

## Corporate Medical Policy

### Lipid Apheresis

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<b>Origination:</b>	11/2013
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#### Description of Procedure or Service

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Therapeutic apheresis describes a variety of technologies used to remove select components from the plasma to treat disorders such as familial hypercholesterolemia (FH) and other significant hyperlipidemia, and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately removes components, such as low-density lipoprotein (LDL) particles from the plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

##### Background

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

The apheresis procedure is designed to 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 removes plasma 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 (alpha HDL) to pre- $\beta$ -like HDL (pre-beta-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- $\beta$ -like HDL is then reinfused into the patient.

##### Diseases Treated With LDL Apheresis

Lipid apheresis is used for disorders with marked hyperlipidemia, primarily familial hypercholesterolemia (FH). 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 low-density lipoprotein cholesterol (LDL-C) levels that are approximately 2 to 3 times the levels that are considered acceptable (i.e., greater than 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. Due to the total lack of functioning LDL receptors, serum levels of LDL-C may be elevated 6-fold (greater than 500

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mg/dL). 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 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 the plasma.

## Regulatory Status

Two low-density lipoprotein (LDL) apheresis systems have received approval from the U.S. Food and Drug Administration (FDA) for marketing. In February 1996, the dextran sulfate device Liposorber LA-15® System (Kaneka Pharma), 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.

In 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]  $\geq 60$  mL/min/1.73 m<sup>2</sup> OR
- The patient is post-renal transplantation.

No devices have been FDA approved 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.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## **Policy**

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**BCBSNC will provide coverage for LDL apheresis when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

**HDL delipidation is considered investigational for all applications as noted below. BCBSNC does not provide coverage for investigational services or procedures.**

## **Benefits Application**

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## **When Lipid Apheresis is covered**

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LDL apheresis is considered medically necessary for patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis.

LDL apheresis is considered medically necessary for patients with heterozygous familial hypercholesterolemia (HFH) who have failed diet therapy and maximum tolerated combination drug therapy AND who meet the following FDA approved indications: (All LDL levels represent the best achievable LDL level after a program of diet and drug therapy.)

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1. Functional hypercholesterolemic heterozygotes with LDL  $\geq$  300 mg/dL
2. Functional hypercholesterolemic heterozygotes with LDL  $\geq$  200 mg/dL AND documented coronary artery disease

## When Lipid Apheresis is not covered

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LDL apheresis is considered investigational for all other clinical indications with the exception of those listed above, including nonfamilial hypercholesterolemia, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy.

Therapeutic apheresis with selective HDL delipidation and plasma reinfusion is considered investigational for any clinical indication.

## Policy Guidelines

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The evidence for the use of lipid apheresis in patients with homozygous and heterozygous familial hypercholesterolemia (FH) unable to achieve target low-density lipoprotein cholesterol (LDL-C) with maximally tolerated pharmacotherapy, includes multiple nonrandomized prospective and retrospective small cohort studies, as well as systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown 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 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.

The evidence for the use of lipid apheresis for patients with non-FH, 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 pre-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 the effects of technology on health outcomes.

The evidence for the use of lipid apheresis for patients with treatment-resistant nephrotic syndrome, 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 healthy outcomes.

The evidence for the use of lipid apheresis for other conditions (e.g., preeclampsia, sudden sensorineural hearing loss, diabetic foot ulcerations, nonarteritic acute anterior ischemic optic neuropathy, peripheral arterial disease) includes primarily noncomparative studies, along with 2 RCT evaluating lipid apheresis in sudden sensorineural hearing loss. Relevant outcomes are change in disease status and treatment-related morbidity. These studies are characterized by

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heterogeneity in the patient populations and outcomes measured. The body of evidence consists primarily of only noncomparative studies (case series or cohort studies). Comparative studies are needed to evaluate outcomes in similar patient groups who are treated with and without lipid apheresis. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of therapeutic apheresis with selective HDL delipidation and plasma reinfusion in patients with acute coronary syndrome, includes 1 RCT. Relevant outcomes are overall mortality, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. This RCT reported improvements in certain biochemical measures (eg, pre-beta-like HDL and alpha HDL levels). There was no significant change in atheroma volume. Larger randomized trials with longer follow-up and clinically relevant outcomes are needed to determine the impact of delipidated HDL plasma for acute coronary syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 36516, S2120, 0342T*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## **Scientific Background and Reference Sources**

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 8/9/12

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Lipid apheresis in the treatment of severe, refractory hypercholesterolemia. TEC Assessments 1999; Volume 14, Tab 3.

National Institute for Health and Clinical Excellence (NICE). National Collaborating Centre for Primary Care. Identification and management of familial hypercholesterolaemia. London (UK). 2008 Aug. 45p. (Clinical guideline; no.71).

Kavey RE, Allada V, Daniels SR et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006; 114(24):2710-38.

Food and Drug Administration (FDA). Pre-market approval (P940016) for H.E.L.P. Plasmate® Futura Apheresis System. Retrieved from [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma\\_template.cfm?id=p940016](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p940016)

Medical Director review 3/2013

Specialty Matched Consultant Advisory Panel review 4/2013

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 8/8/13

Van de Woestijne AP, van der Graaf Y, Liem AH, et al. Low high-density lipoprotein cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid-lowering medication. *J Am Coll Cardiol*. 2013 Nov 12;62(20):1834-41.

Sacks FM, Rudel LL, Conner A, Akeefe H, Kostner G, Baki T, et al. Selective delipidation of plasma HDL enhances reverse cholesterol transport in vivo. *J Lipid Res*. 2009 May;50(5):894-907.

Waksman R, Torguson R, Kent KM, Pichard AD, et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. *J Am Coll Cardiol*. 2010 Jun 15;55(24):2727-35.

Medical Director review 11/2013

Specialty Matched Consultant Advisory Panel review 4/2014

Medical Director review 4/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 8/14/14

Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 8/13/15

Food and Drug Administration. Summary of Safety and Probable Benefit: LDL Apheresis System (HDE number H120005). 2013; [http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/H120005b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/H120005b.pdf). Accessed September 4, 2015.

Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. Aug 21 2014;35(32):2146-2157. PMID 25053660

Specialty Matched Consultant Advisory Panel review 4/2016

Medical Director review 4/2016

Specialty Matched Consultant Advisory Panel review 4/2017

Medical Director review 4/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 5/2017

Medical Director review 5/2017

Specialty Matched Consultant Advisory Panel review 4/2018

Medical Director review 4/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 5/2018

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Specialty Matched Consultant Advisory Panel review 4/2019

Medical Director review 4/2019

Specialty Matched Consultant Advisory Panel review 4/2020

Medical Director review 4/2020

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.02.04, 6/2020

Specialty Matched Consultant Advisory Panel review 4/2021

Medical Director review 4/2021

## **Policy Implementation/Update Information**

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12/31/13 New policy developed. LDL apheresis is covered for patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis. LDL apheresis is covered for 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 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 AND documented coronary artery disease. LDL apheresis is not covered for all other clinical indications, with the exception of those listed above. HDL delipidation is not covered for any clinical indication. Medical Director review 11/2013. Notification given 12/31/2013 for effective date 3/11/2014. (mco)

5/13/14 Specialty Matched Consultant Advisory Panel review 4/2014. Medical Director review 4/2014. No changes to Policy Statements. (mco)

11/11/14 Reference added. "Description" section updated. "Policy Guidelines" section updated. "When not covered section" updated. No change to Policy Statement. (td)

7/1/15 Specialty Matched Consultant Advisory Panel review 4/2015. Medical Director review 4/2015. Policy Statements remain unchanged. (td)

10/1/15 Description section updated. Policy Guidelines section updated. References updated. Policy intent unchanged. (td)

5/31/16 Specialty Matched Consultant Advisory Panel review 4/2016. Medical Director review 4/2016. (td)

5/26/17 Minor edits only. Specialty Matched Consultant Advisory Panel review 4/2017. Medical Director review 4/2017. (jd)

6/30/17 Description and Background sections updated. Removed "6-month trial" from the second medically necessary policy statement in the When Covered section. Additional specific examples added to the LDL apheresis investigational statement in the When Not Covered section. Policy Guidelines extensively revised and references updated. Medical Director review 5/2017. (jd)

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- 5/11/18 Specialty Matched Consultant Advisory Panel review 4/2018. Medical Director review 4/2018. (jd)
- 5/14/19 References updated. Specialty Matched Consultant Advisory Panel review 4/2019. Medical Director review 4/2019.(jd)
- 4/28/20 Specialty Matched Consultant Advisory Panel review 4/2020. Medical Director review 4/2020. (jd)
- 5/4/21 References updated. Specialty Matched Consultant Advisory Panel review 4/2021. Medical Director review 4/2021. (jd)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.