09-J5000-07

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Reviewed: 11/12/25

Revised: 12/15/25

Subject: Olezarsen Sodium (Tryngolza) SQ Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive metabolic disorder caused by mutations in lipoprotein lipase and is estimated to affect 1 to 2 patients per million. Lipoprotein lipase is an enzyme that is present in the vascular endothelial surface that degrades circulating triglycerides (TGs) found in chylomicrons and other triglycerides-rich lipoproteins in the bloodstream. This degradation process occurs approximately 3 to 4 hours post-prandial; however, a non-functional enzyme prevents lipolysis. Clinical presentation of FCS includes hypertriglyceridemia (e.g., fasting level above 880 mg/dL), episodes of acute pancreatitis and/or abdominal pain, hepatosplenomegaly, eruptive xanthomas on the skin and lipemia retinalis. As part of the diagnosis process, patients should be screened for secondary causes of elevated TGs (e.g., hypothyroidism, uncontrolled diabetes), and genetic testing can be used to confirm the diagnosis of FCS. Management of FCS involves limiting daily fat intake to less than 15 to 20 grams (less than 10-15% of total daily calories) and avoidance of alcohol and simple, refined carbohydrates. Lipid-lowering therapy such as fibrates, statins, niacin, and omega-3 fatty acids have been used but have limited clinical activity as they act by either decreasing VLDL or increasing lipoprotein lipase activity.

On December 19, 2024, the FDA approved olezarsen (Tryngolza) as adjunct to diet to reduce TGs in adults with FCS. Olezarsen (Tryngolza) is an ASO-GalNAc3 conjugate that binds to apolipoprotein C-III mRNA leading to mRNA degradation and resulting in a reduction of serum apolipoprotein C-III protein. A reduction of apolipoprotein C-III protein leads to increased clearance of plasma VLDL and TGs.

As summarized in the prescribing information, the efficacy and safety of olezarsen (Tryngolza) was evaluated in a Phase 3 randomized, double-blind, placebo-controlled clinical trial in adult patients with genetically identified FCS and fasting TG levels greater than or equal to 880 mg/dL (Trial 1; NCT04568434). After a 4-week run-in period, patients continued a low-fat diet (i.e., ≤ 20 grams fat per

day) and were randomized to either olezarsen (Tryngolza) 80 mg (n=22) or placebo (n=23) via subcutaneous injection every 4 weeks for 53 weeks. Patient demographic and baseline characteristics were generally similar between groups with the proportion of patients with diabetes at enrollment being 32% in the treatment group compared with 26% in the placebo group. Patients in the olezarsen (Tryngolza) and placebo groups were treated with statins (27%), omega-3 fatty acids (42%), fibrates (49%), or other lipid lowering therapies (13%) at study entry. Seventy-one percent (71%) of patients in the olezarsen (Tryngolza) and placebo groups combined had a history of documented acute pancreatitis in the prior 10 years. Mean (SD) and median fasting TG levels at baseline were 2,604 (1,364) mg/dL and 2,303 mg/dL, respectively (range of 334 to 6,898 mg/dL). The primary endpoint was percent change in fasting TGs from baseline to Month 6 (average of Weeks 23, 25, and 27) compared to placebo, which was -42.5% (95% CI: -74.1%, -10.9%; p=0.0084) as noted in Table 1.

Table 1: Mean Baseline (BL) and Mean Percent (%) Changes from Baseline in Lipid/ Lipoprotein Parameters in Patients with FCS at Month 6

Parameter (mg/dL)	Olezarsen 80 mg N = 22		Placebo N = 23		Olezarsen 80 mg vs. Placebo
	BL	% change Month 6	BL	% change Month 6	Treatment Difference % change (95% CI) at Month 6
Triglycerides	2613.1	-30	2595.7	+12	-42.5[a] (-74.1, -10.9)
Non-HDL-C	262.9	-18	271.3	+5.7	-23.4 (-45.3, -1.5)
LDL-C	22.8	+64	16.7	+9	+55.0[b] (0.7, 109.4)
Total ApoB	58.4	+20	59.7	+9	+11.7 (-12.6, 35.9)
ApoB-48	11.6	-51	14.2	+25	-75.9 (-149.8, -2.0)

Abbreviations: apoB = apolipoprotein B; non-HDL-C = non high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Note: Analyses results were based on an analysis of covariance model with treatment, the two randomization stratification factors, prior history of pancreatitis within 10 years prior to Screening (yes vs. no), previous treatment with the unconjugated ASO (yes vs. no) as the fixed effects and log-transformed Baseline value as a covariate. Missing data was imputed using placebo washout imputation. The 95% CIs of treatment differences were calculated using a robust variance estimator. For triglycerides and non-HDL, a test of residual normality did not indicate significant departure from normal distribution.

[a] Reached statistical significance (p value < 0.05).

[b] Mean LDL-C levels increased but remained within normal range (i.e., < 70 mg/dL for 74% of patients treated with olezarsen)

The median percent change from baseline and median absolute TG values over time demonstrated a consistent lowering effect during the 12-month treatment period. Additionally over the 12-month treatment period, one patient in the olezarsen (Tryngolza) group and 7 patients in the placebo group experienced acute pancreatitis; all of these patients had a prior history of pancreatitis within 10 years prior to screening.

The most common adverse reactions associated with olezarsen (Tryngolza) were injection site reactions (19% versus 9% for placebo), decreased platelet count (12% versus 4% for placebo), and arthralgia (9% versus 0% for placebo).

POSITION STATEMENT:

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of olezarsen (Tryngolza) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria ("1" to "6"):

1. Age 18 years of age and older
2. Diagnosis of familial chylomicronemia syndrome (FCS) confirmed by **ONE** of the following ("a" or "b"):
   - Laboratory documentation of the genetic test and FCS scoring, if applicable, must be submitted
   a. Genetic test for FCS demonstrating biallelic pathogenic variants in affected genes (e.g., LPL, ApoA5, ApoC2, LMF1, GPIHBP1)
   b. Genetic test for FCS is inconclusive and **ONE** of the following:
      i. Familial chylomicronemia syndrome score greater than or equal to 10
      ii. North American FCS score of greater than or equal to 45
3. Fasting triglyceride (TG) levels greater than or equal to 880 mg/dL for 3 consecutive measurements – documentation must be submitted
4. Olezarsen (Tryngolza) will be prescribed in conjunction with a FCS diet (e.g., low fat ≤ 20 g per day, avoidance of simple, refined carbohydrates)
5. The medication is prescribed by a specialist with expertise in the diagnosis and management of FCS (e.g., endocrinologist, cardiologist, geneticist, lipidologist)
6. The dose does not exceed 80 mg administered subcutaneously once monthly

Duration of approval: 6 months

Continuation of olezarsen (Tryngolza) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria ("1" to "5"):

1. Authorization or reauthorization for olezarsen (Tryngolza) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of triglycerides in adults with familial chylomicronemia syndrome (if another health plan, documentation of a health plan-paid claim for olezarsen (Tryngolza) during the 90 days immediately before the authorization request must be submitted); **OR** the member previously met **ALL** indication-specific initiation criteria
2. The member has had a beneficial response to therapy (e.g., reduction in fasting triglycerides, episodes of pancreatitis and/or abdominal pain) without any adverse events necessitating discontinuation (e.g., hypersensitivity, thrombocytopenia) – documentation must be provided

3. Olezarsen (Tryngolza) will be prescribed in conjunction with a FCS diet (e.g., low fat ≤ 20 g per day, avoidance of simple, refined carbohydrates)
4. The medication is prescribed by a specialist with expertise in the diagnosis and management of FCS (e.g., endocrinologist, cardiologist, geneticist, lipidologist)
5. The dose does not exceed 80 mg administered subcutaneously once monthly

Duration of approval: 1 year

Olezarsen (Tryngolza) is considered **experimental or investigational** for the treatment of all other off-label indications, including other causes of hypertriglyceridemia and atherosclerotic cardiovascular disease (ASCVD). There is insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Olezarsen (Tryngolza) is indicated as an adjunct to a low-fat diet (≤20 g fat per day) to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). The recommended dose is 80 mg administered subcutaneously once monthly.
- Olezarsen (Tryngolza) autoinjector should be stored in the refrigerator between 2°C and 8°C (36°F and 46°F) in the original carton. Once taken out of the refrigerator, the autoinjector can be stored at room temperature between 15°C and 30°C (59°F and 86°F) in the original carton for up to 6 weeks. If not used within the 6 weeks stored at room temperature, discard olezarsen (Tryngolza). Do not freeze or expose the product to heat; however, the product should be protected from light.
- Prior to initiation, patients and/or caregivers should be trained on the proper preparation and administration. The single-dose autoinjector should be removed from the refrigerator 30 minutes prior to the injection and allow to warm to room temperature. Do not use other warming methods. Inspect the product visually for particulate matter prior to administration. The solution should be clear and colorless to yellow. Do not use if cloudiness, particulate matter, or discoloration is observed. Inject olezarsen (Tryngolza) subcutaneously into the abdomen or front of the thigh. The back of the upper arm can also be used as an injection site if a healthcare provider or caregiver administers the injection.

Dose Adjustments

- No dose adjustment is necessary in patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to > 90 mL/min). Olezarsen (Tryngolza) has not been studied in patients with severe renal impairment or end-stage renal disease.

- No dose adjustment is recommended in patients with mild hepatic impairment. Olezarsen (Tryngolza) has not been studied in patients with moderate or severe hepatic impairment.

Drug Availability

- Olezarsen (Tryngolza) injection is a sterile, preservative-free, clear, colorless to yellow solution supplied in a single-dose autoinjector, and each autoinjector is filled to deliver 0.8 mL of solution containing 80 mg of olezarsen.
- Olezarsen (Tryngolza) is available in cartons containing one 80 mg single-dose autoinjector each (NDC 71860-101-01).

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Olezarsen (Tryngolza) is contraindicated in patients with hypersensitivity to the product or any excipients.

Precautions/Warnings

- **Hypersensitivity Reactions:** Hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias) have been reported in patients treated with olezarsen (Tryngolza). Advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to promptly seek medical attention and discontinue use of olezarsen (Tryngolza) if hypersensitivity reactions occur.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologics [Hospital Outpatient Use ONLY]
J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

E78.3	Hyperchylomicronemia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

REFERENCES:

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3. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2025. URL http://www.dynamed.com. Accessed 2/1/25.
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.
5. Moulin P, Dufour R, Averna M, et al. Identification and diagnosis of patients with familial chylomicronemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". Atherosclerosis. 2018; 275:265-272.
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2025 Oct 29]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
7. Tryngolza (olezaren) [package insert]. Carlsbad, CA: Ionis Pharmaceuticals, Inc., January 2025.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/12/25.

GUIDELINE UPDATE INFORMATION:

04/01/25	New Medical Coverage Guideline: Olezaren (Tryngolza) as an adjunct to diet for the reduction of triglycerides in adults with familial chylomicronemia syndrome (FCS).
12/15/25	Review and revision to the guideline, consisting of revising the position statement to allow for inconclusive FCS genetic testing results with FCS scoring and expanded specialist prescribers and updating references.