Tryngolza Prior Authorization with Quantity Limit Program Summary

Your health benefit plan may not cover certain prescription drug products or drug categories included in this document. Please consult your benefit plan materials for details about your particular benefit. This document may include drugs that are not included on your plan's formulary. For drug coverage status, please consult your plan's formulary.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
08-01-2025	02-13-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Tryngolza™ (olezarsen) Subcutaneous injection	Adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Familial Chylomicronemia Syndrome (FCS)	Familial Chylomicronemia Syndrome (FCS) is a rare (1 to 2 people per million) autosomal recessive (biallelic inheritance pattern) disorder characterized by impaired clearance of triglyceride (TG)-rich lipoproteins from plasma, leading to severe hypertriglyceridemia (HTG) and an increased risk of acute pancreatitis.(2,4) FCS occurs when an individual inherits two pathogenic loss-of-function alleles of a single gene, leading to absent lipolytic activity.(3) Lipoprotein lipase (LPL) breaks down chylomicrons (large, TG-rich lipoprotein particles produced by enterocytes after a meal) through hydrolysis of serum TG into free fatty acids. These loss-of-function pathogenic variants occur in either the LPL gene (the most commonly affected gene accounting for 60-80% of cases) or in genes related to the function of LPL, which include but are not limited to ApoA5, ApoC2, LMF1, GPIHBP1, and G3PDH1. Mutations in these genes lead to the accumulation of chylomicrons and HTG.(2-4) A diagnosis of FCS can be confirmed by genetic analyses for these loss-of-function mutations in either the LPL gene or in genes related to the function of LPL (including but not limited to ApoA5, ApoC2, LMF1, GPIHBP1, and G3PDH1). It is important to keep in mind that genetic data are not always 100% positive and many mutations remain unknown.(2-5) FCS-specific gene panel sequencing is considered to be the gold standard diagnostic test in cases of high clinical suspicion.(3) A diagnosis of FCS can also be clinically made. Firstly, the patient should be checked for severe refractory HTG (nonresponsive or minimally responsive [less than 20% response]) with TG levels >880 mg/dL (10 mmol/L) which are nominally or nonresponsive to standard TG-lowering therapies, despite adherence to a very low fat diet. TG levels should be >880 mg/dL for 3 consecutive blood draws with little to no benefit seen from standard lipid-lowering therapies. Any cause of secondary HTG (alcohol use, obesity, insulin resistance, hypothyroidism, uncontrolled diabetes, chronic renal failure, Cushing syndrome, HIV, fatty liver disease, poor diet, or medications [e.g., beta-blockers, oral estrogens, retinoids, atypical antipsychotics, bile-acid-binding resins, protease inhibitors, corticosteroids, tamoxifen] should be excluded. An important step in the clinical diagnosis of FCS involves reviewing medical and family history of the patient to identify past acute pancreatitis episodes (in absence of gallstones, alcoholism) or recurrent idiopathic abdominal pain.(2,4,5)

	Pancreatitis is the most serious and potentially life-threatening complication resulting from high triglycerides. Therefore, the goal of therapy is to reduce TG levels in order to reduce the risk of acute pancreatitis which is characterized by marked increases in patient morbidity and mortality in FCS.(3,4,5) Conventional lipid-lowering therapies (fibrates, statins, omega-3 fatty acids, niacin, ezetimibe, PCSK9 inhibitors) are ineffective in FCS patients due to the complete absence of lipolytic activity.(2-4) Current first-line treatment relies on the adoption of a strict low-fat diet (less than 20-25 fat g/day).(2,3,5) In addition, patients need to restrict alcohol intake and avoid medications that may elevate TG. Many FCS patients report that they continue to experience symptoms while adhering to the very low-fat diet. Long-term compliance with such a low-fat diet is extremely difficult to maintain, negatively impacts the patients' quality of life, and does not mitigate the high risk of pancreatitis in all subjects.(2,5) Notably, incident pancreatitis events were markedly reduced by 88% in patients who received Tryngolza.(3) Lipidologists and endocrinologists are first in line in the recognition and management of FCS patients because of severe and uncontrolled hypertriglyceridemia. Pancreatologists and gastroenterologists have the possibility of encountering patients in the event of acute pancreatitis attacks. Collaboration and cooperation between different medical specialties is essential to improve diagnosis. This is important since the increased understanding of the molecular basis of familial chylomicronemia has led to the development of targeted therapies.(5)
Efficacy	Tryngolza was demonstrated in the BALANCE trial (NCT04568343) which was a randomized, placebo-controlled, double-blind, phase 3 clinical trial in adult patients with genetically identified FCS and fasting triglyceride (TG) levels greater than or equal to 880 mg/dL. After a greater than or equal to 4-week run-in period where patients continued to follow a low-fat diet with fat of less than or equal to 20 g/day. 66 patients were randomly assigned to receive doses every 4 weeks of Tryngolza 80 mg (n=22) or matching volume of placebo (n=23) via subcutaneous injection over a 53-week treatment period. The two primary endpoints were the difference in the percent change in fasting TG level from baseline to month 6 as compared between: 1) the olezarsen 80 mg and placebo arms; and 2) the olezarsen 50 mg and placebo arms. TG levels were significantly reduced at 6 months compared with placebo with the 80 mg dose of olezarsen compared with placebo (−42.5%; 95% CI). While olezarsen 80 mg demonstrated statistically significant findings for the primary endpoint, olezarsen 50 mg did not. Findings from the BALANCE trial showed a significant improvement in TG levels with olezarsen 80 mg.(1)
Safety	Tryngolza is contraindicated in patients with a history of serious hypersensitivity to olezarsen or any of the excipients in Tryngolza. Hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias, requiring medical treatment have occurred.(1)

REFERENCES

Number	Reference
1	Tryngolza prescribing information. Ionis Pharmaceuticals, Inc. December 2024.
2	Falko JM. Familial Chylomicronemia Syndrome: A Clinical guide for endocrinologists. *Endocrine Practice*. 2018;24(8):756-763. doi:10.4158/ep-2018-0157
3	Spagnuolo CM, Hegele RA. Etiology and emerging treatments for familial chylomicronemia syndrome. *Expert Review of Endocrinology & Metabolism*. 2024;19(4):299-306. doi:10.1080/17446651.2024.2365787
4	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. doi:10.1016/j.atherosclerosis.2018.06.814
5	Stroes E, Moulin P, Parhofer KG, Rebours V, Löhr JM, Averna M. Diagnostic algorithm for familial chylomicronemia syndrome. *Atherosclerosis Supplements*. 2016;23:1-7. doi:10.1016/j.atherosclerosissup.2016.10.002

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Tryngolza	olezarsen sod subcut soln auto-inject	80 MG/0.8ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Tryngolza	olezarsen sod subcut soln auto-inject	80 MG/0.8 ML	1	Injection Device	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Tryngolza	olezarsen sod subcut soln auto-inject	80 MG/0.8ML	Accord Enhanced ; Accord Standard ; Choice NetR - A Select ; Choice NetR - F Performance ; Choice NetR-HIM

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of familial chylomicronemia syndrome (FCS) as confirmed by ONE of the following: 1. Genetic confirmation of bi-allelic pathogenic variants in affected genes (e.g., LPL, ApoA5, ApoC2, LMF1, GPIHBP1, G3PDH1) **OR** 2. ALL of the following: A. Fasting triglyceride (TG) levels greater than 880 mg/dL for 3 consecutive measurements **AND** B. Secondary causes of hypertriglyceridemia have been ruled out (e.g., alcohol use, chronic kidney disease, hypothyroidism,

Module	Clinical Criteria for Approval
	uncontrolled diabetes, medications [e.g., atypical antipsychotics, beta-blockers, corticosteroids, oral estrogens]) **AND** C. History of pancreatitis or unexplained recurrent abdominal pain **AND** D. No response (TG decrease less than 20%) to conventional lipid lowering therapies (e.g., fibrates, omega-3 fatty acids, statins, niacin, ezetimibe, PCSK9 inhibitors) **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, endocrinologist, geneticist, lipidologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, endocrinologist, geneticist, lipidologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months