Drug Use Research & Management Program
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New Drug Evaluation: Tryngolza™ (Olezarsen) injection

Date of Review: February 2026
Generic Name: Olezarsen

End Date of Literature Search: 11/15/2025
Brand Name (Manufacturer): Tryngolza (Ionis Pharmaceuticals, Inc)
Dossier Received: yes

Plain Language Summary:

- Olezarsen is a new medicine used to reduce triglyceride levels in patients with a genetic condition causing very high triglyceride levels. This condition is called familial chylomicronemia syndrome. Patients with a very high triglyceride level (≥ 1000 mg/dl) are at an increased risk for certain complications, including stomach pain and inflammation of the pancreas, known as pancreatitis.
- No other medications reduce triglyceride levels in this condition. Dietary and fat restrictions are currently the only recommended treatments. These dietary restrictions are difficult for patients to maintain.
- In one study, olezarsen injected subcutaneously, or under the skin, once a month reduced triglyceride levels by a meaningful amount when compared to placebo over 6 months in patients who were also following a low-fat diet. We do not know much olezarsen reduces risk of pancreatitis in patients with familial chylomicronemia syndrome.
- Side effects with olezarsen include a decreased platelet count and increased liver enzymes. This is important because platelets help stop bleeding and high liver enzymes is a sign of liver inflammation that can lead to liver damage.
- We recommend olezarsen will be covered for people with familial chylomicronemia syndrome who are enrolled in the fee-for-service Oregon Health Plan after a prior authorization request by the prescriber is approved.

Research Questions:

1. Is there evidence demonstrating the efficacy of olezarsen in reducing triglyceride (TG) levels and episodes of acute pancreatitis in patients with Familial Chylomicronemia Syndrome (FCS)?
2. Is there evidence that olezarsen is safe for reducing TG levels and episodes of acute pancreatitis in patients with FCS?
3. Are there specific subpopulations for which olezarsen is better tolerated or more effective when used for FCS?

Conclusions:

- There is low-quality evidence that olezarsen 80 mg subcutaneous (SC) once monthly lowers TG levels significantly more than placebo at 6 months (least squares mean [LSM] difference -43.5%; 95% confidence interval [CI) -69.1 to -17.9; p<0.001) in participants with FCS. While there is biologic plausibility that this reduction will decrease risk for in acute pancreatitis and there was a nominal decrease in pancreatitis in the phase 3 study, there remains insufficient data showing a benefit in lowering pancreatitis in FCS.

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- There is limited long-term data demonstrating safety of olezarsen. Safety concerns include elevated hepatic transaminases, thrombocytopenia and associated bleeding. There was an increase in mild thrombocytopenia without serious bleeding in clinical studies and patients with thrombocytopenia at baseline were excluded. This will need to be monitored in clinical practice and more long-term safety data is needed to better define the risk with olezarsen.
- There is supportive data that olezarsen 50 mg and 80 mg reduce TG levels in patients with moderate hypertriglyceridemia (TG level 150-499 mg/dl) at high cardiovascular (CV) risk and severe hypertriglyceridemia (TG level ≥ 500 mg/dl) without FCS on background lipid lowering therapy. At the time of this review, olezarsen is not FDA approved for this indication.

Recommendations:
- Make olezarsen as non-preferred in the "*Other Dyslipidemia Drug*" preferred drug list (PDL) class.
- Include clinical prior authorization criteria to ensure olezarsen is used according to supporting evidence and FDA labeling **(Appendix 3**).

Background:
Familial chylomicronemia syndrome is a rare autosomal recessive genetic disorder that causes a deficiency in lipoprotein lipase (LPL) enzyme activity through inactivation of the LPL gene resulting in persistence of triglyceride rich chylomicrons.[1] Although the onset of symptoms usually occurs in childhood or adolescence, FCS is often underdiagnosed or the diagnosis is delayed and up to 30% of patients with FCS remain undiagnosed until adulthood. FCS affects an estimated 1 to 13 individuals per 1,000,000 in the United States and is characterized by severely elevated chylomicrons and plasma triglycerides (TGs) and an increased risk of pancreatitis.[1,2] Clinical presentation includes a TG level greater than 885 mg/dl repeatedly, or greater than 1000 mg/dl, lack of response to standard treatments, and history of acute pancreatitis. Patients have a 60% to 90% lifetime risk of pancreatitis. There is often a lack of other secondary risk factors, such as obesity and diabetes. Other manifestations can include eruptive cutaneous xanthomas, lipemia retinalis, episodic abdominal pain, and hepatosplenomegaly.[1,2]

Genetic testing remains the gold standard for diagnosing FCS. The North American Familial Chylomicronemia Score (NAFCS) calculator was developed to use clinical criteria to determine a diagnosis of FCS and may be useful for patients who have not been tested genetically or in whom genetic testing was inconclusive.[1] It is recommended only when patients are not responsive to fibrates and high-dose omega-3 fatty acids (< 20% reduction in TGs). The NAFCS calculator includes the following variables: young age of onset, BMI less than 25 kg/m^2, history of abdominal pain or pancreatitis, absence of secondary risk factors, persistent fasting TG greater than 885 mg/dl, TG to total cholesterol ratio greater than 3.5 mg/dl, apoB < 1 g/L, and nonresponse to conventional medications.[1]

The goal of treatment in FCS is to prevent acute pancreatitis and reduce plasma TG levels to less than 885 mg/dl. There is no current evidence-based definitive TG target and there are no high-quality clinical guidelines addressing FCS. There are currently no FDA approved treatments for FCS. Standard triglyceride-lowering treatments with fibrates, niacin, and omega-3 fatty acids are typically not effective in FCS due to a lack of LPL activity in FCS patients. Standard of care remains a restrictive low-fat diet (< 20 grams daily) to reduce the accumulation of chylomicrons, complete avoidance of alcohol, and physical activity. While standard lipid-lowering drugs are generally not effective for patients with FCS as they have no impact on chylomicron metabolism, they may be beneficial in patients with concomitant risk factors for atherosclerotic cardiovascular disease (ASCVD).[1,2]

Olezarsen is the first FDA-approved treatment for FCS and is an antisense oligonucleotide targeting apolipoprotein C-III (APOC3) mRNA to reduce APOC3 production. Olezarsen was FDA approved through expedited approval pathways, including fast track, breakthrough therapy, and priority review.[2] Inhibiting

APOC3 may reduce TG levels by enhancing LPL activity and reducing serum apolipoprotein C-III protein, a key regulator of TG metabolism. Volanesorsen is an APOC3 inhibitor approved in Europe for the treatment of FCS. It was not approved in the United States because of concerns about thrombocytopenia.[1] Olezarsen is a second generation APO3 inhibitor targeting hepatic APOC3 mRNA. It has the same chemical composition as volanesorsen but differs with the addition of a triantennery N-acetyl galactosamine, which allows for lower dosing. It was approved by the FDA for the treatment of FCS in adults and has been studied in moderate to severe hypertriglyceridemia. Pilozasiran is a small interfering RNA (siRNA) targeting hepatic APOC3 mRNA that was recently FDA approved and will be brought back for review.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:
Clinical trials used to support FDA approval are described and evaluated below in **Table 1**.

Olezarsen received FDA approval based on one randomized, phase 3, double-blind, controlled trial comparing olezarsen 50 mg SC once monthly, olezarsen 80 mg SC once monthly, and placebo in adults 18 years of older with FCS and fasting TG levels greater than 880 mg/dl with and without a history of pancreatitis.[3] The FDA typically requires two adequate and well controlled trials to provide substantial evidence for efficacy. However, the FDA allowed one study due to the rarity of the condition and lack of alternative treatment options for FCS.[2]

In the phase 3 randomized controlled trial (RCT), patients underwent genetic testing to confirm loss-of-function variants and a diagnosis of FCS. If the patient was not already following a low-fat diet, they were enrolled in a 2-week dietary run-in period. Patients were instructed to consume no more than 20 g of fat per day, and alcohol use was discouraged. Patients were randomized to olezarsen 50 mg (n=21), 80 mg (n=22), or placebo (n=23).[3] The primary outcome was change from baseline in fasting TG level at 6 months.

Of the 144 participants screened, 66 (46%) were eligible for randomization. There was a statistically significant difference in percent change in fasting TG level from baseline to 6 months between olezarsen 80 mg and placebo (least-squares mean [LSM] reduction of 43.5%; 95% confidence interval [CI) -69.1 to -17.9; p<0.001).[3] However, there was no significant difference between olezarsen 50 mg and placebo (LSM -22.4%; 95% CI -47.2% to 2.5; p=0.08) at 6 months.[3] There were 7 events of acute pancreatitis in the placebo group (30.4%) compared to 2 in the pooled olezarsen group (4.7%) (rate ratio 0.12; 95% CI 0.02 to 0.66).[3]

There are important limitations to consider in this study. Differences in baseline characteristics increase the risk of selection bias. In this RCT there was a higher percentage of patients with a history of acute pancreatitis in the olezarsen groups compared to placebo, more white patients in the placebo group, more participants from North America in the placebo group, and more participants ≥65 years of age in the placebo group. [3] All study participants were required to follow strict dietary restrictions, and it is unclear how much dietary changes impacted the results. Since the 50 mg comparison was not significant, the hierarchical design of the study limited statistical comparison for the secondary outcomes and conclusions cannot be made regarding these outcomes, including acute pancreatitis and changes in other lipoproteins. The magnitude of benefit on TG reduction was lower than what the authors predicted and used to power the study. Lastly, the outcome assessors included probable and possible cases of acute pancreatitis as pancreatitis episodes in the study.

A phase IIb randomized, controlled study in adults with either moderate hypertriglyceridemia (TG 150-499 mg/dl) and elevated CV risk or with severe hypertriglyceridemia (TG≥ 500 mg/dl) was used by the FDA as a confirmatory study.[4] Of the 304 participants screened, 49% failed screening, related to extensive inclusion and exclusion criteria and 92% of patients were white. This limits the generalizability of the study results. Most patients did not have clinical ASCVD and had moderate hypertriglyceridemia (90%) with a TG level less than 500 mg/dl. There was a significant reduction in TG levels at 6 months in both olezarsen 50 mg (treatment difference 49.3%; 95% CI 39.5 to 59) and olezarsen 80 mg (treatment difference 53.1%; 95% CI 43.4 to 62.9) groups and more patients in each olezarsen group achieved a TG level less than 150 mg/dl compared to placebo.[4]

Since FDA approval, additional phase 3 trials have been published in patients with hypertriglyceridemia without FCS. In two large phase 3, multicenter, double-blind, RCTs with identical designs, patients with severe hypertriglyceridemia (fasting TG level of at least 500 mg/dl) were randomized to receive olezarsen 50 mg, olezarsen 80 mg, or placebo for 48 weeks (n=1063). [5] The median age across both trials was 54 years and only 23.6% were women. A total of 88.4% of participants were white and almost all patients were on at least one lipid-lowering medication with 64% receiving a fibrate.[5] Treatment with olezarsen resulted in a statistically significant greater reduction in the triglyceride level at 6 months compared to placebo across both trials with a placebo-adjusted difference from baseline of -49.2% and -62.9% in the olezarsen 50 mg group and a difference of -72.2% and -54.5% in the olezarsen 80 mg group. The reduction in TG levels was maintained through 12 months. Across both trials, there was a reduction in acute pancreatitis episodes with pooled olezarsen doses compared to placebo (7 episodes vs. 22 episodes) with a rate ratio of 0.15; 95% CI 0.05 to 0.40). [5] The results were similar in patients with moderate hypertriglyceridemia (TG level 150 to 400 mg/dl) and elevated CV risk (LSM change in TG level of -58.4%; 95% CI -65.1% to -51.7% in olezarsen 50 mg and -60.6%; 95% CI -67.1 to -54% in olezarsen 80 mg compared to placebo).[6]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Acute pancreatitis
2) Hospitalization due to pancreatitis
3) Serious adverse events
4) Study withdrawal due to an adverse event
5) Reduction in TG level

Primary Study Endpoint:

1) Percent change in fasting triglyceride level from baseline to 6 months (average of weeks 23, 25, and 27)

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR /NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
Stroes, et al.[3] 2024 BALANCE NCT04568434 PC, DB, MC, phase 3 RCT	1. Olezarsen 80mg SC every 4 weeks 2. Olezarsen 50mg SC every 4 weeks 3. Placebo SC every 4 weeks * Diet stabilization for 2 weeks with 2-week qualification period: prior to therapy start 53 weeks	Demographics: -Median Age 45 years old -Female 52.2% -Ethnicity White 84.8% -History of pancreatitis: 71% -Baseline TG 2630 mg/dL Key Inclusion Criteria: -Genetically confirmed diagnosis of FCS -Fasting TG ≥880 mg/dL -Age ≥18 years old - ≤ 20g of fat per day diet - Non-pregnant, non-lactating and surgically sterile, postmenopausal, abstinent, or on highly effective contraceptive Key Exclusion Criteria: -Clinically significant abnormalities in medical history or physical examination -Active pancreatitis -Platelets < 100,000 - AST/ALT > 3 x ULN -eGFR < 45 ml/min - Uncontrolled hypertension - History of bleeding diathesis or coagulopathy - Malignancy within 5 years - Active infection with HIV, HCV, or HBV	ITT: 1.22 2.21 3.23 PP: 1.18 2.19 3.22 Attrition: 1. 3 (13.6%) 2. 2 (9.5%) 3. 1 (4.3%)	Primary Endpoint: Percent change in fasting TG from baseline at Month 6 1. -33.3% 2. -10.3% 3. 11.2% Mean difference: 80 mg vs placebo: -43.5% 95% CI, -69.1 to -17.9; P<0.001 50 mg vs. Placebo: -22.4%; 95% CI, -47.2 to 2.5; P=0.08 Secondary Endpoint: * Mean change in fasting TG from baseline to 12 months 1. -39.7% 2. -21.5% 3.: 21.6% Treatment difference: 80 mg vs. Placebo: -59.4%; 95% CI -90.7 to -28.1 50 mg vs. Placebo: -43.8%; 95% CI –73.9% to -13.7% Acute Pancreatitis 1. 1 (4.5%) 2. 1 (4.8%) 3. 7 (30.4%) Pooled olezarsen vs. Placebo: RR 0.12; 95% CI 0.02 to 0.66 Secondary endpoints considered exploratory due to hierarchical design and lack of statistical finding for second	NA NS NA NA	Discontinuations due to AE: 1. 2 (9.1%) 2. 1 (4.8%) 3. 0 SAE: 1. 3 (14%) 2. 4 (19%) 3. 9 (39%)	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear; Randomization was performed using an interactive response technology system. Some differences in baseline characteristics. Performance Bias: Low; double blinded using matching volume of placebo. Detection Bias: Unclear; outcome assessors blinded for adjudication of pancreatitis events; large treatment difference in triglyceride levels could result in unblinding. Attrition Bias: Low; low attrition rates (<10%), ITT analysis used for primary outcome. Reporting Bias: Low. Protocol available online and all outcomes prespecified. Other Bias: High. Study financially supported by drug manufacturer. Ionis Pharmaceuticals involved in data interpretation and preparation of manuscript. **Applicability**: Patient: Rare disease limits sample size. 54% of screened patients did not meet randomization criteria. FCS is often present in adolescents, who were excluded. Intervention: Doses selected based on phase 2 study in ASCVD and expected reduction in TG with each dose. Reductions in study are smaller than what was expected. Only the 80 mg is FDA approved. Comparator: Placebo group comparator appropriate since no other approved treatments are available. Outcomes: Reduction in TG levels is a surrogate outcome. Uncertainty around magnitude of benefit on acute pancreatitis. Included 28 secondary outcomes. Setting: 29 sites in US, Canada, EU and UK. 19/66 patients are from the US.

				primary endpoint; p values not reported				
Bergmark, et al.[4] 2024 Bridge-TIMI 73a NCT05355402 PC, MC, phase 2 RCT	1. Olezarsen 80mg SC every 4 weeks 2. Olezarsen 50mg SCevery 4 weeks 3. Placebo SC every 4 weeks *on stable lipid-lowering therapy 53 weeks	Demographics: Mean age: 62 y/o 90% with TG < 500 mg/dl 42% women 92% white 97% on lipid lowering therapy Median TG 241.5 mg/dl Key Inclusion Criteria: -TG 150-499 mg/dl with either clinical ASCVD or an increased ASCVD risk OR TG ≥ 500 mg/dl -Stable lipid lowering therapy -Age ≥18 years old - Non-pregnant, non-lactating and surgically sterile, postmenopausal, abstinent, or on highly effective contraceptive Key Exclusion Criteria: -HbA1C ≥ 9.5% - ACS/TIA within 6 months - Active pancreatitis in last 4 weeks - AST/ALT > 3 x ULN -eGFR < 30 ml/min - Uncontrolled hypertension - Malignancy within 5 years - active infection with HIV, HCV, or HBV	ITT: 1.57 2.58 3.39 PP: 1.49 2.50 3.38 Attrition: 1. 2% 2. 5% 3. 0%	Primary Endpoint: Percent change in TC levels from baseline to 6 months 1. -60.9% 2. -57.1% 3. -7.8% Mean difference: 80 mg vs placebo: -53.1% 95% CI, -43.4 to 62.9; P<0.001 50 mg vs. Placebo: -49.3%95% CI, -39.5 to -59; P<0.001 Secondary Endpoints: TG level of < 150 mg/dl 1. 93% 2. 86% 3. 12% P< 0.001 for both comparisons 95 CI NR	NA NA NA	DC due to AE: 4. 3 (5%) 5. 7 (12%) 6. 0 SAE: 4. 7 (12%) 5. 4 (7%) 6. 2 (5%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear; unclear randomization and allocation concealment; proportion of women lower in olezarsen group, more patients in placebo group were taking a fibrate. Performance Bias: Low; double blinded using matching placebo volume. Detection Bias: Unclear; unclear blinding of outcome assessors. Attrition Bias:Low; low overall attrition and similar between groups. Reporting Bias: Low. Protocol available online and all outcomes prespecified. Other Bias: High; funded by Ionis pharmaceuticals **Applicability**: Patient: 8-week screening period including diet/lifestyle stabilization and qualification period limits applicability. ~50% of those screened did not meet inclusion/exclusion criteria. 90% of patients were white. Intervention: TG lowering therapy. Unclear dose response based on this study. Comparator: Placebo controlled; lack of active comparator Outcomes: TG lowering is a surrogate outcome; unclear impact on CV outcomes Setting: 28 sites in North America

Abbreviations : ACS = acute coronary syndrome; AE = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; CI = confidence interval; CV = cardiovascular; DC = discontinuation; DB = double-blind; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITT = intention to treat; LSM = least squares mean; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RR: rate ratio; SAE = serious adverse events; SC = subcutaneous; TG = triglyceride; ULN = upper limit of normal.

Clinical Safety:
In the primary phase 3 study, the most common adverse events that occurred more frequently with olezarsen compared to placebo were injection site reactions, thrombocytopenia, and arthralgia (**Table 2**). Discontinuations due to adverse events were 7% in the pooled olezarsen group and 0% in placebo. Safety concerns with olezarsen include thrombocytopenia and bleeding, injection site reactions, and hepatic adverse events.

Table 2: Adverse reactions that occurred in > 5 % of patients and at a higher frequency than placebo

Adverse reaction	Olezarsen (n=43)	Placebo (n=23)
Injection site reactions	8 (19%)	2 (9%)
Decreased platelet count	5 (12%)	1 (4%)
Arthralgia	4 (9%)	0

Due to safety concerns regarding thrombocytopenia with volanesorsen, bleeding and thrombocytopenia is a concern for olezarsen. In clinical trials more participant on olezarsen experienced platelet reductions compared to placebo. Although none were categorized as severe, the study excluded patients with platelet counts < 100 x 10^9/L at baseline so it remains unknown if serious thrombocytopenia will occur. There was no increased risk of major bleeding with olezarsen compared to placebo.

In the larger phase 3 studies in patients without FCS, there were more frequent elevations in liver transaminases and thrombocytopenia with the 80 mg dose of olezarsen, suggesting a dose response for adverse reactions. Increases in glycated hemoglobin levels were also observed with both doses among patients with diabetes.

References:

1. Javed F, Hegele RA, Garg A, et al. Familial chylomicronemia syndrome: An expert clinical review from the National Lipid Association. *J Clin Lipidol.* 2025;19(3):382-403.
2. FDA Integrated Review. Tryngolza (olezarsen). 12/2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/218614Orig1s000IntegratedR.pdf.
3. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *The New England journal of medicine.* 2024;390(19):1781-1792.
4. Bergmark BA, Marston NA, Prohaska TA, et al. Olezarsen for Hypertriglyceridemia in Patients at High Cardiovascular Risk. *The New England journal of medicine.* 2024;390(19):1770-1780.
5. Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk. *The New England journal of medicine.* 2025.
6. Bergmark BA, Marston NA, Prohaska TA, et al. Targeting APOC3 with Olezarsen in Moderate Hypertriglyceridemia. *The New England journal of medicine.* 2025;393(13):1279-1291.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRYNGOLZA safely and effectively. See full prescribing information for TRYNGOLZA.

TRYNGOLZA (olezarsen) injection, for subcutaneous use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
TRYNGOLZA is an *APOC-III*-directed antisense oligonucleotide (ASO) indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of TRYNGOLZA is 80 mg administered subcutaneously once monthly. (2.1)
- Administer TRYNGOLZA 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. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 80 mg/0.8 mL in a single-dose autoinjector. (3)

----------CONTRAINDICATIONS----------
History of serious hypersensitivity reactions to olezarsen or any of the excipients in TRYNGOLZA. (4)

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity reactions have been reported in patients treated with olezarsen. Advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to promptly seek medical attention and discontinue use of TRYNGOLZA if hypersensitivity reactions occur. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence >5% of TRYNGOLZA-treated patients and >3% higher frequency than placebo) were injection site reactions, decreased platelet count, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ionis Pharmaceuticals Inc. at toll free number 1-833-644-6647 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Olezarsen is an antisense oligonucleotide targeting messenger RNA for apolipoprotein C-III (apoC-III) of which regulates triglyceride levels. Additionally, olezarsen has a conjugated ligand three N-acetyl-galactosamine (GalNAc) residue to facilitate target delivery to liver cells. Reduction in apoC-III protein leads to decreased triglyceride and very low-density lipoprotein.
Oral Bioavailability	Subcutaneous administration; not applicable
Distribution and Protein Binding	91.0 L central Vd, 2960 L peripheral Vd; Protein binding = >99%
Elimination	Urinary excretion (<1%) after 24 hours
Half-Life	Approximately 30 days
Metabolism	Metabolized by endo-and exonucleases to short oligonucleotide fragments of varying sizes within the liver. Oligonucleotides are not part of the CYP metabolic pathways.

Abbreviations: CYP = cytochrome P450; L=liters; Vd= Volume of distribution.

APOLIPOPROTEIN C-III (APOC3) Inhibitors

Goal(s):

- Promote use of APOC3 Inhibitors that is consistent with medical literature.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- Olezarsen (Tryngolza)
- Plozasiran (Redemplo)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the prescriber a specialist in lipid management?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Does the patient have a diagnosis of familial chylomicronemia syndrome (FCS), confirmed by genetic testing? Please submit a copy of the genetic testing results	**Yes**: Go to #5	**No:** Go to #7
5. Does the patient have a current triglyceride level of 885 mg/dl or greater?	**Yes:** Go to #6 **Recent TG Level_____** **Date _____**	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient agree to adhere to a low-fat diet (≤ 20 g of fat per day)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for an FDA-approved indication?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have clinically diagnosed severe hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL?	**Yes:** Go to #9 **Recent TG Level_____** **Date _____**	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient failed to have adequate benefit with, or have a contraindication to, an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of a positive clinical response (i.e. clinically meaningful reduction in triglyceride level or reduction in episodes of acute pancreatitis)?	Yes: Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/26 (MH)
Implementation: TBD