Drug Coverage Policy

Effective Date.....06/15/2025
Coverage Policy Number.....IP0733
Policy Title.....Tryngolza

Familial Chylomicronemia Syndrome – Tryngolza

- Tryngolza™ (olezarsen subcutaneous injection – Ionis)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview
Tryngolza, an apolipoprotein C-III (*APO-III*)-directed antisense oligonucleotide, is indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).[1] It

is recommended to maintain a low-fat diet (≤ 20 grams of fat per day) in conjunction with Tryngolza.

Disease Overview
FCS is an ultrarare, genetic form of severe hypertriglyceridemia that impacts 1 to 10 per 1,000,000 persons in the US. Patients with FCS may have triglyceride levels in the thousands. Of note, normal triglyceride levels are < 150 mg/dL with levels above 500 mg/dL categorized as severe hypertriglyceridemia. In general, patients with FCS do not have adequate responses to triglyceride-lowering therapies (e.g., fibrates, omega-3 fatty acids). The high triglyceride levels lead to symptoms such as severe abdominal pain, inflammation of the pancreas (acute pancreatitis), and fatty deposits in the skin. Lipemia retinalis may occur, a condition in which the retinal veins of the eyes appear milky. Patients may develop symptoms of FCS in infancy but may not have the disease be known until adulthood. FCS is caused by biallelic pathogenic variants in five known genes (i.e., lipoprotein lipase [*LPL*], glycosylphosphatidylinositol-anchored high-density lipoprotein [HDL]-binding protein 1 [*GPIHBP1*], apolipoprotein A-V [*APOA5*], apolipoprotein C-II [*APOC2*], or lipase maturation factor 1 [*LMF1*]).

Clinical Efficacy
The efficacy of Tryngolza was evaluated in a randomized, placebo-controlled, double-blind, Phase III trial in patients with genetically identified FCS.[1,2] A fasting triglyceride level ≥ 880 mg/dL was required. At study entry, patients who received the FDA-approved dose of Tryngolza (n = 22) had baseline mean triglyceride levels of 2,613 mg/dL; the value for this parameter in patients who received placebo (n = 23) was 2,585 mg/dL. Background medications were statins (27%), omega-3 fatty acids (42%), fibrates (49%), or other lipid-lowering therapies (13%). The difference between Trygolza 80 mg and placebo in the percent change in fasting triglycerides from baseline to Month 6 was -42.5%.

Guidelines
Guidelines do not address Tryngolza. There are recommendations regarding the diagnosis and/or identification of FCS.[3,4] An expert panel (2018) states the FCS is characterized by very high plasma triglyceride concentrations (> 885 mg/dL) in the untreated state.[3] Patients with FCS experience physical complications including incapacitating abdominal pain, and severe recurrent acute pancreatitis. Other clinical symptoms include eruptive xanthomas, lipemia retinalis, and lower body weight. Neurologic symptoms may be present (e.g., irritability, memory problems, dementia). Pathogenic variants are also present in FCS-genes (i.e., *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*). An FSC score ≥ 10 is a strong predictor of the condition.[3] Also, patients with a North America Familial Chylomicronemia Syndrome (NAFCS) score ≥ 45 are very likely to have classical FCS.

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Policy Statement
Prior Authorization is required for prescription benefit coverage of Trynfolza. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tryngolza as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tryngolza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Tryngolza as noted in the criteria as. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information.

Tryngolza is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Familial Chylomicronemia Syndrome.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Documentation is provided that patient has a fasting triglyceride level ≥ 880 mg/dL; AND
   - **C)** The patient has undergone genetic testing and meets ONE of the following (i or ii):
     - **i.** Documentation is provided that molecular genetic test results demonstrate biallelic pathogenic variants in at least one gene causing familial chylomicronemia syndrome; OR
       Note: Examples of genes causing Familial Chylomicronemia Syndrome include lipoprotein lipase (*LPL*), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*), apolipoprotein A-V (*APOA5*), apolipoprotein C-II (*APOC2*), or lipase maturation factor 1 (*LMF1*).
     - **ii.** Documentation is provided that molecular genetic test results are inconclusive and the patient has ONE of the following (a, b, c, d, or e):
       - **a)** Patient has a familial chylomicronemia syndrome score ≥ 10; OR
       - **b)** Patient has a North American familial chylomicronemia syndrome score ≥ 45; OR
       - **c)** Patient has a history of pancreatitis; OR
       - **d)** Patient has a history of eruptive xanthomas; OR
       - **e)** Patient has a history of lipemia retinalis; AND
   - **D)** The medication will be used concomitantly with a low-fat diet; AND
   - **E)** Medication is prescribed by a cardiologist, an endocrinologist, or a physician who focuses in the treatment of disorders related to severe hypertriglyceridemia.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy , and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Tryngolza for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Hypertriglyceridemia (in the absence of a confirmed diagnosis of familial chylomicronemia syndrome).** A trial evaluated Tryngolza in patients with either moderate hypertriglyceridemia and elevated cardiovascular risk or with severe hypertriglyceridemia.[5] However, Tryngolza is not FDA-approved for this use.[1]

References

1. Tryngolza™ subcutaneous injection [prescribing information]. Carlsbad, CA: Ionis; December 2024.
2. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al, for the Balance investigators. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N Engl J Med*. 2024;390(19):1781-1792.

3. Moulin P, Dufour R, Averna M, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): expert panel recommendations and proposal of an "FCS score". *Atherosclerosis*. 2018;275:265-272.
4. Hegele RA, Ahmad Z, Ashraf A, et al. Development and validation of clinical criteria to identify familial chylomicronemia syndrome (FCS) in North America. *J Clin Lipidol*. 2024 Nov 12. [Online ahead of print].
5. Bergmark BA, Marston NA, Prohaska RA, et al, for the Bridge-TIMI73 investigators. Olesarsen for hypertriglyceridemia in patients at high cardiovascular risk. *N Engl J Med*. 2024;390(19):1770-1780.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy	06/15/2025

The policy effective date is in force until updated or retired.