Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: RELiZORB

Description/Background

RELiZORB is a single-use, point-of-care digestive enzyme cartridge that can be connected in-line with enteral feeding paths, for use in individuals who do not secrete sufficient levels of the pancreatic digestive enzyme, lipase, which breaks down ingested fats for easier digestion and absorption. The RELiZORB system is designed to mimic the normal function of lipase release. The RELiZORB cartridge contains the digestive enzyme lipase. As 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.

Regulatory Status

The Food and Drug Administration (FDA) cleared RELiZORB through the Premarket Notification process. In 2017 RELiZORB received clearance for use in pediatric patients (ages 5 years and above) and adult patients to hydrolyze fats in enteral formula. A 2023 update expanded the FDA approval to include pediatrics ages 2 and above.

Product code: PLQ

Medical Policy Statement

The Food and Drug Administration approved digestive enzyme cartridges (e.g. Relizorb^{TM}) have been established. They may be considered a useful therapeutic option for individuals who meet specific selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusion:
Digestive enzyme cartridges (e.g. Relizorb™) when ALL the following are met:

- Age 2 and above
- Criteria for Enteral Nutrition has been met
- Used with enteral tube feeding for the treatment of pancreatic insufficiency due to cystic fibrosis
- There is documented failure of pancreatic enzyme replacement therapy (i.e. malnutrition, poor growth [pediatric], bloating, cramping, gassiness, diarrhea, fatty stools, nausea, vomiting constipation, abdominal discomfort).
- Failure to achieve or maintain target body mass index (BMI)
- Overnight enteral feeding with lipase delivery throughout the feeding is required to meet caloric and nutritional demands.

Exclusions:

- Use of in-line digestive enzymes cartridges not meeting the criteria above

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

B4105

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Relizorb is proposed to be useful for people who have pancreatic insufficiency and need enteral nutrition (e.g. individuals with cystic fibrosis [CF]). Relizorb is a cartridge, which contains the pancreatic enzyme lipase. The cartridge connects to the enteral tube feeding system and is FDA approved for individuals who have difficulty digesting and absorbing fats. Manufacturers declare that the cartridge enzymes convert 90% of the fat in the enteral nutrition to fatty acids and mono-glycerides.

Presently, individuals who cannot digest food normally are prescribed a pancrelipase medication, which contains lipases, proteases and amylases for fat conversion. There is limited peer-reviewed, published literature available regarding the use of in-line digestive enzyme cartridges with enteral feeding. Of note, both clinical trials were industry-funded studies. There

was also overlap of authors in the retrieved abstracts and they contained authors who were affiliated with the manufacturer.

Schwarzberg et al (2019) released an article advocating for insurance reimbursement for the immobilized lipase cartridge (ILC). The intended population was the cystic fibrosis community with the goal of invoking support of ILC use to assist with nutrient absorption for tube-fed patients. ILC was evaluated as a device and not as a drug, thus randomized, placebo-controlled trials were not completed. Four small (< 40 subjects) retrospective, single-center chart reviews indicated that use of the ILC supported weight gain. During the 3 years the ILC has been available, >725,000 cartridges have been used by nearly 2000 patients. Weight gain was used as relevant clinical proof that the ILC improved micronutrient absorption. Despite widespread usage, there have been no medical device reports or adverse events reported to the U.S. Food and Drug Administration (FDA) and there have been no device recalls. The authors concluded that while additional data needs to be generated, use of an immobilized lipase cartridge to support enteral feedings is making a positive difference for many individuals with CF and is a rational alternative to the historical but illogical current standard of care. Its use has the potential to improve health for people with CF and its cost may be mitigated by the real possibility of reduced pulmonary decline in a well-nourished person with CF.

Katkin et al (2024; up-to-date) address pancreatic insufficiency as the most common gastrointestinal complication of cystic fibrosis. The limited available data regarding Relizorb efficacy includes small studies which suggest that Relizorb can help reduce early morning satiety and bloating for some individuals as well as improve fat absorption when compared with the patients baseline pancreatic enzyme replacement therapy regimen.

Sathe et al (2021) evaluated the effectiveness of in-line immobilized lipase cartridges (ILC) in enterally fed patients with cystic fibrosis. Baseline anthropometric data were obtained and subsequent measurements of height, weight, and body mass index were collected at 6 and 12 months (n=100; age 0-45). Over 12 months of use in patients >2 years of age (n=93), there were significant improvements seen in height and weight z-scores with an improvement trend seen in BMI. The frequency of achieving the 50th percentile increased steadily for weight and BMI from baseline to 12 months but not for height. Authors concluded that better growth is possible over standard of care. The association of ILC use with significant improvements in anthropometric parameters over a 12-month period in people with cystic fibrosis demonstrates the effectiveness of ILC as a rational enzyme therapy during enteral feedings.

The Cystic Fibrosis Foundation (CFF) released an article (Schwarzenberg et al 2019) advocating for insurance reimbursement for Relizorb. Rationale quoted the multiple RCTs, which have indicated that ILCs support weight gain. Freedman et al (2017) is a randomized study which used ILC over a 1-week period to determine the safety, tolerability and fat absorption when provided to individuals with CF. Enrolled subjects had been receiving enteral feeding with oral pancreatic enzyme replacement therapy (PERT) supplementation for a mean of 6.6 years and had baseline plasma omega-3 fatty acid concentrations that were well below the range observed in healthy subjects. As one indication of the improved absorption of fat, CF patients who used the ILC had plasma omega-3 fatty acid concentrations come into the range of normal compared to no change in those receiving PERT alone with enteral feedings. Authors concluded that this study provides evidence that the standard of care is sub-optimal with respect to nutrient absorption. The CFF indicated that during the 3 years the ILC has been available, >725,000 cartridges have been used (n=2000 patients). During this time no

medical device reports or adverse events have been reported to the US Food and Drug Administration (FDA) and no device recalls have been instituted.

Stevens et al (2018) evaluated safety, tolerability and improvement of fatty acid status in red blood cell (RBC) membranes (a marker of long-term fatty acid absorption) with an in-line digestive cartridge (Relizorb) that hydrolyzes fat in enteral formula. The Absorption and Safety with Sustained use of Relizorb Evaluation (ASSURE) Study was a prospective, single-arm, multicenter, 90-day open-label (not intended to compare outcomes between participants who did and did not use Relizorb) study in patients with Cystic Fibrosis. Thirty-six subjects who were given overnight enteral nutrition with the use of Relizorb. The primary end-point was change over time in RBC uptake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Gastrointestinal symptoms were collected to evaluate safety and tolerability. Relizorb was not found to be associated with any unanticipated adverse events. Increased RBC levels of DHA+EPA indicated that fat absorption significantly improved. In the ASSURE study, omega-3 FA erythrocyte levels increased with longer-term RELiZORB use, supporting the role of Relizorb in normalizing deficient DHA and EPA levels and maintaining them over longer periods when RELiZORB was utilized with overnight enteral nutrition feeds. Authors concluded that it is not possible to draw definitive conclusions from the current and previous RELiZORB studies about the influence of Relizorb use on changes in patient anthropometric measurements. While weight, BMI z-scores and percentiles were not significantly different from baseline to 90 days, 61% (20/33) patients in the ASSURE study had improvements in weight z scores and percentiles over the course of the study. Because the current study did not measure body tissue composition, it is unknown whether study participants improved their tissue composition without changing body weight or size. It may turn out that nutritional health may be more accurately measured using biomarkers other than the traditional body weight and body mass index.

Abu-El-Haija et al (2018) reported on a consensus statement regarding nutrition in pediatric pancreatic diseases through a joint European Society for Pediatric Gastroenterology, Hepatology and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition working group that performed an evidence-based search of the literature on nutrition in acute pancreatitis, acute recurrent pancreatitis and chronic pancreatitis with a focus in pediatrics. The literature was summarized, quality of evidence reviewed and expert recommendations developed. A consensus of at least 75% was required to approve a recommendation. Authors reported that literature on pediatric pancreatitis is limited. Gaps were noted in the knowledge relating to: optimal nutrition for acute pancreatitis in children; 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 chronic pancreatitis; 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 in acute recurrent pancreatitis, whether in pediatrics or adults. A recommendation was made against routine pancreatic enzyme replacement therapy in children diagnosed with acute recurrent pancreatitis who do not have exocrine pancreatic insufficiency. The lack of information in the literature indicated that most recommendations were expert lead rather than having a strong evidence base. Further research was recommended to address the aforementioned gaps. The authors concluded that early enteral nutrition with a return to a normal-fat diet appears most optimal for children along the spectrum of acute pancreatitis, acute recurrent pancreatitis and cerebral palsy.

Well-designed clinical trials supporting the efficacy of in-line digestive enzyme cartridges for the treatment of pancreatic insufficiency caused by multiple conditions including, but not limited to: celiac disease, chronic pancreatitis, Crohn's disease, diabetes mellitus, gastrectomy, pancreatic cancer, pancreatic duct obstruction, small bowel resection, and short bowel syndrome are lacking.

Summary:
Some studies suggest that in line digestive enzyme cartridges may be a therapeutic option for individuals with pancreatic insufficiency due to cystic fibrosis. In-line cartridges used for emulsion of fat during enteral feeding may demonstrate equivalent or improved clinical outcomes when compared to conventional methods for CF patients. There is insufficient evidence to support the effectiveness of digestive enzyme cartridges for the treatment of pancreatic insufficiency caused by other conditions.

Supplemental Information

POSITION STATEMENTS

Cystic Fibrosis Foundation
The CF Foundation acknowledges that the majority of individuals with CF are pancreatic insufficient therefore the provision of safe and effective pancreatic enzyme replacement is a key therapy in CF. However, the CF Foundation does not recommend for or against a specific method of providing pancreatic enzyme therapy during enteral tube feedings in individuals with CF. In the absence of clinical trials, no specific recommendations can be made regarding the use of pancreatic enzyme therapy with enteral feedings.

North American Society of Pediatric Gastroenterology, Hepatology and Nutrition Pancreas Committee
The NASPGHNP committee discusses pancreatic enzyme replacement therapy (PERT) in children with acute and chronic pancreatitis who have steatorrhea, poor growth and/or nutritional deficiencies. Authors concluded that a review of the literature revealed lack of information and data in the area of nutrition in pediatric pancreatology—a limitation that led to most recommendations being expert recommendations rather than strongly evidence-based.

Government Regulations
National:
No National Determination was noted for Relizorb.

Local:

Local Coverage Determination: Enteral Nutrition (L38955); Effective 9/5/21; For services performed on or after 1/1/24

Enteral nutrition is covered for a beneficiary who requires feedings via an enteral access device to provide sufficient nutrients to maintain weight and strength commensurate with the beneficiary's overall health status and has a permanent:

A. full or partial non-function or disease of the structures that normally permit food to reach the small bowel; OR,
B. disease that impairs digestion and/or absorption of an oral diet, directly or indirectly, by the small bowel.

Typical examples of conditions associated with impaired digestion and/or absorption of an oral diet by the small bowel that may qualify for coverage include inflammatory bowel disease, surgical resection of small bowel, cystic fibrosis, chronic pancreatitis, and advanced liver disease (not all inclusive).

If the coverage requirements for enteral nutrition are met, medically necessary nutrients, administration supplies, and equipment are covered.

In-line digestive enzyme cartridges (B4105) are reasonable and necessary for beneficiaries who:
A. meet the coverage criteria for enteral nutrition; AND,
B. have a diagnosis of Exocrine Pancreatic Insufficiency (EPI) (refer to the Group 1 Codes in the LCD-related Policy Article for applicable diagnoses).

More than 2 in-line digestive enzyme cartridges (B4105) per day will be denied as not reasonable and necessary.

Enteral feeding supply kit allowances (B4034, B4035, B4036 and B4148), are all-inclusive, with the exception of B4105 in-line digestive enzyme cartridge. Separate billing for any item including an item using a specific HCPCS code, if one exists, or B9998 (ENTERAL SUPPLIES, NOT OTHERWISE CLASSIFIED) will be denied as unbundling.

LCA: Enteral Nutrition – Policy Article (A58833); Revision Effective 10/1//23

Group 1

Group 1 Paragraph
The presence of an ICD-10 code listed in this section is not sufficient by itself to assure coverage. Refer to the section on "Coverage Indications, Limitations, and/or Medical Necessity" for other coverage criteria and payment information.

For HCPCS code B4105:

Group 1 codes:

Code	Description
E08.69	Diabetes mellitus due to underlying condition with other specified complication
E09.69	Drug or chemical induced diabetes mellitus with other specified complication
E10.69	Type 1 diabetes mellitus with other specified complication
E11.69	Type 2 diabetes mellitus with other specified complication
E13.69	Other specified diabetes mellitus with other specified complication
E84.19	Cystic fibrosis with other intestinal manifestations
E84.8	Cystic fibrosis with other manifestations
E84.9	Cystic fibrosis, unspecified
K50.018	Crohn's disease of small intestine with other complication
K50.118	Crohn's disease of large intestine with other complication
K50.818	Crohn's disease of both small and large intestine with other complication

K50.918	Crohn's disease, unspecified, with other complication
K51.818	Other ulcerative colitis with other complication
K51.918	Ulcerative colitis, unspecified with other complication
K86.0	Alcohol-induced chronic pancreatitis
K86.1	Other chronic pancreatitis
K86.81	Exocrine pancreatic insufficiency
K90.0	Celiac disease
Q45.3	Other congenital malformations of pancreas and pancreatic duct
Z90.410	Acquired total absence of pancreas
Z90.411	Acquired partial absence of pancreas

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Enteral Nutrition
Nutritional Counseling – BCN only

References

1. Abu-El-Haija, M., Uc, A., et al. "Nutritional Considerations in Pediatric Pancreatitis: A Position Paper from the NASPHAN Pancreas Committee and ESPHAN Cystic Fibrosis/Pancreas Working Group. *JPGN* 2018;67:131-143.
2. Alcresta Therapeutics. Relizorb. 2022. https://www.relizorb.com/hcp. Accessed October 2, 2024.
3. Centers for Medicare & Medicaid Services. Local Coverage Article: Enteral Nutrition – Policy Article (A58833); September 5, 2021; https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=58833&ver=17&bc=0. Accessed October 2, 2024.
4. Centers for Medicare & Medicaid Services. Local Coverage Determination: Enteral Nutrition (L38955); September 5, 2021; https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38955&ver=24&keyword=Enteral%20Nutrition&keywordType=all&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed October 2, 2024.
5. Cystic Fibrosis Foundation. Pancreatic Enzymes Clinical Care Guidelines. 2019. https://www.cff.org/Care/Clinical-Care-Guidelines/Nutrition-and-GI-Clinical-Care-Guidelines/Pancreatic-Enzymes-Clinical-Care-Guidelines/. Accessed October 2, 2024.
6. Freeman AJ, Maqbool A, Bellin M, et al. Medical management of chronic pancreatitis in children: a position paper by the North American society of pediatric gastroenterology, hepatology and nutrition pancreas committee. *J Pediotr Gostroenterol Nutr*. 2021;72: 324-340.
7. Freedman S, Orenstein D, Black P, et al. Increased fat absorption from enteral formula through an in-line digestive cartridge in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2017;65(1):97–101.
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9. Schwarzenberg SG, Borowitz D, et al. “Challenging Barriers to an Option for Improved Provision of Enteral Nutrition.” *Journal of CF* 2019;18:447-449
10. Schwarzenberg SG, Dorsey J. “Pancreatic Enzymes Clinical Care Guidelines.” Bethesda, MD: Cystic Fibrosis Foundation; 2013. www.cff.org/Care/Clinical-Care-Guidelines/Nutrition-and-GI-Clinical-Care-Guidelines/Pancreatic-Enzymes-Clinical-Care-Guidelines. Accessed November 30, 2022.
11. Schwarzenberg SJ, Borowitz D; 20 gastroenterologists, 23 CF physicians, 17 CF dietitians and 1 PharmD. Challenging barriers to an option for improved provision of enteral nutrition. *J Cyst Fibros*. 2019 Jul;18(4):447-449. PMID: 31230797.
12. Schwarzenberg SJ, Hempstead SE, McDonald CM, et al. Enteral tube feeding for Individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-Informed guidelines. 2016;15(6):724-735.
13. Stevens J, Wyatt C, et al. “Absorption and safety with sustained use of Relizorb evaluation (ASSURE) study in patients with cystic fibrosis receiving enteral feeding.” *JPGN* 2018;67:527-532.
14. U. S. Food and Drug Administration (FDA), Class II Medical Devices, “RELiZORB,” July 12, 2017. https://www.accessdata.fda.gov/cdrh_docs/pdf16/k163057.pdf. Accessed October 2, 2024.
15. U. S. Food and Drug Administration (FDA), Class II Medical Devices, “RELiZORB,” K231156. August 30, 2023. https://www.accessdata.fda.gov/cdrh_docs/pdf23/K231156.pdf. Accessed October 2, 2024

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 10/2/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/19	2/19/19		Joint policy established
5/1/20	2/18/20		Routine maintenance
3/1/21	12/15/20		Routine maintenance
3/1/22	12/14/21		• Routine maintenance • Updated Medicare LCD and article
3/1/23	12/20/22		• Relizorb changed to EST • Rationale, references and supplemental information updated
3/1/24	12/19/23		• Routine maintenance (slp) • Vendor managed: N/A
3/1/25	12/17/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: RELIZORB

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria applies
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*