PRIOR AUTHORIZATION POLICY

POLICY: Familial Chylomicronemia Syndrome – Redemplo Prior Authorization Policy
- Redemplo® (plozasiran subcutaneous injection – Arrowhead)

REVIEW DATE: 11/24/2025; selected revision 12/10/2025, 02/04/2026

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Redemplo, an apolipoprotein C-III (apoC-III)-directed small interfering ribonucleic acid (siRNA), is indicated as an adjunct to diet to reduce triglycerides (TGs) for familial chylomicronemia syndrome (FCS) in adults.[1] It is recommended to maintain a low-fat diet (≤ 20 grams of fat per day) in conjunction with Redemplo.

Disease Overview

FCS is an ultra-rare, genetic form of severe hypertriglyceridemia that impacts 1 to 10 per 1,000,000 persons in the US. Patients with FCS may have triglyceride levels in the thousands.[2-4] Of note, normal triglyceride levels are < 150 mg/dL with levels above 500 mg/dL categorized as severe hypertriglyceridemia. In general, patients with FCS do not have adequate responses to triglyceride-lowering therapies (e.g., fibrates, omega-3 fatty acids). The high triglyceride levels lead to symptoms such as severe abdominal pain, inflammation of the pancreas (acute pancreatitis), and

fatty deposits in the skin. Lipemia retinalis may occur, a condition in which the retinal veins of the eyes appear milky. Patients may develop symptoms of FCS in infancy but may not have the disease be known until adulthood. FCS is caused by biallelic pathogenic variants in five known genes (i.e., lipoprotein lipase [*LPL*], glycosylphosphatidylinositol-anchored high-density lipoprotein [HDL]-binding protein 1 [*GPIHBP1*], apolipoprotein A-V [*APOA5*], apolipoprotein C-II [*APOC2*], or lipase maturation factor 1 [*LMF1*]).[2-4] Tryngolza® (olezarsen subcutaneous injection), an apoC-III-directed antisense oligonucleotide, is indicated as an adjunct to diet to reduce triglyceride levels in adults with FCS.[5]

Clinical Efficacy

The efficacy of Redemplo was evaluated in a randomized, placebo-controlled, double-blind, Phase III trial in adults with genetically identified or clinically diagnosed.[1,6] A fasting triglyceride level ≥ 880 mg/dL was required. At study entry, patients who received the FDA-approved dose of Redemplo (n = 26) had baseline mean triglyceride levels of 2,008 mg/dL; the value in patients who received placebo (n = 25) was 2,053 mg/dL. Patients were treated with statins (43%), omega-3 fatty acids (29%), and fibrates (69%). In total, 25% of patients were not receiving background TG-lowering therapies. The difference between Redemplo 25 mg and placebo in the percent change in fasting triglycerides from baseline to Month 10 was -59%.

Guidelines

An expert clinical review from the National Lipid Association states that Redemplo and Tryngolza show great promise in the treatment of FCS.[3] There are recommendations regarding the diagnosis and/or identification of FCS.[3,4] An expert panel (2018) states the FCS is characterized by very high plasma triglyceride concentrations (> 885 mg/dL) in the untreated state.[3] Patients with FCS experience physical complications including incapacitating abdominal pain, and severe recurrent acute pancreatitis. Other clinical symptoms include eruptive xanthomas, lipemia retinalis, and lower body weight. Neurologic symptoms may be present (e.g., irritability, memory problems, dementia). Pathogenic variants are also present in FCS-genes (i.e., *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*). An FCS score ≥ 10 (often referred to as the Moulin et al scoring criteria) is a strong predictor of the condition.[3] Also, patients with a North America Familial Chylomicronemia Syndrome (NAFCS) score ≥ 45 are very likely to have classical FCS.[4] Refer to Appendix A and Appendix B for FCS scoring and NAFCS scoring.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Redemplo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Redemplo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Redemplo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Redemplo as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records,

prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

Redemplo® (plozasiran subcutaneous injection - Arrowhead) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Familial Chylomicronemia Syndrome.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a fasting triglyceride level ≥ 880 mg/dL at baseline **[documentation required]**; AND
     Note: This refers to baseline prior to treatment with a triglyceride-lowering medication. Examples of triglyceride-lowering medications include statins, niacin, fibrates, and omega-3 fatty acids.
   - **C)** Patient meets at least ONE of the following (i, ii, or iii):
     - **i.** Molecular genetic test results demonstrate biallelic pathogenic variants in at least one gene causing familial chylomicronemia syndrome **[documentation required]**; OR

     Note: Examples of genes causing Familial Chylomicronemia Syndrome include lipoprotein lipase (*LPL*), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*), apolipoprotein A-V (*APOA5*), apolipoprotein C-II (*APOC2*), or lipase maturation factor 1 (*LMF1*).
     - **ii.** Molecular genetic test results are inconclusive, and the patient has ONE of the following (a or b) **[documentation required]**; OR
       - **a)** Patient has a Moulin familial chylomicronemia syndrome score ≥ 10; OR
       - **b)** Patient has a North American familial chylomicronemia syndrome score ≥ 45; OR
     - **iii.** Patient has received a clinical diagnosis of familial chylomicronemia syndrome based on the presence of ALL of the following (a, b, and c):
       - **a)**
       - **b)** Patient meets ONE of the following ([1] or [2]):
         - **(1)** History of acute pancreatitis not caused by alcohol or cholelithiasis; OR
         - **(2)** History of recurrent hospitalizations for severe abdominal pain without other explainable cause; AND
       - **c)** Absence of secondary hypertriglyceridemia (e.g., obesity, uncontrolled diabetes); AND
       - **d)** Lack of response to a traditional triglyceride-lowering medication; AND

Note: Examples of triglyceride-lowering medications include statins, niacin, fibrates, and omega-3 fatty acids.

D) The medication will be used concomitantly with a low-fat diet; AND

E) Medication is prescribed by a cardiologist, an endocrinologist, a lipidologist, or a physician who focuses in the treatment of disorders related to severe hypertriglyceridemia.

CONDITIONS NOT COVERED

Redemplo® (plozasiran subcutaneous injection - Arrowhead) is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Hypertriglyceridemia (in the absence of a confirmed diagnosis of familial chylomicronemia syndrome).** A trial evaluated Redemplo in patients with severe hypertriglyceridemia.[7] However, Redemplo is not FDA-approved for this use.[1]

REFERENCES

1. Redemplo® subcutaneous injection [prescribing information]. Pasadena, CA: Arrowhead; November 2025.
2. Javed F, Saadatagah S, Larouche M, Naderian M, et al. Recognition and management of persistent chylomicronemia: a Joint Expert Clinical Consensus by the National Lipid Association and the American Society for Preventative Cardiology. *J Clin Lipidol*. 2025;19:723-736.
3. 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.
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*. 2025;19(1):83-94.
5. Tryngolza® subcutaneous injection [prescribing information]. Carlsbad, CA: Ionis; January 2025.
6. Watts GF, Rosenson RS, Hegele RA, et al, for the PALISADE Study Group. Plozasiran for managing persistent chylomicronemia and pancreatic risk. *N Engl J Med*. 2025;392(2):127-137.
7. Gaudet D, Pall D, Watts GF, et al. Plozasiran (ARO-APOC3) for severe hypertriglyceridemia: The SHASTA-2 randomized clinical trial. *JAMA Cardiol*. 2024;9(7):620-630.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/24/2025
Selected Revision	**Familial Chylomicronemia Syndrome.** The requirement for a fasting triglyceride level ≥ 880 mg/dL was clarified to state at baseline. A Note was added to clarify that baseline is prior to a triglyceride-lowering medication. For a patient with inconclusive molecular genetic test result, the option for approval for a familial chylomicronemia score ≥ 10 was clarified to state Moulin familial chylomicronemia score. History of pancreatitis, history of eruptive	12/10/2025

	xanthomas, and history of lipemia retinalis were removed as options of approval for a patient with inconclusive genetic test results. Requirements for a clinical diagnosis were added as an alternative to genetic testing if the patient meets all of the following: documentation of a fasting triglyceride level ≥ 880 mg/dL at baseline; history of recurrent episodes of acute pancreatitis not caused by alcohol or cholelithiasis; history of recurrent hospitalizations for severe abdominal pain without other explainable cause; absence of secondary hypertriglyceridemia (for example, obesity, uncontrolled diabetes); and lack of response to traditional triglyceride-lowering medications. A Note of examples of triglyceride-lowering medications was added throughout the policy and includes statins, niacin, fibrates, and omega-3 fatty acids.	
Selected Revision	**Familial Chylomicronemia Syndrome.** The requirement for a patient to be diagnosed by biallelic pathogenic variants, inconclusive genetic test results, or a clinical diagnosis was modified to state at least one of the following. The requirement for a fasting triglyceride level ≥ 880 mg/dL at baseline for a clinical diagnosis was removed, along with the corresponding Note. The requirement for recurrent episodes of pancreatitis was modified to state a history of acute pancreatitis. The clinical diagnosis was modified to require one of a history of acute pancreatitis not caused by alcohol or cholelithiasis or history of recurrent hospitalizations for severe abdominal pain without other explainable cause and not both. Lipidologist was added to the specialist requirement.	02/04/2026

Appendix A. Familial Chylomicronemia Syndrome Score Diagnostic Criteria (for Patients with Fasting TGs > 885 mg/dL).[3*]

Fasting TG levels > 885 mg/dL for three consecutive blood analyses (measured at least 1 month apart; presence of eruptive xanthoma may be used as a surrogate for high TG levels): **+5** • Fasting TG levels > 1,770 mg/dL at least once: **+1**
Previous TG levels < 177 mg/dL: **-5**
No secondary factor (i.e., alcohol, diabetes, metabolic syndrome, hypothyroidism, steroid therapy, and additional drugs; exceptions include pregnancy and ethinyl estradiol; if diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis postpartum): **+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 age: • < 40 years: **+1** • < 20 years: **+2** • < 10 years: **+3**

TG(s) – Triglyceride(s); * The FCS score is the sum of all items cited above and a score ≥ 10 suggests that FCS is very likely.

Appendix B. North American Familial Chylomicronemia Syndrome Score Diagnostic Criteria.[4†]

Characteristics Included in Patient Scenarios	Categories and Definitions for Patient Scenarios
Patient Age	• Adult: ≥ 20 years of age • Adolescent: ≥ 10 to 19 years of age • Child: ≥ 1 to 9 years of age • Infant: < 1 year of age
Hypertriglyceridemia Onset	Defined as Hypertriglyceridemia ≥ 440 mg/dL, categorized into early vs. late onset. • Early onset: In infancy or childhood • Later onset: In adolescence or adulthood
Body Mass Index	• ≥ 25.0 kg/m^2 in adults or ≥ 85th percentile in children/adolescents • < 25 kg/m^2 in adults or < 85th percentile in children/adolescents
Abdominal Pain/ Pancreatitis	In all scenarios, panelists assumed symptoms were related to chylomicronemia in a patient. • No history of abdominal pain or pancreatitis • Recurrent abdominal pain but no history of pancreatitis • History of pancreatitis (with or without abdominal pain)
Secondary Factors	Defined as factors that may contribute to the patient's hypertriglyceridemia. For example, lifestyle factors (e.g., high alcohol intake, ultra-processed diet), clinical conditions (e.g., non-pancreatitis induced diabetes, HIV), medications (e.g., antidepressants, antiretrovirals).* • ≥ One secondary factor • No secondary factors
Fasting TG Levels	Defined fasting as routine fasting (e.g., 6 to 12 hours depending on patient age) prior to outpatient laboratory tests. Panelists assumed it did not include a scenario in which the patient had been fasting during a hospitalization for many days to control acute pancreatitis or in attempts to bring TG levels down. Panelists also assumed the patient was not yet complying with severe dietary fat restriction (< 20 g/day for adults, < 10% calories from fat for adolescents and children). We categorized the last three laboratory values for adults and on the last two laboratory values for children into two categories: • Not all severely elevated: one to two TG readings 440 to 880 mg/dL, remainder > 880 mg/dL. • All severely elevated: all TG readings > 880 mg/dL
TG/TC Ratio	Defined as the ratio of TG over TC, categorized into: • Normal/low: ≤ 8 mg/dL • High: > 8 mg/dL
ApoB Reading	ApoB laboratory value, categorized into: • Normal/high: ≥ 1 g/L • Low: < 1.0 g/L (100 mg/dL)
Treatment Non-Response	In all scenarios describing patients ≥10 years old, panelists assumed fibrates and high-dose omega-3 fatty acids did not produce a sustained response in TG levels even when the patient was compliant with therapy (i.e., TG levels do not decrease by 20% or more from these treatments and do not remain reduced).

† This tool can be used to assist in the diagnosis of familial chylomicronemia syndrome. It should be utilized in patients ≥ 1 year of age with triglyceride (TG) levels ≥ 440 mg/dL. It may be useful in patients who have not been yet tested genetically for FCS, or in whom genetic testing was inconclusive. If patients ≥ 10 years of age, the tool should only be used for patients who are not responsive to fibrates and high-dose omega-3 fatty acids even when the patient is compliance with therapy; HIV – Human immunodeficiency virus; * A more comprehensive list of secondary factors are available; TG – Triglyceride; TC – Total cholesterol; ApoB – Apolipoprotein B.