Lipid Apheresis

Policy # 00710
Original Effective Date: 01/01/2021
Current Effective Date: 01/01/2021

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.

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 in patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis to be **eligible for coverage.****

Based on review of available data, the Company may consider LDL apheresis **to be eligible for coverage**** in patients with heterozygous familial hypercholesterolemia who have failed diet therapy and maximum tolerated combination drug therapy (see Policy Guidelines section) AND who meet the following U.S. Food and Drug Administration (FDA) approved indications (all LDL levels represent the best achievable LDL level after a program of diet and drug therapy):

1. Functional hypercholesterolemic heterozygotes with LDL ≥300 mg/dL
2. Functional hypercholesterolemic heterozygotes with LDL ≥200 mg/dL[a] AND documented coronary artery disease.[a]

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 nonfamilial hypercholesterolemia, nephrotic syndrome, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy to be **investigational.***

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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.***

[a] For definitions of maximum tolerated drug therapy and documented coronary artery disease, see the Policy Guidelines section.

Policy Guidelines

A scientific statement from American Heart Association (see Supplemental Information section) for the treatment of heterozygous familial hypercholesterolemia (FH) has indicated that adults should be treated with available pharmacotherapy with an initial goal of reducing low-density lipoprotein cholesterol (LDL-C) by at least 50%, usually with a statin. This treatment can be followed by achieving an LDL-C of less than 100 mg/dL (absent coronary artery disease [CAD] or other major risk factors]) or 70 mg/dL (presence of CAD or other major risk factors). The following approach for pharmacotherapy is suggested:

- High-intensity statin therapy to target >50% LDL-C reduction, such as rosuvastatin or atorvastatin.
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding ezetimibe.
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding a PCSK9 inhibitor or colesevelam (or other bile acid sequestrant or niacin).
- If the patient is adherent and LDL-C is above the target goal after 3 months, proceed to complex therapy combination such as a 4-drug combination plus LDL apheresis.

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.

Because LDL apheresis represents a chronic, lifelong therapy, Plans may consider requiring precertification or prior approval to ensure that the patient meets patient selection criteria.

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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, familial hypercholesterolemia 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 in their thirties and forties, while women develop the disease in their fifties. Depending on the patient, heterozygous familial hypercholesterolemia may or may not respond adequately to lipid-lowering drugs.

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 coronary heart disease by 20 years of age. These patients typically do not adequately respond to drug or diet modification therapies. In the past, patients with homozygous familial hypercholesterolemia 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

LDL 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. HDL delipidation and plasma reinfusion removes plasma from the body, processed through a delipidation device, and then returned 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:

"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 m^2 **or**
The patient is post renal transplantation."

No devices have been approved by the FDA specifically for HDL delipidation. The Lipid Sciences Plasma Delipidation System-2 (Lipid Sciences) was tested in clinical studies, but the company ceased business operations in 2012.

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Rationale/Source

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.

Familial Hypercholesterolemia

For individuals with homozygous FH who are unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and a systematic review. Relevant outcomes are overall survival, 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 pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with heterozygous FH who are unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are overall survival, 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. 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 pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful 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 post treatment. 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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

For individuals with preeclampsia who receive LDL apheresis, the evidence includes a prospective case series. Relevant outcomes are overall survival, 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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

Acute Coronary Syndrome
For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes an RCT. Relevant outcomes are overall survival, 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 the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

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 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.

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 2019, the American Society for Apheresis updated guidelines on the use of apheresis for 7 conditions (see Table 1).

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

Recommendation	Category	Gradea
Homozygous familial hypercholesterolemia	I	1A
Heterozygous familial hypercholesterolemia	II	1A
Focal segmental glomerulosclerosis	II	2C
Lipoprotein (a) hyperlipoproteinemia	II	1B
Peripheral vascular diseases	II	IB
Phytanic acid storage disease (Refsum disease)	II	2C

Sudden sensorineural hearing loss	IIIb	2A

[a] Grade 1A: strong recommendation, high-quality evidence; grade 1B: strong recommendation, moderate-quality evidence; grade 2A: weak recommendation, high-quality evidence; grade 2C: weak recommendation, low-quality evidence.
[b] Optimum role not established.

American Heart Association
In 2015, the American Heart Association issued a scientific statement on the treatment of heterozygous FH indicating that high-risk adults should be treated with available pharmacotherapy with an initial goal of reducing low-density LDL-C by at least 50%, usually with a statin, and treatment should be intensified based on the response. It also stated that there are no data to inform pediatric treatment goals, whether to target an LDL-C level of less than 100 or 130 mg/dL or to aim to achieve a 50% reduction in LDL-C from baseline.

For homozygous FH, the American Heart Association has recommended that lipid apheresis should be considered by 5 years of age or earlier in exceptional circumstances and should be used after maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The LDL-C selection criteria for lipid apheresis include a reduction in LDL-C of less than 50% by other treatments and residual severe LDL-C elevation of more than 300 mg/dL or more than 200 mg/dL with prevalent cardiovascular disease.

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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02791802	Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes	1000	Aug 2021

NCT: national clinical trial.

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10/07/2020 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019

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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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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	E78.00-E78.01

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    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.

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