

Lipid Apheresis

Policy # 00710

Original Effective Date: 01/01/2021

Current Effective Date: 09/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider low-density lipoprotein (LDL) apheresis **eligible for coverage**** in individuals with **homozygous** familial hypercholesterolemia who are unable to achieve adequate LDL-cholesterol control despite maximally tolerated lipid-lowering therapy.

Based on review of available data, the Company may consider LDL apheresis **to be eligible for coverage**** in individuals with severe, refractory **heterozygous** familial hypercholesterolemia who meet **ALL** of the following criteria:

- Have failed diet therapy; **AND**
- Are unable to achieve adequate LDL-cholesterol control despite maximum tolerated combination drug therapy (see Policy Guidelines section); **AND**
- Meet **ONE** of the following U.S. Food and Drug Administration (FDA) approved indications:
 - Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 300 mg/dL; **OR**
 - Functional hypercholesterolemic heterozygotes with LDL greater than or equal to 200 mg/dL with documented coronary artery disease (CAD).

Note:

Documented CAD includes a history of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or alternative revascularization procedure, or progressive angina documented by exercise or nonexercise stress test.

When Services Are Considered Not Medically Necessary

The use of low-density lipoprotein (LDL) apheresis when patient selection criteria are not met is considered to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers LDL apheresis for other uses, including but not limited to **ANY** of the following, to be **investigational**:*

- Nonfamilial hypercholesterolemia
- Nephrotic syndrome
- Sudden sensorineural hearing loss
- Severe diabetic foot ulcerations
- Peripheral artery disease
- Preeclampsia
- Non-arteritic acute anterior ischemic optic neuropathy
- Acute coronary syndrome.

Based on review of available data, the Company considers therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion for all indications, including but not limited to acute coronary syndrome, to be **investigational**.*

Policy Guidelines

Documentation of maximum tolerated lipid-lowering therapy should include use, contraindication, intolerance, or inadequate response to clinically appropriate therapies based on diagnosis and FDA labeling, including:

- High-intensity statin therapy;
- Ezetimibe;
- PCSK9-targeted therapy (e.g., evolocumab, alirocumab);
- Evincumab or lomitapide when clinically appropriate.

The frequency of LDL apheresis varies but typically averages once every 2 weeks to obtain an interapheresis level of LDL-C at less than 120 mg/dL. Patients with homozygous FH may be treated more frequently. Patients are simultaneously treated with diet and drug therapy.

Background/Overview

Hyperlipidemia

A dominantly inherited disorder, FH results from a variant in the gene that encodes for the specific cell surface receptor responsible for LDL uptake by the cells. The heterozygous form affects about 1 in 500 people. The number of LDL receptors is halved in this condition, resulting in serum LDL cholesterol levels that are approximately 2 to 3 times levels considered acceptable (ie, > 300 mg/dL). Affected male patients typically develop coronary heart disease (CHD) in their thirties and forties, while women develop the disease in their fifties. Depending on the patient, heterozygous FH may or may not respond adequately to lipid-lowering drugs.

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Homozygous hypercholesterolemia is rare, occurring in only 1 in 1 million subjects. Due to the total lack of functioning LDL receptors, serum levels of LDL cholesterol may be elevated 6-fold (> 500 mg/dL). Homozygotes may develop severe aortic stenosis and CHD by 20 years of age. These patients typically do not adequately respond to drug or diet modification therapies. In the past, patients with homozygous FH may have been treated with plasma exchange, but the advent of LDL apheresis provides a more targeted approach by permitting selective removal of LDL from plasma.

Treatment

Low-Density Lipoprotein

Low-density lipoprotein apheresis (also referred to as lipid apheresis) involves the extracorporeal removal of apolipoprotein B (apo B)-containing lipoproteins, including LDL, lipoprotein(a), and very low-density lipoprotein.

The apheresis procedure is designed to isolate plasma. The LDLs are then selectively removed from the plasma by immunoadsorption, heparin-induced extracorporeal LDL precipitation, dextran sulfate adsorption, or double-filtration plasmapheresis of lipoprotein. In immunoadsorption, polyclonal antihuman apo B antibodies from sheep selectively bind and remove LDL, because apo B is the protein moiety of LDL. In heparin-induced extracorporeal LDL precipitation, LDL and other particles containing apo B are precipitated by heparin at an acidic pH. Dextran sulfate adsorption removes LDL by binding the positively charged apo B to dextran sulfate particles bound to cellulose. High-density lipoprotein (HDL) delipidation and plasma reinfusion removes plasma from the body, processed through a delipidation device, and then returns it to the patient. The delipidation procedure selectively removes cholesterol from HDL, converting the major α -HDL to pre- β -like HDL, a form of HDL that enhances cholesterol transport to the liver and is thought to reduce atherosclerosis development and burden. The plasma with pre- β -like HDL is then reinfused into the patient.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Two LDL apheresis systems have been approved by the U.S. FDA for marketing. In 1996, the Liposorber LA-15[®]‡ System (Kaneka Pharma), dextran sulfate device, was approved by the FDA through the premarket approval process for use to "acutely remove LDL-C from the plasma of high-risk patient populations for whom diet has been ineffective or not tolerated."

In 1997, the HELP[®]‡ System (B. Braun), a heparin-induced extracorporeal LDL precipitation, was approved by the FDA through the premarket approval process for the same indication. FDA product code: MMY.

In 2013, the Liposorber LA-15 System was approved for additional indications through the humanitarian device exemption process for the treatment of pediatric patients with primary focal segmental glomerulosclerosis when the following conditions apply:

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"Standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful or not well-tolerated, and the patient has a GFR [glomerular filtration rate] ≥ 60 mL/min/1.73 m² or the patient is post renal transplantation."

In 2020, the FDA changed the preexisting Humanitarian Use Device (HUD) 2014 designation for the Plasma Delipidation System (PDS-2™ System)‡ to a Humanitarian Device Exemption (HDE). These regulatory pathways are intended to encourage development of devices for rare diseases. The 2020 HDE is indicated "to reduce coronary artery atheroma in adult patients with homozygous FH who are either inadequately responsive to or intolerant of maximal therapy for homozygous FH, including the latest medications and other device therapies approved by the FDA."

The modification to a HDE approval was due to safety considerations and limitations of the clinical evidence provided, which necessitated that the device use be limited to treatment of patients who are either inadequately responsive or intolerant of maximal therapy for homozygous FH. The Summary of Safety and Probable Benefit reports data on 6 patients with substantial occurrence of hypotension and bradycardia. Delipidation and reinfusion is limited to 7 treatments.

In 2025, FDA noted that the LIPOSORBER®‡ LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has been either ineffective or not tolerated:

Group A - Clinically diagnosed Familial Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dL;

Group B - Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dL;

Group C - Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 70 mg/dL and either documented coronary artery disease or documented peripheral artery disease; and

Group D - Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with lipoprotein(a) (Lp(a)) ≥ 60 mg/dL (or 130 nmol/L) and either documented coronary artery disease or documented peripheral artery disease.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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Description

This use of LDL apheresis has been proposed to treat various types of FH and other significant hyperlipidemia and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately removes LDL particles from plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

Summary of Evidence

Familial Hypercholesterolemia

For individuals with homozygous FH who are unable to achieve target LDL cholesterol (LDL-C) with maximally tolerated contemporary lipid-lowering therapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and a systematic review. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis, with means ranging from 57% to 75%. Currently, the direct evidence does not demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Randomized controlled trials (RCTs) comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible and are unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated contemporary lipid-lowering therapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with heterozygous FH who are unable to achieve target LDL-C with maximally tolerated contemporary lipid-lowering therapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis with means ranging from 58% to 63%. Currently, there is no direct evidence that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Randomized controlled trials comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible and are unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated contemporary lipid-lowering therapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Nonfamilial Hypercholesterolemia

For individuals with non-FH who receive LDL apheresis, the evidence includes multiple retrospective and prospective nonrandomized cohort studies. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have reported improvements in lipid levels pretreatment and posttreatment. Randomized trials in patient populations that are well-characterized regarding previous treatments, lipid levels, and comorbidities are necessary to demonstrate improvements in health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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Nephrotic Syndrome

For individuals with treatment-resistant nephrotic syndrome who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Using variable schedules of LDL apheresis with short-term follow-up, these studies have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer-term follow-up are necessary to determine whether outcomes are improved with the use of LDL apheresis in nephrotic syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Other Indications

For individuals with sudden sensorineural hearing loss who receive LDL and fibrinogen apheresis, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. One RCT compared LDL apheresis with the standard treatment of prednisolone, hydroxyethyl starch, and pentoxifylline; it reported no statistically significant differences in hearing recovery between groups. The second RCT compared the combination of a single lipid apheresis procedure plus standard treatment with standard treatment alone; it reported statistically significant differences in hearing recovery with the addition of apheresis to standard treatment. An a priori primary endpoint, power calculations, and the statistical plan to control for type I error for multiple comparisons were not reported in the second trial. Further evaluation and replication of these findings are required given the inconsistent reporting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with severe diabetic foot ulcerations who receive LDL apheresis, the evidence includes a single prospective case series. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity. In the case series, patients underwent from 1 to 7 treatment procedures and were followed for 2 to 73 months. Authors reported improved wound healing and reductions in the risk of lower leg amputations, but results were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with peripheral artery disease who receive LDL apheresis, the evidence includes a single prospective case series. Relevant outcomes are change in disease status and treatment-related morbidity. Improvements in symptomatic parameters such as coldness, numbness, and resting pain were reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with preeclampsia who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Improvements in gestation were reported but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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For individuals with non-arteritic acute anterior ischemic optic neuropathy who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Improvement in visual outcomes was reported but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Acute Coronary Syndrome

For individuals with acute coronary syndrome who receive selective HDL delipidation and plasma reinfusion, the evidence includes an RCT. Relevant outcomes are OS disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Results have shown improvements in certain biochemical measures (eg, pre- β -like HDL and α -HDL levels). There were no significant changes in atheroma volume. Larger randomized trials, with longer follow-up and clinically relevant outcomes, are needed to determine the impact of delipidated HDL plasma on acute coronary syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with acute coronary syndrome who receive LDL apheresis, the evidence includes RCT. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Results revealed a nonsignificant improvement in the mean LDL reduction and percentage change in total plaque volume in the intensive-lipid lowering group (including apheresis) as compared to standard therapy with statins alone. Larger randomized trials, with longer follow-up and clinically relevant outcomes, are needed to determine the impact of LDL apheresis on acute coronary syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence (NICE) updated its guidance on FH:

- 1.3.3.1 "Healthcare professionals should consider offering LDL [low-density lipoprotein] apheresis for the treatment of adults and children/young people with homozygous FH. The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease.

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1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist center on a case-by-case basis and data recorded in an appropriate registry."

American Society for Apheresis

In 2023, the American Society for Apheresis (ASFA) published the Ninth Special Issue containing evidence-based recommendations for therapeutic apheresis. ASFA continues to support lipoprotein apheresis for selected patients with familial hypercholesterolemia. (Table 1).

Table 1. Guidelines on Use of Low-Density Lipoprotein Apheresis

Recommendation	Category	Grade
Homozygous familial hypercholesterolemia	I	1A
Heterozygous familial hypercholesterolemia	II	1A
Focal segmental glomerulosclerosis	II	2C
Lipoprotein (a) hyperlipoproteinemia	II	1B
Peripheral vascular diseases	II	1B
Phytanic acid storage disease (Refsum disease)	II	2C
Sudden sensorineural hearing loss	III	2A

ASFA Definitions: Category I disorders are those for which apheresis is accepted as first-line therapy. Category II disorders are those for which apheresis is accepted as second-line therapy. Category III disorders are those for which the optimum role of apheresis has not been established, and individualized decision-making is necessary. Category IV disorders are those for which published evidence suggests apheresis is ineffective or harmful. ASFA recommendation grades range from Grade 1 (strong recommendation) to Grade 2 (weak recommendation), with evidence quality ranging from A (high quality evidence) to C (low quality evidence).

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American Heart Association

In 2024, the American Heart Association (AHA) published a scientific statement regarding lipoprotein apheresis. The statement notes that lipoprotein apheresis is an FDA-approved adjunctive therapeutic option for children and adults with homozygous familial hypercholesterolemia (HoFH) and selected patients with heterozygous familial hypercholesterolemia (HeFH) who remain inadequately controlled despite intensive lipid-lowering therapy. The statement further notes that lipoprotein apheresis can acutely reduce LDL-cholesterol levels by approximately 75% to 85% and remains an important treatment option for patients with severe familial hypercholesterolemia who do not achieve adequate LDL-cholesterol reduction with available pharmacologic therapies. The AHA also notes that observational studies suggest improvement in cardiovascular outcomes; however, randomized controlled outcome trials are limited. Use of lipoprotein apheresis (LA) for elevated Lp(a) levels (with or without elevated LDL-C levels) may be clinically important due to the lack of effective Lp(a)-lowering therapies, but data in this population are limited. Observational studies suggest improvement in cardiovascular outcomes; however, randomized controlled outcome trials are limited.

No guidelines on therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

National Coverage Decision 110.14 on apheresis lists the indications for which apheresis is a covered benefit in cellular and immune-complex mediated disorders. There is no determination for hypercholesterolemia or LDL apheresis.

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27. FDA U.S. Food and Drug Administration. LIPOSORBER LA-15 System. Product Code: MMY Filed: August 15, 2019. Amended: January 22, 2020, April 8, 2020

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10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. New policy.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Added acute coronary syndrome to investigational statement.
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2023	Medical Policy Committee review
08/09/2023	Medical Policy Implementation Committee approval. No change to coverage.
08/01/2024	Medical Policy Committee review
08/14/2024	Medical Policy Implementation Committee approval. No change to coverage.
08/07/2025	Medical Policy Committee review
08/13/2025	Medical Policy Implementation Committee approval. No change to coverage.
08/06/2026	Medical Policy Committee review
08/12/2026	Medical Policy Implementation Committee review
08/20/2026	Medical Quality Management Committee approval. Added “The use of low-density lipoprotein (LDL) apheresis when patient selection criteria are not met is considered to be not medically necessary.”

Next Scheduled Review Date: 08/2027

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0342T, 36516
HCPCS	S2120
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

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3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.