BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

TRYNGOLZA™ (olezarsen) subcutaneous injection
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Tryngolza (olezarsen) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Gastroenterologist or Cardiologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis familial chylomicronemia syndrome (FCS) established by **EITHER** of the following:
    a. Biallelic pathogenic variants that cause a loss of function in **ANY** of the following:
        i. Lipoprotein lipase (LPL)

ii. Apolipoprotein C-II (APOC2)
iii. Apolipoprotein A 5 (APOA5)
iv. Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1)
v. Lipoprotein maturation factor 1 (LMF1)

b. FCS score of greater than or equal to 10 (see Definitions section)

4. There is documentation of baseline test fasting triglyceride level of greater than or equal to 880 mg/dL on 3 occasions that are at least 1-month apart from each other

5. **BOTH** of the following:
   a. There is at least one triglyceride level of at least 1700 mg/dL
   b. There is **NO** history of a triglyceride level less than 180 mg/dL

6. Individual has **ALL** of the following:
   a. FCS signs and symptoms began before 20 years of age
   b. Individual has clinical features of FCS which may include unexplained recurrent abdominal pain, nausea, fatigue, diarrhea, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis, plasma to have a milky (lactescent or lipemic) appearance
   c. Individual has a history of recurrent pancreatitis documented as medical record diagnosis of acute pancreatitis or hospitalization/emergency room visits with severe abdominal pain that was ultimately identified as pancreatitis
   d. A medication history has been completed to exclude drug-induced pancreatitis

7. There are **NO** secondary causes for hypertriglyceridemia including but not limited to **ANY** of the following:
   a. Alcohol abuse
   b. Uncontrolled diabetes
   c. Unhealthy diet
   d. Metabolic syndrome
   e. Hypothyroidism
   f. Use of glucocorticoids, ethinylestradiol and other additional drugs

8. Individual has documented failure (after 3-months use of maximumly tolerated doses), contraindication per FDA label, intolerance, or is not a candidate for **ALL** the following:
   a. Fibrates
   b. Omega-3 fatty acids
   c. Statins
   d. Other lipid-lowering medications

9. Requested agent will be used as an adjunct to diet to reduce triglycerides

10. Individual is on a diet that restricts total daily fat to less than or equal to 20 g/day or 15% of total energy intake

11. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

12. Individual does not have severe renal impairment (eGFR < 30 mL/min) or end-stage renal disease

13. Individual does not have moderate or severe hepatic impairment (total bilirubin> 1.5 times the upper limit of normal with any aspartate aminotransferase (AST))

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Tryngolza (olezarsen) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Gastroenterologist or Cardiologist

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains at least a 40% reduction in plasma triglyceride levels over baseline
    b. Achieved and maintains at least a 70% reduction in plasma apolipoprotein C-III levels over baseline
    c. There has been a reduction in the number of episodes of pancreatitis over baseline
    d. There has been a reduction in number of visits to urgent care or hospitalizations for signs and symptoms of pancreatitis over baseline

3. Individual has been adherent with the medication and dietary restriction that limits dietary fat to less than or equal to 20 g/day or 15% of total energy intake

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Severe thrombocytopenia (platelet count less than 50,000/mm^3)
    b. Severe hyperglycemia that requires new antidiabetic medication

6. Individual does not have severe renal impairment (eGFR < 30 mL/min) or end-stage renal disease

7. Individual does not have moderate or severe hepatic impairment (total bilirubin> 1.5 times the upper limit of normal with any aspartate aminotransferase (AST))

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Tryngolza (olezarsen) is an apolipoprotein C-III (apoC-III)-directed antisense oligonucleotide (ASO) indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). Olezarsen 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 TG and VLDL.

Monogenic chylomicronemia (Fredrickson type 1 hyperlipoproteinemia or lipoprotein lipase deficiency) is characterized by triglyceride (TG) levels above 885 mg/dL (10 mmol/L). It is a rare autosomal recessive condition most commonly due to LPL deficiency. LPL activity is reduced due to bi-allelic (both alleles) mutations in either of the LPL gene or mutations in both alleles of other genes encoding proteins supporting LPL activity: apolipoprotein C-II (APOC2), apolipoprotein A 5 (APOA5), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), or lipoprotein maturation factor 1 (LMF1)). Familial chylomicronemia syndrome (FCS) usually presents in childhood with the majority developing symptoms before age of ten years, is characterized by excessive increase in plasma triglyceride levels from accumulation of chylomicrons, which manifests biochemically as severe hypertriglyceridemia. Clinical manifestations can include recurrent episodes of acute pancreatitis, abdominal pain, nausea, fatigue, diarrhea, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis and failure to thrive. It has been consistently reported that FCS strongly increases the risk of acute pancreatitis (AP). FCS is not associated with severe atherosclerosis. The mainstay of treatment is fat restriction, reducing total fat to <10% of calories or <20 grams per day, in combination with weight maintenance, exercise, and avoidance of processed foods, alcohol and smoking. Standard lipid-lowering medications and plasmapheresis are not effective.

Multifactorial chylomicronemia (Fredrickson hyperlipoproteinemia type 5) is caused by complex genetic susceptibility including heterozygous rare large-effect gene variants for monogenic chylomicronemia and/or accumulated common small-effect TG-raising polymorphisms, often along with acquired factors. In this condition there is elevation in VLDL and chylomicrons levels but no deficiency in LPL or its activator, apo C-II. Some individuals with this condition have clinical characteristics of FCS. Multifactorial (polygenic) chylomicronemia syndrome (MCS) is 50 to 100 times more common as FCS and is associated with many secondary factors, hepatosteatosis, renal impairment or proteinuria. Secondary factors include alcohol abuse, uncontrolled diabetes, unhealthy diet, metabolic syndrome, hypothyroidism, glucocorticoids, ethinylestradiol use and other additional drugs. MCS is also characterized by an increase in AP, but it is less than what is seen in FCS. Plasma TG levels in MCS are much more sensitive to dietary and/or fibrate treatment.

A diagnostic FCS score helps distinguish between FCS and MCS based on eight biologic/clinical items. The FCS score has an overall sensitivity 88% (95% confidence interval: 0.97, 0.76), an overall specificity of 85% (95% confidence interval: 0.94, 0.75), and a receiver operating characteristic (ROC) curve best cut-off corresponding to score of $\geq$ 10 (area under the ROC curve 0.91).

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

FCS score:

- overall sensitivity 88% (95% confidence interval: 0.97, 0.76)
- overall specificity of 85% (95% confidence interval: 0.94, 0.75)
- receiver operating characteristic (ROC) curve best cut-off corresponding to score of ≥ 10 (area under the ROC curve 0.91)

Familial Chylomicronemia Syndrome (FCS) score	
	Score
Fasting TGs >10 mmol/L for 3 consecutive blood analyses (done at least 1 month apart)[#]	+5
Fasting TGs > 20 mmol/L at least once[#]	+1
Previous TGs <2 mmol/L[#]	-5
No secondary factors† (except pregnancy and ethinyl estradiol)	+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 at age: <40 years <20 years <10 years	 +1 +2 +3
FCS score: ≥10: FCS very likely ≤9: FCS unlikely ≤8: FCS very unlikely	
[#]To convert Triglyceride values from mmol/L to mg/dL, multiply the value in mmol/L by 88.57 [#]To convert Triglyceride values from mg/dL to mmol/L, divide the value in mg/dL by 88.57 †Secondary factors include alcohol abuse, diabetes, metabolic syndrome, hypothyroidism, corticosteroid use and additional drugs	

Characteristics of different types of primary chylomicronemia syndrome		
	Monogenic (familial chylomicronemia syndrome– FCS)	**Polygenic (multifactorial chylomicronemia syndrome - MCS)**
Triglyceride level	> 10 mmol/L	< 10 mmol/L
Onset of symptoms	Early age, childhood and adolescent	Adult
Frequency	5%	95%
Clinical findings	Chylomicronemia, eruptive xanthoma, lipemia retinalis, abdominal pain, recurrent pancreatitis, hepatosplenomegaly	
Secondary factors which initiate symptoms	- None listed	High amount fatty food intake, alcohol, diabetes mellitus, obesity,

		hypothyroidism, metabolic syndrome, nephrotic syndrome, drugs (estrogen, corticosteroid, retinoid, betablockers, thiazide, resin, second generation antipsychotic and antiretroviral agents)
Secondary risk factor treatment improves symptoms	- None listed	++++
Effect of traditional lipid lowering therapy (fibrate, nicotinic acid, omega-3 fatty acid)	Minimal or no effect	Moderate effect
Milky plasma with a creamy layer on top	+++	+
Plasma apoB < 100 mg/dL	+	
Triglyceride/Cholesterol ratio > 2.2 mmol/L (5 mg/mg)	+++	
Genetic background	Frequently: LPL, APOC2 mutations Rare cases: APOA5, GPIHBP1, LMF1	Single copy or monoallelic (i.e. heterozygous) rare variants in LPL, APOC2, APOA5, GPIHBP1 and LMF1 gene and polygenic risk from common variants associated with TG levels

Resources:

Tryngolza (olezarsen) subcutaneous injection product information, revised by Ionis Pharmaceutical, Inc. 12-2024. Available at FDA https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed January 03, 2025.

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