VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Familial Chylomicronemia Syndrome – Tryngolza Prior Authorization Policy
- Tryngolza™ (olezarsen subcutaneous injection – Ionis)

REVIEW DATE: 12/23/2024

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.

POLICY STATEMENT

Prior Authorization is recommended 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 required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tryngolza is recommended in those who meet the following criteria:

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)** Patient has a fasting triglyceride level ≥ 880 mg/dL **[documentation required]**; AND
   - **C)** The patient has undergone genetic testing and meets ONE of the following (i or ii):
     - **i.** Molecular genetic test results demonstrate biallelic pathogenic variants in at least one gene causing familial chylomicronemia syndrome **[documentation required]**; 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.** Molecular genetic test results are inconclusive and the patient has ONE of the following (a, b, c, d, or e) **[documentation required]**;
       - **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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tryngolza is not recommended in the following situations:

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]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/23/2024

Appendix A. Familial Chylomicronemia Syndrome Score Diagnostic Criteria (for Patients with Fasting TGs > 885 mg/dL).[3*]

Fasting TG levels > 885 mg/dL for three consecutive blood analyses (measured at least 1 month apart; presence of eruptive xanthoma may be used as a surrogate for high TG levels): **+5** • Fasting TG levels > 1,770 mg/dL at least once: **+1**
Previous TG levels < 177 mg/dL: **-5**
No secondary factor (i.e., alcohol, diabetes, metabolic syndrome, hypothyroidism, steroid therapy, and additional drugs; exceptions include pregnancy and ethinyl estradiol; if diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis postpartum): **+2**
History of pancreatitis: **+1**
Unexplained recurrent abdominal pain: **+1**
No history of familial combined hyperlipidemia: **+1**
No response (TG decrease < 20%) to hypolipidemic treatment: **+1**
Onset of symptoms age: • < 40 years: **+1** • < 20 years: **+2** • < 10 years: **+3**

TG(s) – Triglyceride(s); * The FCS score is the sum of all items cited above and a score ≥ 10 suggests that FCS is very likely.

Appendix B. North American Familial Chylomicronemia Syndrome Score Diagnostic Criteria.[4†]

Characteristics Included in Patient Scenarios	Categories and Definitions for Patient Scenarios
Patient Age	• Adult: ≥ 20 years of age • Adolescent: ≥ 10 to 19 years of age • Child: ≥ 1 to 9 years of age • Infant: < 1 year of age
Hypertriglyceridemia Onset	Defined as Hypertriglyceridemia ≥ 440 mg/dL, categorized into early vs. late onset. • Early onset: In infancy or childhood • Later onset: In adolescence or adulthood
Body Mass Index	• ≥ 25.0 kg/m^2 in adults or ≥ 85th percentile in children/adolescents • < 25 kg/m^2 in adults or < 85th percentile in children/adolescents
Abdominal Pain/ Pancreatitis	In all scenarios, panelists assumed symptoms were related to chylomicronemia in a patient. • No history of abdominal pain or pancreatitis • Recurrent abdominal pain but no history of pancreatitis • History of pancreatitis (with or without abdominal pain)
Secondary Factors	Defined as factors that may contribute to the patient's hypertriglyceridemia. For example, lifestyle factors (e.g., high alcohol intake, ultra-processed diet), clinical conditions (e.g., non-pancreatitis induced diabetes, HIV), medications (e.g., antidepressants, antiretrovirals).[*] • ≥ One secondary factor • No secondary factors
Fasting TG Levels	Defined fasting as routine fasting (e.g., 6 to 12 hours depending on patient age) prior to outpatient laboratory tests. Panelists assumed it did not include a scenario in which the patient had been fasting during a hospitalization for many days to control acute pancreatitis or in attempts to bring TG levels down. Panelists also assumed the patient was not yet complying with severe dietary fat restriction (< 20 g/day for adults, < 10% calories from fat for adolescents and children). We categorized the last three laboratory values for adults and on the last two laboratory values for children into two categories: • Not all severely elevated: one to two TG readings 440 to 880 mg/dL, remainder > 880 mg/dL. • All severely elevated: all TG readings > 880 mg/dL
TG/TC Ratio	Defined as the ratio of TG over TC, categorized into: • Normal/low: ≤ 8 mg/dL • High: > 8 mg/dL
ApoB Reading	ApoB laboratory value, categorized into: • Normal/high: ≥ 1 g/L • Low: < 1.0 g/L (100 mg/dL)
Treatment Non-Response	In all scenarios describing patients ≥10 years old, panelists assumed fibrates and high-dose omega-3 fatty acids did not produce a sustained response in TG levels even when the patient was compliant with therapy (i.e., TG levels do not decrease by 20% or more from these treatments and do not remain reduced).

[†] This tool can be used to assist in the diagnosis of familial chylomicronemia syndrome. It should be utilized in patients ≥ 1 year of age with triglyceride (TG) levels ≥ 440 mg/dL. It may be useful in patients who have not been yet tested genetically for FCS, or in whom genetic testing was inconclusive. If patients ≥ 10 years of age, the tool should only be used for patients who are not responsive to fibrates and high-dose omega-3 fatty acids even when the patient is compliance with therapy; HIV – Human immunodeficiency virus; [*] A more comprehensive list of secondary factors are available; TG – Triglyceride; TC – Total cholesterol; ApoB – Apolipoprotein B.