary intake of foods containing omega-3 fats. Participants did not receive EN the night before the in-clinic EN and did not use PERT products in association with the in-clinic feeding. During Period C, the 7-day open-label safety period participants received 500 to 1000 mL of Impact Peptide 1.5 as their overnight EN delivered through a single digestive cartridge. Impact Peptide 1.5 was used during this period to assess the tolerability of digestive cartridge with a formula containing a relatively high fat and LCT content. Participants were instructed to maintain their usual treatment regimen, including their usual dose of PERT products, in conjunction with EN. The efficacy endpoint was change in plasma FA concentrations of DHA and EPA, as markers of fat absorption, for 24 hours. For in-clinic feedings, blood samples were obtained for plasma FA analysis just before the feeding and at 1, 3, 7, 9, 12, and 24 hours after initiation. Plasma DHA and EPA were measured using a validated ultra-high performance liquid chromatography method. Safety and tolerability endpoints were recorded throughout the study, including GI events associated with fat malabsorption (e.g., abdominal pain, bloating, and steatorrhea). Participants completed a study-specific questionnaire at study entry and exit which was used to capture information about EN and PERT use and the effect of EN, with and without cartridge use, on appetite and breakfast consumption. There were no unanticipated adverse device effects. Three, 11, and 4 non-GI AEs occurred in Periods A, B, and C, respectively, and most non-GI AEs were mild in severity and related to respiratory events commonly experienced by patients with CF. There were no GI AEs reported that were associated with digestive or placebo cartridge use in Period B. Despite receiving a formula with a higher fat content and a higher percentage of LCTs in Period C, the overall number of reported GI events, as well as several individual events such as abdominal pain, bloating, constipation, and diarrhea, was lower with digestive cartridge use during Period C compared with Period A (Table 2).

Table 2. Number of Gastrointestinal Events Amongst Thirty-Three Participants in Periods A and C

GI Symptoms	Period A Baseline Run-In Period (PERT)	Period C Open-Label Safety Period (Digestive Cartridge + PERT)
Abdominal Pain	29	19
Bloating	14	7
Constipation	8	0
Diarrhea	7	3
Gas	30	38
Indigestion	9	4
Nausea	9	6
Steatorrhea	7	7

GI Symptoms	Period A Baseline Run-In Period (PERT)	Period C Open-Label Safety Period (Digestive Cartridge + PERT)
Vomiting	4	5
Total Events	117	89

GI: gastrointestinal; PERT: pancreatic enzyme replacement therapy.

During Period C more participants reported preservation of appetite and their ability to eat breakfast during digestive cartridge use compared with PERT alone pre-study. At study entry 50% of participants reported missing breakfast while using PERT alone, while 33.3% reported missing breakfast using digestive cartridge during Period C. In addition, 46.9% of participants reported a reduction in appetite after EN use pre-study while using PERT alone, compared with 30.3% using digestive cartridge in Period C. Also, compared with placebo use AUC₀₋₂₄ (SD) for total DHA + EPA was significantly higher with digestive cartridge use by a factor of 2.8 (537.0 [400.5] ug x h/mL vs 192.2 [198.7] ug x h/mL, respectively; P<0.001) and compared with placebo use the C_{max} (SD) of total DHA + EPA was significantly higher with digestive use cartridge use 2.2 (42.8 [22.9] ug/mL vs 20.1 [13.5] ug/mL; P<0.001). The major limitation of this study was small sample size. The authors concluded “This study demonstrated that digestive cartridge use was safe, well tolerated, and resulted in an almost 3-fold increase in absorption of omega-3 FAs DHA and EPA, a marker of fat absorption in adults and children with CF and EPI requiring EN. Furthermore, a decrease in occurrence of severity of reported GI symptoms and an increase in reported preservation of appetite and ability to consume breakfast was observed with digestive cartridge use.”

Observational Studies

In 2018, Stevens et. al. conducted the Absorption and Safety with Sustained use of RELiZORB Evaluation (ASSURE) Study in patients with cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI) receiving enteral feeding which was designed to evaluate safety, tolerability, and efficacy of sustained use of RELiZORB over 90-days using enteral nutrition (EN) as part of their regular nutrition regimen. The ASSURE trial was a prospective, single-arm, multicenter, open-label study (ClinicalTrials.gov Identifier: NCT02750501). The study was conducted between July 20, 2016, and March 30, 2017. Patients were eligible for the study if they were ≥4 years of age, had a confirmed diagnosis of CF, a documented history of EPI, were taking enteral formula a minimum of 4 times per week, were using PERT, and were consuming an unrestricted fat diet. The omega-3 index was utilized in this study provided a measure of tissue DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid levels) which is a reliable estimation of LCPUFA (long-chain polyunsaturated fatty acids) absorption in patients with CF. The omega-3 index has the advantage of being a measure of long-term tissue LCPUFA concentrations, being unchanged by patient fasting or fed state, and being easily measured through blood collection. Forty-four patients were enrolled as participants in the study, 5 patients discontinued before the RELiZORB treatment period Day 0), 39 used RELiZORB at least 36 patients completed the study. The mean age range of the 39 participants ranged in age from 5 to 33 years, had a mean duration of enteral tube feeding of 6.2 years (range 0.7-17.5 years), a mean BMI of 17.7 kg/m², and 9 (23.1%) had CF related diabetes. Each feeding delivered a mean (SD) volume of 756 (186) mL at a rate of 120 (77) mL/h, and 5.8 PERT (3.1) capsules were used per EN feeding. Over the course of the 90-day experimental treatment period, participants used RELiZORB for a mean (SD) of 68.4 (18.43) days with a mean (SD) days per week of enteral tube feedings of 5.3 (1.2) days and a mean (SD) formula volume per day of 755.9 (145.16) mL. The omega-3 index increased from a baseline value of 4.4%, which was below the target range of 8%, to 8.4% at 60 days and 9.4% at 90 days (P < 0.001 for each increase from baseline to 60 and 90 days). The magnitude and significance of omega-3 index increases were similar in the 2

younger age groups (≤ 12 years, 13–18 years) to the overall findings, but in adults (≥ 19 years) the differences were not statistically significant at day 60 ($P = 0.051$), likely because of the small sample size ($n = 5$). In the RELiZORB treatment period at least 1 adverse event was reported by 29 (74%) of patients with greatest incidence related to respiratory issues (46%) which included decreased forced expiratory volume and pulmonary function tests. Limitations of this study include small sample size, was open label and was not intended to compare outcomes between participants who did not use RELiZORB, dietary intake was not recorded limiting the ability to assess whether oral caloric intake was adequate to lead to weight gain and the study may not have been long enough to observe an increase in weight or BMI for patients in a relatively fat-starved condition. The authors concluded this study establishes the safety and tolerability of RELiZORB and shows its potential to normalize fat absorption, improve symptoms commonly associated with fat absorption and enhance nutritional status in patients with CF receiving EN feedings.”

In 2021 Sathe et. al. in an industry sponsored study by Alcresta Therapeutics (RELiZORB; Alcresta Therapeutics, Newton, MA) who provided the product to patients who participated in the program evaluated the effectiveness of in-line immobilized lipase cartridge (RELiZORB) in enterally fed patients with cystic fibrosis (CF). Initially the program was intended to run for 90 days, but eligibility was extended for 12 months. Eligibility criteria included diagnosis of CF, utilized enteral nutrition via gastrostomy tube because of poor nutritional status related to CF and had been receiving oral PERTs for enteral feeding before starting RELiZORB. Baseline patient referral data included a unique external subject ID, number of shipments/boxes, disease/diagnosis code, date of birth, sex, prescriber, date of first and last digestive cartridge shipment, formula volume (mL/hour), height (cm), weight (kg), and body mass index (BMI, kg/m²) at date of enrollment. Data on height, weight, and BMI at all subsequent follow-up intervals was collected. To be included in the analyses patients had to receive ≥ 6 months of the RELiZORB. In order to compare growth in CF patients using enteral feedings in the absence of RELiZORB data was utilized from the CF Foundation Patient Registry (CFFPR) during the calendar year 2014, before RELiZORB was available (CFFPR-2014). The majority of these patients were noted to be pancreatic insufficient (PI) based on documentation of PERT use. Between the start of the program in June 2018 and its termination October 2019, 178 patients were enrolled. The 100 participants (49% girls) who had at least 1 anthropometric measurement available at baseline and subsequent measurements at 6 and 12 months of use were included in the analysis and 95% of these participants were < 18 years of age and in their active growth years. There were significant improvements in height and weight z-scores in the first 6 months of use ($P < 0.001$ and $P = 0.002$, respectively) and over 12 months of use ($P = 0.036$; $P = 0.017$, respectively). The rate of increase in anthropometric measures for patients 2 to 18 years of age was more pronounced in the first 6 months of RELiZORB use (height z-score LS mean [SE]: 0.17 (0.058), $P = 0.005$; weight: 0.20 [0.079], $P = 0.014$) and stabilized or had modest gains from 6 to 12 months of use (height: -0.05 [0.45]; weight -0.01 [0.077] neither statistically significant). These findings were supported in the comparison to the historical control group. Compared with 1868 patients in the CFFPR-2014 group (mean age=10.24 years), the ILC patients (mean age=9.8 years) had statistically significant increases in overall height and weight z-score at 6 months (mean treatment difference =0.20 and 0.24, $P = 0.001$ and 0.048, respectively). At 12-months parity was seen for all anthropometric parameters. In 88 patients 2-18 years of age there was a trend toward significant increase in BMI z- scores ($P = 0.059$). This was not a traditional research study but rather information reported as part of a program evaluation and there were limitations of interpretation of data. The data was real-world use of RELiZORB and no control group was recruited. Also, there was no information regarding those individuals who may have started on CFTR modulator drugs (i.e., ivacaftor) during the observation period which has demonstrated to increase weight and height. The authors concluded, “In summary, this program evaluation demonstrates significant long-term clinical growth improvements in people with CF who use an ILC (immobilized lipase cartridge) to enable digestion of enteral feedings. Future studies providing prospective case-controlled comparisons of the benefits of ILC in enterally fed patients with CF would add to the current literature.”

In 2024, Shrivastava et al completed a retrospective chart review on 29 patients with cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI) receiving supplemental tube feedings utilizing in-line lipase cartridge RELiZORB for continuous 12 months before and initiation of in-line lipase cartridge. Anthropometrics were evaluated at 12 and 6 months before and 6 and 12 months after initiation of RELiZORB. To assess whether each outcome variable of interest (i.e., weight z score, height z score, or BMI z score) changed over time. The z scores were based on comparison to the World Health Organization Growth Chart for patients aged 0–2 years and the Centers for Disease Control and Prevention Growth Chart for patients aged 2–17 years. Height z scores slightly decreased from 12 months before to 6 months before initiation of in-line lipase cartridge (adjusted mean: from –1.14 to –1.18; adjusted mean difference = –0.0464; $P = 0.5139$) and then significantly increased at 6 months after (from –1.18 to –0.93; adjusted mean difference = 0.2540; 95% CI = [0.0487–0.4592]; $P = 0.0153$) and maintained at 12 months after (–0.92, $P = 0.034$). Trends in the weight and BMI z scores were not statistically significant and are detailed as follows: Weight z scores also slightly decreased from 12 months before to 6 months before initiation of in-line lipase cartridge (adjusted mean: from –1.09 to –1.13; adjusted mean difference = –0.0364; $P = 0.7159$) and then increased at 6 months after (from –1.13 to –1.04, adjusted mean difference = 0.0842 ; $P = 0.4047$) and at 12 months after (–0.93, $P = 0.0908$). BMI z scores showed a similar nonstatistically significant changeover the course of 12 months after initiation of in-line lipase cartridge. Limitations of this study include small sample size from a single center. The authors concluded “Study results showed that an in-line lipase cartridge improved weight and height z scores over a 12-month period. The initial decline in the BMI seen at 6 months after initiation of in-line lipase cartridge is likely related to the greater growth in height than in weight on initiation of the device.” They also noted that currently there is no long-term efficacy data for this specific technology and further research should evaluate how the effect of the in-line lipase cartridges on anthropometrics diminishes, persists or further accentuates with ongoing long-term use. Current research has followed patients for 12 months, longer-term follow-up of about 5 years would show whether patients continue to improve along the same growth curve.

Short Bowel Syndrome

As reported by Tsikis et al (2023) and Soden et al (2024), currently clinical trial NCT03530852 is recruiting participants using RELiZORB® in children with short bowel syndrome who are dependent on parenteral nutrition to assess if RELiZORB® may offer a safe alternative to reducing parenteral nutrition dependence and achieving enteral autonomy in pediatric intestinal failure. This study is a 90-day, phase 3, open labeled exploratory study and the completion date is noted as September 30, 2028.

Kinberg et al (2025) in a single-center retrospective study was performed in pediatric patients with short bowel syndrome (SBS) on enteral nutrition (EN) who used immobilized lipase cartridge (ILC) (RELiZORB). Efficacy was measured by changes in parenteral nutrition (PN), EN, growth parameters, and stool output from baseline to post-cartridge use. Thirteen patients were included with a mean age of 10.8 years and 50% were female. The most common etiology of SBS was necrotizing enterocolitis (39%) and 8 (62%) patients were PN dependent. The results of the interim analysis showed a mean duration of 6.8 months, PN calorie and volume decreased in 50%, EN calorie increased in 73%, weight gain in 100%, and improved stool output in 100%. Clogged cartridges were reported in 23% of patients and were resolved with better formula mixing. Two patients discontinued ILC within 2 weeks due to worsening diarrhea. Findings may suggest that ILC may improve fat malabsorption and increase EN tolerance in pediatric SBS patients, however, larger multicenter randomized studies are needed to further evaluate, efficacy, tolerability, and safety of ILC in this population.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Cystic Fibrosis Foundation

In 2023, the Cystic Fibrosis Foundation (CFF) issued a new cystic fibrosis position statement regarding nutritional considerations for a new era that included the following: “For people with cystic fibrosis (pwCF) using enteral tube feeds, using an inline enzyme cartridge with immobilized lipase has been shown to be safe and effective for digesting nutrients and promoting weight gain. This data has become available since publications of the CFF Enteral Feeding Guidelines in 2016.”

American Gastroenterology Association

In 2023, in an updated clinical practice guideline American Gastroenterology Association (AGA) on the epidemiology, evaluation, and management of exocrine pancreatic insufficiency: expert review included the following:

- “Best Practice Advice 1: Exocrine pancreatic insufficiency (EPI) should be suspected in patients with high-risk clinical conditions such as chronic pancreatitis, relapsing acute pancreatitis, pancreatic ductal adenocarcinoma, cystic fibrosis, and previous pancreatic surgery.”
- “Best Practice Advice 11: Once EPI is diagnosed treatment with pancreatic enzyme replacement therapy (PERT) is required. If EPI is left untreated, it will result in complications related to fat malabsorption and malnutrition, having negative impact on quality of life.
 - Currently, all commercially available products are a porcine origin and labeled based on their USP lipase content (Table 3).”

Table 3 U.S. Food and Drug Administration-Approved Formulations of Pancreatic Enzyme Replacement Therapy

Brand	Type	Available Lipase Strengths (USP)
Creon	Enteric-coated microspheres	3,000/6,00/12,000/24,000/36,000
Zenpep	Enteric-coated beads	3,000/5,000/10,000/15,000/20,000/25,000/40,000
Pancreaze	Enteric-coated microtablets	2,600/4,200/10,500/16,800/21,000/37,00
Pertzye	Enteric-coated microspheres	4,000/8,000/16,000/24,000
Vlokace	Non-enteric coated tablets	10,444/20,880
Relizorb	In-line lipase cartridge	For enteral feedings formulas

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT	None	
HCPCS		
	B4100	Food thickener, administered orally, per oz
	B4102	Enteral formula, for adults, used to replace fluids and electrolytes (e.g., clear liquids), 500 ml = 1 unit
	B4103	Enteral formula, for pediatrics, used to replace fluids and electrolytes (e.g., clear liquids), 500 ml = 1 unit
	B4104	Additive for enteral formula (e.g., fiber)
	B4105	In-line cartridge containing digestive enzyme (s) for enteral feeding, each
	B4149	Enteral formula, manufactured blenderized natural foods with intact nutrients, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4150	Enteral formula, nutritionally complete with intact nutrients, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4152	Enteral formula, nutritionally complete, calorically dense (equal to or greater than 1.5 kcal/ml) with intact nutrients, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4153	Enteral formula, nutritionally complete, hydrolyzed proteins (amino acids and peptide chain), includes fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit

Codes	Number	Description
	B4154	Enteral formula, nutritionally complete, for special metabolic needs, excludes inherited disease of metabolism, includes altered composition of proteins, fats, carbohydrates, vitamins and/or minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4155	Enteral formula, nutritionally incomplete/modular nutrients, includes specific nutrients, carbohydrates (e.g., glucose polymers), proteins/amino acids (e.g., glutamine, arginine), fat (e.g., medium chain triglycerides) or combination, administered through an enteral feeding tube, 100 calories = 1 unit
	B4157	Enteral formula, nutritionally complete, for special metabolic needs for inherited disease of metabolism, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4158	Enteral formula, for pediatrics, nutritionally complete with intact nutrients, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit
	B4159	Enteral formula, for pediatrics, nutritionally complete soy based with intact nutrients, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit
	B4160	Enteral formula, for pediatrics, nutritionally complete calorically dense (equal to or greater than 0.7 kcal/ml) with intact nutrients, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4161	Enteral formula, for pediatrics, hydrolyzed/amino acids, and peptide chain proteins, includes fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
	B4162	Enteral formula, for pediatrics, special metabolic needs for inherited disease of metabolism, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
Type of Service	Durable Medical Equipment	
Place of Service	Home/Outpatient	

POLICY HISTORY

Date	Action	Action
May 2026	Annual Review	Policy Revised
May 2025	Annual Review	Policy Revised
May 2024	Annual Review	Policy Revised
May 2023	Annual Review	Policy Revised
April 2022	Annual Review	Policy Revised
April 2021	Annual Review	Policy Revised
April 2020	Annual Review	Policy Revised
April 2019	Annual Review	Policy Revised
June 2018	Interim Review	Policy Revised
April 2018	Annual Review	Policy Renewed
April 2017	Annual Review	Policy Renewed
April 2016	Annual Review	Policy Reinstated
August 2013	Annual Review	Policy Retired
September 2012	Annual Review	Policy Renewed
September 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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