Original Effective Date: 01/2018
Current Effective Date: 06/27/2024
Last P&T Approval/Version: 04/24/2024
Next Review Due By: 04/2025
Policy Number: C17943-A

Relizorb (immobilized lipase cartridge) MNR

PRODUCTS AFFECTED

Relizorb (immobilized lipase cartridge)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. EXOCRINE PANCREATIC INSUFFICIENCY DUE TO CYSTIC FIBROSIS:
1. Documented diagnosis of Cystic Fibrosis
   AND
2. (a) Documented diagnosis of pancreatic insufficiency with supporting laboratory evidence (fecal

elastase or elevated fecal fat)
OR
(b) Documented strong clinical suspicion of pancreatic insufficiency based on ONE of the following: i) Member has two CF transmembrane conductance regulator (CFTR) variants known to be associated with pancreatic insufficiency or ii) member has symptoms of pancreatic insufficiency (growth failure and symptoms of steatorrhea, such as diarrhea, bloating, gassiness, and abdominal pain)
AND

3. Documentation the members body mass index (BMI) is not in the target range (BMI at or above the 50th percentile for age, https://www.cdc.gov/growthcharts/)
AND
4. Documented trial and failure (within past 6 months) of at least 30 days of enteral nutrition in conjunction with a trial of pancreatic enzyme therapy (PERT) with at least two preferred/formulary digestive enzyme aids with matching indication OR documented serious side effects, FDA labeled contraindication, or hypersensitivity to all preferred formulary digestive enzyme aids with matching indication
AND
5. Prescriber attests member requires enteral feedings despite optimization of pancreatic enzyme therapy (PERT) and oral nutrition support

CONTINUATION OF THERAPY:

A. EXOCRINE PANCREATIC INSUFFICIENCY DUE TO CYSTIC FIBROSIS:

1. Documentation of adherence to therapy at least 85% of the time as verified by prescriber and member's medication fill history (review Rx history for compliance)
AND
2. Prescriber attests or clinical review has found that patient has NOT experienced any toxicity related to Relizorb (immobilized lipase cartridge)
AND
3. Documentation of improvement or stabilization of members nutritional status (improvement in BMI) or a decrease in symptoms of pancreatic insufficiency (steatorrhea, diarrhea, bloating, gassiness, and abdominal pain)

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy: 6 months
MOLINA REVIEWER NOTE: For Illinois Marketplace, Kentucky Marketplace, Ohio Marketplace, and Kentucky Medicaid, please see Appendix.

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with a cystic fibrosis specialist or physician from a CF center accredited by the Cystic Fibrosis Foundation OR dietician. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

2 years of age and older

QUANTITY:

Maximum quantity of 2 cartridges per day; 2 boxes (60 cartridges) per 30 days

PLACE OF ADMINISTRATION:

The recommendation is that enteral tube feeding products in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Enteral tube feeding

DRUG CLASS:
Digestive Enzyme Cartridge

FDA-APPROVED USES:
Indicated for use in pediatric patients (ages 2 years and above) and adult patients to hydrolyze fats in enteral formula.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Illinois (Source: Illinois General Assembly)
"(215 ILCS 200/60) Sec. 60. Length of prior authorization approval. *A prior authorization approval shall be valid for the lesser of 6 months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined* by the patient's health care professional or the renewal of the plan, and the *approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug* prescribed by the health care professional. All dosage increases must be based on established evidentiary standards and nothing in this Section shall prohibit a health insurance issuer from having safety edits in place. This Section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids. Except to the extent required by medical exceptions processes for prescription drugs set forth in Section 45.1 of the Managed Care Reform and Patient Rights Act, nothing in this Section shall require a policy to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's covered benefits without regard for whether the care, treatment, or services are medically necessary. (Source: P.A. 102-409, eff. 1-1-22.)"
"(215 ILCS 200/65) Sec. 65. Length of prior authorization approval for *treatment for chronic or long-term conditions*. If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, *the approval shall remain valid for the lesser of 12 months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional*. This Section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
Except to the extent required by medical exceptions processes for prescription drugs set forth in Section 45.1 of the Managed Care Reform and Patient Rights Act, nothing in this Section shall require a policy to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's covered benefits without regard for whether the care, treatment, or services are medically necessary. (Source: P.A. 102-409, eff. 1-1-22.)"

Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) "Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition

that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization." (Subsection 3) "Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or benzodiazepines. (b) Paragraph (a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program."
Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

Mississippi (Source: Mississippi Legislature)
"SECTION 13. Length of approvals. (1) A prior authorization approval shall be valid for the lesser of six (6) months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined by the patient's health care professional or the renewal of the policy or plan, and the approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug prescribed by the health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his/her health care professional may extend a prior authorization approval for a longer period, by agreement. All dosage increases must be based on established evidentiary standards, and nothing in this section shall prohibit a health insurance issuer from having safety edits in place. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
(2) Nothing in this section shall require a policy or plan to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment or services are medically necessary.
SECTION 14. Approvals for chronic conditions. (1) If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, including, but not limited to, chemotherapy for the treatment of cancer, the approval shall remain valid for the lesser of twelve (12) months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his or her health care professional may extend a prior authorization approval for a longer period, by agreement. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
(2) Nothing in this section shall require a policy or plan to cover any care, treatment or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment, or services are medically necessary."

Ohio (Source: Ohio Revised Code)
Chapter 3923 Sickness And Accident Insurance Section 3923.041 Policies with prior authorization requirement provisions "(B)(6)(a) For policies issued on or after January 1, 2017, *for a prior approval related to a chronic condition*, the insurer or plan shall honor a prior authorization *approval for an approved drug for the lesser of the following from the date of the approval: (i) Twelve months*; (ii) The last day of the covered person's eligibility under the policy or plan. (b) The duration of all other prior authorization approvals shall be dictated by the policy or plan."

State Medicaid
Kentucky (Source: Kentucky Revised Statutes)

KY304.17A-167 Time span of authorizations
(Subsection 2) "Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization." (Subsection 3) "Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or benzodiazepines. (b) Paragraph (a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program."
Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

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(2) Nothing in this section shall require a policy or plan to cover any care, treatment or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment, or services are medically necessary."

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
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.

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.
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 eicosatetraenoic 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.

The use of Enteral Feeding In-Line Cartridge (EFIC) [e.g., RELiZORB™ immobilized lipase cartridge] to deliver digestive enzymes to enteral formula is ONLY considered medically necessary for children with cystic fibrosis who receive overnight tube feedings, usually by gastrostomy with a feeding pump to help reduce early morning satiety and bloating.

Molina Healthcare will 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 for other patient management for the use of the device.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Relizorb (immobilized lipase cartridge) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Relizorb (immobilized lipase cartridge) include: No published contraindications.

OTHER SPECIAL CONSIDERATIONS:
Fibrosing colonopathy is a rare, serious adverse reaction associated with high-dose use of pancreatic enzyme replacement therapy in the treatment of patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
B4105	In-line cartridge containing digestive enzyme(s) for enteral feeding, each

AVAILABLE DOSAGE FORMS:
Relizorb DEVI, 1 box (30 cartridges)

REFERENCES

1. RELiZORB. RELiZORB website. http://relizorb.com/docs/pdfs/Relizorb-Instructions-for-Use.pdf Accessed December 2017.
2. Relizorb (immobilized lipase cartridge) [instructions for use]. Waltham, MA; Alcresta Therapeutics, Inc.: September 2023.
3. FDA. De Novo classification: RelizorbTM. Food and Drug Administration – Center for Devices and Radiological Health (2015). Available at: https://www.accessdata.fda.gov Accessed December 2017.
4. FDA. Premarket Approval: Relizorb™. Food and Drug Administration – Center for Devices and Radiological Health (2016). Available at: https://www.accessdata.fda.gov Accessed December 2017ClinicalTrials.gov.
5. Safety, Tolerability and Fat Absorption Using Enteral Feeding In-line Enzyme Cartridge (Relizorb),ClinicalTrials.gov Identifier: NCT02598128. Last updated: June 2016. Identifier: NCT02598128. Lastupdated: June 2016 (Final data collection date for primary outcome measure) Available at: https://clinicaltrials.gov/ct2/show/NCT02598128. Accessed December 2017.AlcrestaTherapeutics.

6. Absorption and Safety With Sustained Use of Relizorb Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding. Available at: www.cff.org/Trials/Finder/details/470/ASSURE-Study-of-Relizorb-in-people-with-CF-whoreceive-enteral-tube-feeding. Accessed December2017.
7. Freedman S., et al. Increased Fat Absorption from Enteral Formula Through an In-line Digestive Cartridge in Patients with Cystic Fibrosis. Journal of Pediatric Gastroenterology and Nutrition. 2017Jul;65(1):97-101. Doi: 10.1097/MPG.0000000000001617. PMID: 28471913. Available at: www.ncbi.nlm.nih.gov/pubmed/?term=relizorb Accessed December2017.
8. Freedman S., et al. Options for addressing exocrine pancreatic insufficiency in patients receiving enteral nutrition supplementation. Am J Manag Care. 2017;Jul;23(12 Suppl):S220- s228. Available at:https://ajmc.s3.amazonaws.com/_media/_pdf/AJMC_A746_07_2017_ExocrinePancreaticInsufficiencyOptions_for_Addressing_Exocrine_Pancreatic_Insufficiency.pdf Accessed December 2017

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Duration of Approval Place of Administration	Q2 2024
REVISION- Notable revisions: Age Restrictions FDA-Approved Uses References	Q1 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements FDA-Approved Uses Background Contraindications/Exclusions/ Discontinuation Other Special Considerations HCPCS Code and Descriptions Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Required Medical Information References	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file