Iowa PDL New Drug Review

Proprietary Name: Tryngolza®
Common Name: olezarsen
PDL Category: Endocrine Metabolic Agents

Pharmacology/Usage: Olezarsen, the active ingredient of Tryngolza®, is an antisense oligonucleotide (ASO) directed inhibitor of apolipoprotein C-III (apoC-III) mRNA, conjugated to a ligand containing three N-acetyl galactosamine (GalNAc) residues to enable delivery of the ASO to hepatocytes. It is an ASO-$GalNAc_3$ conjugate that binds to apoC-III mRNA leading to mRNA degradation and resulting in a reduction of serum apoC-III protein. Reduction of apoC-III protein leads to increased clearance of plasma triglycerides (TG) and very-low-density lipoprotein (VLDL).

Indication: As an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Patients with FCS are at risk for pancreatitis during pregnancy because of defects in lipid metabolism and increased triglyceride levels. The safety and efficacy of use have not been established in the pediatric population.

Dosage Form: Solution in a single-dose autoinjector for Injection: 80mg/0.8ml. Preservative-free.

Remove the autoinjector from the refrigerator 30 minutes prior to the injection and allow to warm to room temperature. Do not use other warming methods.

Recommended Dosage: Prior to initiation, train patients and/or caregivers on proper preparation and administration of Tryngolza®.

Inject 80mg administered subcutaneously (SC) once monthly. Inject SC 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.

Maintain a low-fat diet (≤20g fat per day) in conjunction with Tryngolza®.

Administer Tryngolza® as soon as possible after a missed dose. Resume dosing at monthly intervals from the date of the most recently administered dose.

Dose adjustments are not required with mild to moderate renal impairment; however, Tryngolza® has not been studied in patients with severe renal impairment or end-stage renal disease. Dose adjustments are not recommended in patients with mild hepatic impairment; however, Tryngolza® has not been studied with moderate or severe hepatic impairment.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tryngolza®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included injection site reactions (10%), decreased platelet count (8%), and arthralgia (9%).

Hypersensitivity reactions have been reported in patients treated with Tryngolza®. Advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to seek medical attention and discontinue Tryngolza® use if hypersensitivity reactions occur.

Contraindications: In patients with a history of serious hypersensitivity to olezarsen or any of the excipients of the product.

Manufacturer: Ionis Pharmaceuticals

Analysis: The efficacy of Tryngolza® was assessed in a randomized, placebo-controlled, double-blind clinical trial that included adults with genetically identified FCS and fasting TG levels ≥880mg/dL. After a ≥4-week run-in period where patients continued to follow a low-fat diet with ≤20 grams fat per day, patients were randomly assigned to receive doses every 4 weeks of Tryngolza® 80mg (N=22) or matching volume of placebo (N=23) via SC injection over a 53 week treatment period.

Patient baseline characteristics were generally similar across the treatment groups. The proportion of patients with diabetes at enrollment was 32% in the Tryngolza® group as compared with 26% in the placebo group. Patients in the 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. In addition, 71% of patients in the Tryngolza® and placebo groups combined had a history of documented acute pancreatitis in the prior 10 years. The mean and median fasting TG levels at baseline were 2,604mg/dL and 2,303mg/dL, respectively.

The primary endpoint of the study was the percent change in fasting triglycerides from baseline to month 6 (average of weeks 23, 25, and 27) compared to placebo. Results suggested that the difference between the Tryngolza® 80mg group and the placebo group in percent change in fasting TG from baseline to month 6 was -42.5% (p=0.0084). This and additional results are presented in the table below, which was adapted from the prescribing information.

Parameter	Tryngolza® (N=22)		Placebo (N=23)		Tryngolza® vs placebo
	Baseline	% change mth 6	Baseline	% change mth 6	Treatment difference % change at mth 6
TG	2613.1	-30	2595.7	+12	-42.5 (p<0.05)
Non-HDL-C	262.9	-18	271.3	+5.7	-23.4
LDL-C	22.8	+64	16.7	+9	+55.0[1]
Total ApoB	58.4	+20	59.7	+9	+11.7
ApoB-48	11.6	-51	14.2	+25	-75.9

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

Median percent change from baseline and median absolute TG values over time demonstrated a consistent lowering effect during the 12-month treatment period.

Over the 12-month treatment period, the numerical incidence of acute pancreatitis in patients treated with Tryngolza® 80mg was lower compared with placebo (1 patient [5%] in the Tryngolza® 80mg group compared with 7 patients [30%] in the placebo group); all of these patients had a prior history of pancreatitis within 10 years prior to screening.

Place in Therapy: Tryngolza® is an apoC-III-directed antisense oligonucleotide indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). Patients with FCS have very high triglyceride levels, which leads to an increased risk of potentially fatal pancreatitis as well as increased risk of cardiovascular disease (CVD).[2] Because of impairment in the clearance of postprandial lipids, patients with FCS respond poorly to standard TG-lowering medications including fibrates or omega-3 fatty acids and require a lifelong very low-fat diet, which prevents the formation of chylomicrons.[3,4] Patients with FCS typically have TG concentrations >20 mmol/L (1770 mg/dL) and continue to experience symptoms despite good dietary compliance and adherence to available medications.[5,6] Tryngolza® is for once monthly subcutaneous injection. The efficacy of Tryngolza® was demonstrated in a randomized, double-blind, placebo-controlled study that included adults with genetically identified FCS and fasting TG levels ≥880mg/dL. The primary endpoint was the percent change in fasting TG from baseline to month 6 (average of weeks 23, 25, and 27) compared to placebo. Results suggested that the difference between Tryngolza® and placebo was statistically significant in favor of Tryngolza® (-42.5%, p=0.0084). Tryngolza® is the first FDA-approved treatment for adults with FCS.

Summary

It is recommended that Tryngolza® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Tryngolza® [package insert]. Carlsbad, CA: Ionis Pharmaceuticals Inc; 2025.

[2] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. Atherosclerosis 2019; 290: 140-205.

[3] Falko JM. Familial chylomicronemia syndrome: A clinical guide for endocrinologists. *Endocr Pract*. 2018;24(8):756-763. doi: 10.4158/EP-2018-0157.

[4] Baass A, Paquette M, Bernard S, Hegele RA. Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridemia. *J Intern Med*. 2020;287(4):340-348. doi: 10.1111/joim.13016. Epub 2020 Jan 8.

[5] Tryngolza. Dossier. Ionis Pharmaceuticals; January 2025.

[6] 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:S1933-2874(24)00251-4. doi: 10.1016/j.jacl.2024.09.008.