BlueCross BlueShield of Alabama

Name of Blue Advantage Policy

Lipid Apheresis

Policy #: 103
Category: Therapy

Latest Review Date: July 2021
Policy Grade: **Effective 7/14/2021: Active policy but no longer scheduled for regular literature reviews and updates.**

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **low-density lipid apheresis** as a **covered** benefit when the following medical criteria are met:

- Patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis; **OR**
- Patients with heterozygous familial hypercholesterolemia who have failed a 6-month trial of diet therapy and maximum tolerated combination drug therapy* **and** who meet the following FDA-approved indications: (All LDL levels represent their best achievable LDL level after a program of diet and drug therapy.)
    - Functional hypercholesterolemic heterozygotes with LDL ≥ 300 mg/dL; **OR**
    - Functional hypercholesterolemic heterozygotes with LDL ≥200 mg/dL **and** documented coronary artery disease**

*Maximum tolerated combination drug therapy is defined as a trial of drugs from at least two separate classes of hypolipidemic agents such as bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, or Niacin/Nicotinic acids.

**Documented coronary artery disease includes a history of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty (PTCA) or alternative revascularization procedure, or progressive angina documented by exercise or non-exercise stress test.

Blue Advantage will treat **low-density lipid apheresis** as a **non-covered** benefit for any other indications, including use in preeclampsia.

Blue Advantage will treat **therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion for all indications,** including but not limited to acute coronary syndrome, as a **non-covered benefit** and as **investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

This use of low-density lipoprotein (LDL) apheresis has been proposed to treat various types of familial hypercholesterolemia (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.

Lipid Apheresis

Lipid apheresis (also referred to as low-density lipoprotein [LDL] apheresis) involves the extracorporeal removal of apo B–containing lipoproteins, including LDL, lipoprotein(a), and very low-density lipoprotein (VLDL).

The apheresis procedure is designed isolate plasma. The LDLs are then selectively removed from the plasma by immunoadsorption, heparin-induced extracorporeal LDL precipitation (HELP), 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 HELP, 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.

Therapeutic apheresis with selective High-density lipoprotein (HDL) delipidation and plasma reinfusion is a procedure in which plasma is removed from the body by apheresis, processed through a delipidation device and then returned to the patient. The delipidation procedure selectively removes cholesterol from HDL, converting the major alpha HDL to pre-beta-like HDL. The plasma with pre-beta-like HDL is then reinfused to the patient. The pre-beta-like HDL is 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.

Diseases Treated with Lipid Apheresis

Lipid Apheresis is used for disorders with marked hyperlipidemia, primarily familial hypercholesterolemia (FH). FH is a dominantly inherited disorder involving a mutation of 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 low-density lipoprotein cholesterol (LDL-C) levels that are approximately 2 to 3 times levels that are considered acceptable (i.e., >300 mg/dL). Affected male patients typically develop coronary heart disease in their thirties and forties, while women develop coronary heart disease in their fifties. Depending on the patient, heterozygous FH may or may not respond adequately to lipid-lowering drugs.

Homozygous hypercholesterolemia is rare, only occurring in 1 in 1 million subjects. Serum levels of LDL-C may be elevated six-fold (>500 mg/dL), due to the total lack of functioning LDL receptors. Homozygotes may develop severe aortic stenosis and coronary heart disease by age 20 years. These patients typically do not adequately respond to drug or diet modification therapy. 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 the plasma.

KEY POINTS:

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through March 26, 2021.

Summary of Evidence

Familial Hypercholesterolemia

For individuals with homozygous familial hypercholesterolemia (FH) who are unable to achieve target low-density lipoprotein cholesterol (LDL-C) with maximally tolerated pharmacotherapy who receive low-density lipoprotein (LDL) apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and 1 systematic review. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastically lowering LDL by lipoprotein apheresis increases longevity in homozygous FH. Studies have reported reductions in LDL-C levels after apheresis, ranging in mean 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 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 an 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 OS, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastically lowering LDL-C using LDL apheresis decreases cardiovascular morbidity in FH heterozygotes refractory to or intolerant of statins. Studies have reported reductions in LDL-C levels after apheresis with means ranging from 58% to 63%. 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 an improvement in the net health outcome.

Nonfamilial Hypercholesterolemia

For individuals with non-FH who receive LDL apheresis, the evidence includes multiple nonrandomized cohort studies, both retrospective and prospective. Relevant outcomes are overall survival, 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.

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 end point, 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, ultimately, 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 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 that the technology results in an improvement in the net health outcome.

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 high-density lipoprotein (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 (e.g., 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 a 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.

Additional Information
Not applicable.

Practice Guidelines And Position Statements
National Institute for Health and Care Excellence
In 2019, the National Institute for Health and Care Excellence's (NICE) updated its guidance on familial hypercholesterolemia (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.

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

Guideline	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[b]	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 (AHA) issued a scientific statement on the treatment of heterozygous FH indicating 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, and treatment should be intensified based on 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.

KEY WORDS:
Low-density apheresis, LDL apheresis, familial hypercholesterolemia, FH, Liposorber, HELP® System, HDL delipidation, homozygous hypercholesterolemia

APPROVED BY GOVERNING BODIES:
Two lipid apheresis systems have received approval from FDA for marketing. In February 1996, dextran sulfate device "Liposorber LA-15® System" (Kaneka Pharma, New York City, NY) was approved by 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 October 2013, the Liposorber LA-15 System received approval 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 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 forhomozygous 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 September 2007, heparin-induced extracorporeal LDL precipitation "HELP® System" (B. Braun, Melsungen, Germany) was approved by FDA through the premarket approval process for use in the above indication.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT code:

36516	Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion
0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion

HCPCS code:

S2120	Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

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POLICY HISTORY:

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Medical Policy Group, May 2021
Medical Policy Group, July 2021. Effective 7/14/2021: Active policy but no longer scheduled for regular literature reviews and updates.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.