**DISCLAIMER**

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

**RECOMMENDATION**

This policy addresses the cartridge device (e.g. RELiZORB™ immobilized lipase cartridge) to deliver digestive enzymes to enteral formula. This cartridge device does not meet Molina Healthcare's coverage criteria and is considered not medically necessary for all indications.

**LIMITATIONS/EXCLUSIONS:** The use of Enteral Feeding In-Line Cartridge (EFIC) [e.g. RELiZORB™ immobilized lipase cartridge] to deliver digestive enzymes to enteral formula is considered not medically necessary, including but not limited to, patients receiving enteral tube feedings due to insufficient evidence in the peer-reviewed literature documenting the clinical utility and clinical validity of this type of device.

Molina Healthcare will be continue to evaluate and update this policy as relevant clinical evidence becomes available to determine whether cartridge device (e.g. RELiZORB™ immobilized lipase cartridge) to deliver digestive enzymes to enteral formula provides the safety and/or impact on health outcomes or patient management for the use of the device.

**SUMMARY OF EVIDENCE/POSITION**

RELiZORB (Alcresta Pharmaceuticals) is the first digestive enzyme cartridge that was created and designed to mimic the normal pancreatic function by breaking down fats in the enteral tube feeding formula. Relizorb received de novo FDA approval for adult patients who have fat malabsorption.

RELiZORB™ (developed by Alcresta Therapeutics, Inc.) is a first-of-its kind digestive enzyme cartridge developed to mimic the function of the digestive enzyme lipase that is normally secreted by the pancreas. RELiZORB™, utilizing proprietary enzyme immobilization technology, is designed for use with adults on enteral tube feedings who have trouble breaking down and absorbing fats. [NOTE: Not all enteral tube feed formulas are compatible with Relizorb.]
The active ingredient in RELiZORB™ is the digestive enzyme lipase which attaches to polymeric carriers, together called iLipase®. RELiZORB™ is a single-use cartridge that connects in-line with existing enteral pump feed sets and pump extension sets. As the enteral tube feeding formula passes through RELiZORB™, it makes contact with the iLipase® and the fat in the formula is broken down to its absorbable form (fatty acids and monoglycerides) prior to ingestion. The iLipase® remains in the cartridge and does not become part of what is ingested. RELiZORB™ has been shown in some studies to break down up to 90 percent of fats in most enteral feeding tube formulas, including the most difficult to breakdown long-chain polyunsaturated fatty acids which are critical for growth and development.

As the enteral tube feeding formula passes through Relizorb, it makes contact with the iLipase and the fat in the formula is broken down to its absorbable form (fatty acids and monoglycerides) prior to ingestion. The iLipase remains in the cartridge and does not become part of what is ingested. Relizorb has been shown to break down 90% of fats in most enteral feeding tube formulas, including the most difficult to breakdown long-chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and arachidonic acid (AA), which are critical for growth and development.

MECHANISM OF ACTION  RELiZORB is designed to hydrolyze (digest) fats contained in enteral formulas. RELiZORB contains the digestive enzyme lipase bound to beads (iLipase). By hydrolyzing fats from enteral formulas, RELiZORB allows for the delivery of absorbable fatty acids and monoglycerides. Like human pancreatic lipase, the lipase in RELiZORB has sn-1, sn-3 selectivity in the hydrolysis of triglyceride fats. When enteral formula flows through RELiZORB, the lipase bound to the beads hydrolyzes fats in their triglyceride form, including important long-chain polyunsaturated fats (LCPUFAs), releasing omega-3 [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] and omega-6 (linoleic acid (LA) and arachidonic acid (AA)) into their absorbable fatty acid and monoglyceride forms. The iLipase is retained within the RELiZORB cartridge by two filters as enteral formula flows through RELiZORB.

SUMMARY OF EVIDENCE

The FDA approval for Relizorb™, a digestive enzyme cartridge, was based on well-established pre-clinical porcine models that mimics the inability to digest and absorb fat. No human studies were identified with the use of RELiZORB. The FDA approval is based on well-established pre-clinical porcine models that mimic the inability to digest and absorb fat.

A search of ClinicalTrials.gov, identified one randomized, double-blind, crossover trial with an open-label safety evaluation period. This clinical trial enrolled 34 subjects (pediatric and adult) and 33 completed the study. Subjects with confirmed exocrine pancreatic insufficiency used an enteral feeding digestive enzyme cartridge (Relizorb™) connected to enteral pump set. The objective of this study was to evaluate the safety, tolerability, and fat absorption of a new in-line digestive cartridge (Relizorb™) that hydrolyzes fat in enteral formula provided to patients with cystic fibrosis (CF). The authors concluded that the use of this in-line digestive cartridge was safe and well tolerated, and resulted in significantly increased levels of plasma omega-3 FA used with enteral formula, suggesting an overall increased fat absorption. This study is supported by the product manufacturer, Alcresta Pharmaceuticals (NCT02598128). The authors discussed the major limitations of this study which include: small study sample size and a longer-term study is currently ongoing to assess the effects of sustained digestive cartridge use, particularly without concomitant pancreatic enzyme replacement therapy (PERT) use.

There is insufficient published literature for the use of digestive enzyme cartridges. Larger randomized controlled trials are needed to support the safety, efficacy, and the health impact on humans.
There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management for the use of the RELiZORB device at this time:

- Although a 33-patient clinical trial was conducted across several locations in the United States, there is a lack of human subjects on a large scale (ClinicalTrials.gov, 2016).
- There is no evidence in peer-reviewed, randomized, placebo controlled medical/scientific literature supporting the therapeutic efficacy and/or safety of RELiZORB over current therapy or documentation of the clinical utility and clinical validity of this type of device.
- RELiZORB lacks sufficient evidence demonstrating that RELiZORB offers superior outcomes to established therapeutic alternatives.
- There is no adequate and conclusive evidence that RELiZORB therapy is the standard of care within Clinical Practice Guidelines.

For individuals who have pancreatic insufficiency and who receive RELiZORB as an adjunct to maintenance enteral feeding, the evidence consists of multicenter crossover trials. The long-term efficacy of RELiZORB has not been established at this time. RELiZORB has not been evaluated in pediatric populations. Further corroboration of these results is needed in high-quality RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

**CLINICAL PRACTICE GUIDELINES (As of this writing in December 2017)**

National Guideline Clearinghouse search of the database did not locate any evidence-based clinical practice guidelines for this technology. The below guidance article was located during a PubMed search and specifically mentions RELiZORB. Of note, Alcresta Therapeutics sponsored this article. (Reference: Hayes 2017; Search and Summary, published August 31, 2017)

**HAYES**

A comprehensive Health Technology Assessment had not been conducted and a Hayes Directory report addressing the Enteral Feeding In-Line Cartridge (EFIC), or digestive enzymes added to enteral formula via a cartridge device attached to the tubing used for enteral feeding was not available (as of this writing in December 2017).

A ‘Search and Summary’ report (based on a review of abstracts; no full-text articles were retrieved and a comprehensive Health Technology Assessment was not conducted) regarding the use of Relizorb for patients receiving enteral feedings is available and concludes: There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management regarding the use of RELiZORB. [Hayes 2017; Search and Summary, published August 31, 2017]

**Centers for Medicare & Medicaid Services (CMS)**

No National Coverage Determination (NCD) for RELiZORB was identified on the CMS website. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers (as of this writing in December 2017).

**Device Classification Name:** Enzyme Packed Cartridge (Hydrolize fats in enteral formula)
FDA INDICATIONS

RELiZORB is indicated for use in pediatric patients (ages 5 years and above) and adult patients to hydrolyze fats in enteral formula.

Available as: Relizorb is comprised of a clear cylindrical, plastic cartridge with a single inlet connection port and a single outlet connection port. Inside the cartridge, there are small white beads. The digestive enzyme, lipase, is covalently bound to the small white beads. The lipase-bead complex, iLipase (immobilized lipase), is retained within the cartridge during use by filters on both ends of the cartridge. The fat in enteral formulas is hydrolyzed as it comes in contact with iLipase as the formula passes through the cartridge.

FDA Approved: November 20, 2015
Alcresta Pharmaceuticals received †de novo clearance from the FDA on November 20, 2015 for RELiZORB™, as an enzyme packed cartridge. Section 510 (k) premarket approval was granted June 30, 2016. FDA concludes that this device should be classified into class II.

†De Novo FDA Classification: The FDA Modernization Act of 1997 (FDAMA) added the de novo classification option, which is also known as Evaluation of Automatic Class III Designation. This option provides an alternate pathway to classify novel devices of low-to-moderate risk. Devices that are classified through the de novo process may be marketed and used for future 510(k) submissions. Reference: FDA De Novo classification: Relizorb™. Available at: http://www.accessdata.fda.gov. Accessed December 2017

COVERAGE EXCLUSIONS

Digestive Enzyme Cartridges for Enteral Tube Feedings†
Digestive enzymes added to enteral formula via a cartridge device attached to the tubing used for enteral feeding (e.g., RELiZORB™ immobilized lipase cartridge) are considered not medically necessary for all indications, including but not limited to, patients receiving enteral tube feedings. This coverage policy is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

†Digestive Enzyme Cartridge for Enteral Tube Feedings is defined as a ‘device designed to mimic the normal pancreatic function by breaking down fats in enteral tube feeding formula. By breaking down these fats from enteral tube feeding formulas prior to ingestion, more calories from fatty acids and monoglycerides and fat-soluble vitamins are expected to be absorbed in patients who are partially or completely unable to breakdown (hydrolysis) and absorb fats. Fat malabsorption is most common in individuals who cannot produce adequate amounts of digestive enzymes because of compromised pancreatic function, but changes in gastric, duodenal, and liver physiology can also dramatically impact malabsorption related to compromised fat absorption. In these individuals, incomplete break down of fats can result in increased gastrointestinal symptoms and malnutrition, and can adversely affect a patient’s ability to maintain or gain weight and maintain normal development and overall health.’

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

*FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.
SUMMARY OF EVIDENCE/POSITION

CLINICAL LITERATURE
A Hayes Search and Summary (Hayes, 2017) search of the literature yielded 2 abstracts, including 1 randomized crossover trial (n=33) and 1 review article. It is noted that both were industry-funded studies and there was also overlap of authors and some of the authors were affiliated with the manufacturer.

Randomized Crossover Trial (n=33)
Safety, Tolerability and Fat Absorption Using Enteral Feeding In-line Enzyme Cartridge (Relizorb) (Freedman et al., 2017) www.clinicaltrials.gov [Trial number: NCT02598128]

The major limitation in this study is that the study sample size is small. Only 1 feeding through digestive cartridge was, however, used to measure its effect on fat absorption, and only 7 days of digestive cartridge use were used to measure its safety. A longer-term study is currently ongoing to assess the effects of sustained digestive cartridge use, particularly without concomitant pancreatic enzyme replacement therapy (PERT) use.

Study to Evaluate Safety, Tolerability and Fat Absorption Using a Novel Enteral Feeding In-line Digestive Enzyme Cartridge (RELIZORB) in Patients with Cystic Fibrosis Receiving Enteral Feeding

The safety and efficacy of RELiZORB was assessed in a multicenter, prospective, randomized, double-blind, placebo controlled, cross-over study, conducted in 33 patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). Patients aged 4 to 45 years with CF associated EPI, receiving supplemental enteral nutrition (EN) at least four times a week, and using PERT, were eligible for study inclusion. Exclusion criteria included uncontrolled diabetes mellitus, signs and symptoms of liver cirrhosis, portal hypertension, and significant liver disease, history of fibrosing colonopathy or recurring distal intestinal obstructive syndrome.

Thirty-three patients completed the study in the intent-to-treat population (ITT). One patient exited the study due to a pulmonary exacerbation. The ITT population ranged from 5 to 34 years of age, with a mean age of 14.5 years, mean BMI (kg/m2) of 17.5 and mean weight of 41.8 (kg). Of the 33 patients, 14 were between ages 5 and 12, 16 were between ages 13 and 21, and 3 were between 22 to 34 years of age. Twenty patients were male and thirteen were female. Patients enrolled in the study had received enteral nutrition for an average of 6.6 years; the average age of initiation of enteral nutrition was approximately 8 years. Patients self-administered an average of 8-9 PERT capsules (range 2 to 21) with their overnight enteral feeding. There were 12 subjects with a diagnosis of cystic fibrosis-related diabetes (CFRD).

The absorption of fat was calculated by assessing changes in plasma concentrations over 24 hours of physiologically relevant long-chain polyunsaturated fatty acids (LCPUFAs), such as omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA and EPA are not only sources of energy, but are also essential components of cell membranes, and are integral in maintaining normal development and overall health. Changes in fatty acid plasma concentrations of physiologically relevant LCPUFA omega-3 fats such as DHA and EPA were assessed over 24 hours, reflecting the uptake of fat in enteral formula as a result of using RELiZORB with enteral feeding.

Results of this study indicate that RELiZORB use was safe and well tolerated with a lower frequency and severity of gastrointestinal symptoms as compared to current treatment. RELiZORB use with enteral formula also resulted in a 2.8 fold statistically significant (p<0.001) increase in DHA and EPA fatty acids. Adverse effects were noted to be headache, effecting 2/33 or (6.06%) of the participants. No limitations or caveats were noted. Absorption increased regardless of age. RELiZORB use was also associated with a greater preservation of appetite as compared to current treatment practice.

Patients with exocrine pancreatic insufficiency (EPI) have suboptimal secretion of pancreatic digestive enzymes and experience a range of clinical symptoms related to the malabsorption of fat. In patients with EPI unable to meet their nutritional requirements, enteral nutrition (EN) support is used to augment nutritional status. In addition to protein and carbohydrate, EN formulas contain fats as a calorie source, as well as vitamins and minerals to help prevent nutritional deficiencies related to malabsorption. Semielemental enteral nutrition formulas are advantageous as they contain hydrolyzed protein, shorter chain carbohydrates, and may contain medium chain triglycerides as a fat source. However, severely pancreatic insufficient patients may be unable to absorb complex long-chain triglycerides provided by EN formulas due to insufficient pancreatic lipase; replacement pancreatic enzyme products are recommended for these patients. Currently, none of the FDA-approved pancreatic enzyme replacement therapy (PERT) products are indicated for use in patients receiving enteral nutrition and administration of enzymes by mixing into enteral nutrition formula is not supported by guidelines as this route is associated with risks. RELiZORB (immobilized lipase) is a novel in-line digestive cartridge that has been designed to address the unmet need for PERT in patients receiving enteral nutrition. RELiZORB efficacy and compatibility with a range of commercially available polymeric and semielemental formulas with varying nutrient, caloric content, and triglyceride chain lengths have been demonstrated. In most formulas, RELiZORB efficiently hydrolyzed greater than 90% of fats within the formula into absorbable fatty acids and monoglycerides.


Absorption and Safety with Sustained Use of Relizorb Evaluation Study (ASSURE) (**This study has been completed.**) Trial number: NCT02750501

In 2016, the manufacturer, Alcresta, initiated the ASSURE study, a multi-center, open label study to evaluate the safety, tolerability and fat absorption of sustained Relizorb (immobilized lipase cartridge) use for patients with cystic fibrosis and exocrine pancreatic insufficiency who receive enteral tube feeding. During an initial 7-day period, all participants will use a standardized nutrition formula during enteral tube feedings. Following the initial 7 days, participants will use the Relizorb cartridge with the standardized formula for 90 days. Participants can continue taking their normal enzymes with daily meals throughout the study. Researchers will test Relizorb’s effectiveness by measuring the amount of fat absorbed by the body. The study was completed on March 30, 2017; the results have not been released. Clinical trials available at www.ClinicalTrials.gov
**DEFINITIONS**

**Enteral Nutrition (EN)** is commonly defined as the provision of nutritional requirements through a tube in the stomach or small intestine such as a nasogastric (NG) tube or a percutaneous gastrostomy (PEG) tube. EN is used for treating patients with severe malabsorption or patients with a functioning intestinal tract, but with disorders of the pharynx, esophagus, or stomach that prevent nutrients from reaching the absorbing surfaces in the small intestine. EN involves administering special nutritional liquids directly into the gastrointestinal tract through nasogastric, gastrostomy, or jejunostomy tubes. Enteral feedings are delivered by syringe, gravity, or via an electric infusion pump. Feedings can be delivered on an intermittent or continuous basis. Individuals may require enteral nutritional therapy to provide sufficient nutrients to maintain weight and strength commensurate with their overall health status if their nutritional needs cannot be met through dietary adjustments and/or oral supplements.

**Fat Malabsorption** Inadequate assimilation of dietary substances due to defects in digestion, absorption, or transport.

**Lipase** A digestive enzyme that breaks down fats (triglycerides) into absorbable fatty acids and monoglycerides.

**Parenteral Nutrition**, also known as total parental nutrition (TPN), is typically reserved for situations when there is inadequate or insufficient absorption of nutrients through the gastrointestinal tract. This method of nutrition contains nutrients such as glucose, amino acids, lipids and added vitamins and dietary minerals delivered intravenously through a peripheral or central vein.

PN is used for patients with medical conditions that impair gastrointestinal absorption to a level incompatible with life. A nutritionally adequate hypertonic solution consisting of glucose (sugar), amino acids (protein), electrolytes (sodium, potassium), vitamins, minerals, and lipids (fats) is administered daily. An infusion pump is generally used to assure a steady flow of the solution either on a continuous (24-hour), intermittent, or cyclic schedule. If intermittent, a heparin lock device and diluted heparin are used to prevent clotting inside the catheter.

**APPENDIX**

N/A

**CODING INFORMATION:** THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

*CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).*

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B4035: Enteral feeding supply kit; pump fed, per day, includes but not limited to feeding/flushing syringe, administration set tubing, dressings, tape
B403L6: Enteral feeding supply kit; gravity fed, per day, includes but not limited to feeding/flushing syringe, administration set tubing, dressings, tape

REFERENCES

Package Insert, FDA, Drug Compendia


Clinical Trials, Definitions, Peer-Reviewed Publications


Government Agencies, Professional Societies, and Other Authoritative Publications


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