



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Apheresis for Familial Hypercholesterolemia

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

Coverage Policy

CIGNA covers apheresis for severe, refractory familial hypercholesterolemia (FH) as medically necessary for EITHER of the following:

- homozygous FH with low-density lipoprotein (LDL) cholesterol levels > 500 mg/dL
- failure of a six-month treatment plan of diet and maximum tolerated drug therapy (unless contraindicated) **AND EITHER** of the following:
 - heterozygous FH with LDL cholesterol levels ≥ 300 mg/dL
 - heterozygous FH with LDL cholesterol levels ≥ 200 mg/dL and documented coronary heart disease

General Background

Familial hypercholesterolemia (FH) is an inherited anomaly of low-density lipoprotein (LDL) receptors that was first described in 1973 by Goldstein et al. It affects up to 2% of the U.S. population. FH leads to extremely high blood levels of LDL cholesterol, ultimately resulting in early atherosclerotic disease. It is an autosomal-dominant trait that occurs in two forms: heterozygous (i.e., one mutant gene inherited) and homozygous (i.e., two mutant genes inherited). Heterozygous FH occurs in approximately one in 500 persons in the general population, more

frequently in men than in women. Plasma cholesterol levels in heterozygous FH are generally in the range of 300–500 mg/dL (Goldman, 2000). In contrast, the homozygous form of FH, although more severe, is extremely rare, occurring in approximately one case per million persons. Plasma cholesterol levels can exceed 800–1000 mg/dL in homozygous FH (Goldman, 2000). Early diagnosis and lifelong treatment are essential to reduce the risk of cardiovascular disease, increase life expectancy and improve quality of life. Children with this disorder develop atherosclerotic disease very early in childhood, are at extreme risk of early coronary events and often die suddenly or experience acute myocardial infarction in the first decade of life. Thompson et al. (2008) report that in children, data suggest LDL apheresis should be started around age six or seven years, and that starting it after age 10 years may be too late to prevent the development of aortic stenosis. Generally, the earlier the treatment is started the better the prevention of complications.

The primary goal of treatment is to reduce plasma LDL cholesterol levels in order to reduce the risk of developing atherosclerosis and coronary artery disease. Treatment strategies for FH include the following:

- LDL apheresis
- drug therapy
- diet therapy
- orthotopic liver transplant
- gene therapy (a more recent development)

Standard treatment for hypercholesterolemia includes lifestyle changes, diet and lipid-lowering medications. Although most patients with hypercholesterolemia respond to medical management, some patients with heterozygous FH and most patients with homozygous FH are refractory to treatment.

Drug therapy is usually necessary in combination with diet, weight loss, and exercise, as any of these interventions alone may not achieve lower cholesterol levels. There are a number of cholesterol-lowering medications that are currently used. The first and more effective choice are drugs called "statins." Other drugs that may be used in combination with or instead of the statins are: bile acid sequestrant resins (for example, cholestyramine), ezetimibe, nicotinic acid (niacin), gemfibrozil, and fenofibrate.

Individuals who have homozygous familial hypercholesterolemia need more aggressive therapies to treat their significantly elevated levels of cholesterol. Often drug therapies are not sufficient to lower LDL cholesterol levels at the desired goal and these individuals may require periodical LDL apheresis, a procedure to "clean up" LDL from the blood stream, or highly invasive surgery such as a liver transplant.

Lipid apheresis is an invasive procedure that selectively removes LDL cholesterol and other lipoproteins from the plasma of refractory patients. LDL apheresis involves separation of the patient's blood into cellular and plasma fractions, treatment of the plasma to remove the lipoprotein particles and recombination of the plasma and cells, followed by transfusion of the purified blood. The apheresis devices separate blood cells from plasma, using either a filter or a centrifuge. The plasma is then channeled through a purification column that selectively removes particles containing lipoproteins and triglycerides, without removing high-density lipoproteins. Treatment lasts three to four hours, during which time the LDL cholesterol concentration is reduced by 70–80%. The procedure is repeated approximately every two weeks in severe heterozygous FH and at seven- to ten-day intervals in the rare patient with homozygous FH (Illingworth, 2001).

Apheresis procedures are performed in outpatient settings by specially trained clinicians. LDL apheresis is contraindicated in patients for whom the use of heparin would cause excessive or uncontrolled anticoagulation, for whom anticoagulation cannot be safely achieved (e.g., hemophilia, recent surgery), or for known hypersensitivity to heparin or ethylene oxide. Potential adverse reactions that have been associated with LDL apheresis include, but may not be limited to, hypotension, nausea/vomiting, flushing/blotching, chest pain, fainting, lightheadedness, anemia, abdominal discomfort, numbness/tingling, tachycardia, shortness of breath, hemolysis, bradycardia, arrhythmia, hives, vasovagal reaction and prolonged bleeding (FDA PMA P910018, P940016).

U.S. Food and Drug Administration

Apheresis may be indicated to reduce LDL levels in FH patients who do not reach LDL target levels and are considered to be at high risk (i.e., documented evidence of atherosclerotic heart disease). The U.S. Food and

Drug Administration (FDA) criteria recommend LDL apheresis for patients who have failed prior treatment plans consisting of diet therapy and maximum drug therapy (defined as a trial of drugs from at least two separate classes of hypolipidemic agents) for at least six months and who have homozygous FH with LDL levels > 500 mg/dL, heterozygous FH with LDL levels of ≥ 300 mg/dL, or heterozygous FH with LDL levels ≥ 200 mg/dL plus documented coronary heart disease (Vella, Pineda, O'Brien, 2001; FDA PMA P910018 and P940016). Diagnosis of coronary heart disease includes documentation of coronary artery disease by coronary angiography or a history of myocardial infarction (MI), coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA), or alternate revascularization procedure (e.g., atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test. The FDA does not mention documentation by coronary calcium scoring.

A number of methods using various devices are available for selective removal of low-density lipoproteins. The FDA has given premarket approval to the Liposorber L-15 system and the Heparin-induced Extracorporeal Lipoprotein Precipitation HELP™ system for clinical use in treating patients with severe, refractory FH. A dextran sulfate cellulose (DSC) system, the Kaneka Liposorber® L-15 system (distributed by Kaneka Pharma America Corporation, New York), uses disposable dextran sulfate columns. As the plasma is passed over the columns, they selectively bind very low-density lipoprotein (VLDL), LDL, and lipoprotein A, commonly called Lp(a). Dextran sulfate has a structure similar to that of the LDL receptor in the human body and seems to act as a pseudo receptor for LDL. The HELP system (B. Braun Medical, Inc., Bethlehem, PA) employs a technique referred to as heparin-induced extracorporeal LDL precipitation. This system uses heparin, a natural anticoagulant, as the medium to precipitate VLDL, LDL, and Lp(a) from extracorporeal plasma. It is hypothesized that the heparin acts with LDL molecules to form LDL-heparin complexes, which are then separated from the plasma.

Systems that are being studied but have not yet received FDA approval include, but are not limited to, DALI® System (Fresenius HemoCare Adsorber Technology, St. Wendel, Germany) and Liposorber D® System (Kaneka Corporation, Osaka, Japan), both of which are whole blood adsorbers and adsorb apoB-containing lipoproteins such as LDL, VLDL and lipoprotein(a).

Literature Review

Published evidence evaluating the effectiveness of LDL apheresis for the treatment of FH comes in a variety of forms, including reviews, case reports, case series, and both nonrandomized and randomized trials. Several clinical trials have demonstrated that lipid apheresis is associated with a greater reduction in LDL levels when compared to medication alone. Overall, there is a large body of evidence in the published scientific literature to support the safety and efficacy of LDL apheresis for the treatment of FH. Many authors have reported that LDL apheresis, both with and without lipid-lowering drugs, has been shown to reduce total cholesterol levels, LDL cholesterol, and Lipoprotein(a), in addition to inducing atherosclerosis regression, improving myocardial blood flow and endothelial function, and in decreasing the rate of cardiovascular events (Nishimura, et al., 1999; Matsuzaki, et al., 2002; Bambauer, et al., 2003; Moga and Harstell, 2004; Koga, 2005; Ziajka, 2005; Thompsen and Thompson, 2006).

Authors have recently reported on long-term safety and efficacy of LDL apheresis treatment in children. Palcoux and colleagues (2008) studied patients who started LDL apheresis in childhood (prior to age 15) to assess feasibility, safety and efficacy (n=27). Most cases were diagnosed prior to age five years (63%); the average age of initiation of treatment was 8.5 ± 3 years, and the mean length of follow-up was 12.6 ± 6 years. The authors noted that LDL apheresis was feasible in young children, resulted in efficient biological results and cardiac events, and aside from minor side effects and technical problems the procedure was safe. A second group of authors, Hudgins et al. (2008), performed an analysis of a registry of 29 patients who began LDL apheresis prior to age 18 years at 15 different sites since the FDA approved the treatment devices, to evaluate long-term safety and efficacy. Twenty patients were available for follow-up (seven discontinued treatment and two died from unrelated causes). Patients were treated for as long as 21 years. Based on the author's findings, in this group of patients the mean age at the start of treatment was 9 ± 4 years and the mean treatment duration was 6 ± 4 years. Baseline LDL cholesterol (521 ± 126 mg/dl) was acutely lowered by 75% and chronically lowered (calculated average between treatments) by 48% with biweekly treatments. Of 12 patients who had atherosclerotic disease of the coronary arteries and/or aorta at baseline, six progressed to more severe symptomatic disease. The treatment was well tolerated by all subjects. The authors noted that while LDL apheresis was effective in lowering LDL cholesterol, target LDL levels were not achieved. The authors also

conducted a chart review of nine patients treated at the Rogosin Institute. For this group of patients cholesterol values following treatment were similar.

Sachais and colleagues (2005) published results from a retrospective analysis of both clinical and laboratory data, in addition to cardiovascular outcomes for a cohort of patients (n=34) receiving LDL-apheresis for FH between 1996 and 2003. The average length of treatment was 2.5 years. The data collected included laboratory values, adverse events, cardiovascular events and interventions. Apheresis was performed every two weeks. Adverse reactions were rare. All patients had markedly decreased LDL cholesterol and triglycerides after each treatment without a significant change in HDL cholesterol. After treatment with LDL apheresis for an average of 2.5 years, the patients had a 3.2- fold decrease in cardiovascular events (myocardial infarction, stroke, transient ischemic attack, rupture of an aortic aneurysm) and an over 20-fold decrease in cardiovascular interventions (coronary bypass surgery, carotid endarterectomy, coronary artery angioplasty, coronary artery stent placement). The patients reported decreased episodes of angina symptoms and improved quality of life.

Four small case series (n=5 to n=120) were conducted between 2000 and 2002 by NY Presbyterian Hospital, Weill Medical College of Cornell University Center for Human Nutritional Research, the Boston Heart Foundation with Harvard/MIT, and the University of Munich (Germany). The case studies indicate that apheresis using immunoabsorption columns, dextran cellulose columns or heparin precipitation is a safe and efficacious procedure for lowering LDL cholesterol in severe FH.

Randomized, controlled clinical trials have supported the effectiveness of LDL apheresis in slowing the progression of coronary heart disease and in improving several circulatory parameters. Kroon et al. (1996) conducted a randomized trial of 42 men with primary hypercholesterolemia and extensive atherosclerosis who were refractory to drug therapy. LDL apheresis combined with drug therapy was compared to drug therapy alone. The LDL apheresis-drug therapy combination aggressively lowered lipids, decreased the thickness of the carotid artery and prevented an increase in stenosis of the lower limbs as measured by Doppler. Gordon et al. (1998) reported the long-term safety, lipid lowering, and clinical efficacy of LDL apheresis for a five-year period that included both the initial controlled study and the follow-up phase. The controlled trial of patients (n=64) with FH that was unresponsive to diet and drug therapy demonstrated an immediate reduction of LDL cholesterol in both homozygotes and in heterozygotes, as well as a decrease in the rate of cardiovascular events. Donner et al. (1997) reported the long-term (three-year) effects on coronary heart disease of LDL apheresis plus lipid-lowering drugs. The authors' findings showed that, in 34 patients who had coronary artery disease and heterozygous FH and were not adequately responsive to lipid-lowering drugs, the progression of cardiac lesions regressed or slowed in response to the dual treatment.

The Alberta Heritage Foundation for Medical Research, (now the Institute for Health Economics [IHE]), conducted a technology assessment (Moga, Harstell, 2004) to evaluate the safety and effectiveness of using apheresis to lower the concentration of LDL cholesterol in patients with FH. There were no systematic reviews or randomized controlled trials published from 1998 to 2003. The authors evaluated controlled studies that compared the efficacy and safety of LDL apheresis using the dextran sulfate cellulose (DSC) system and/or the HELP system with conventional drug therapy for lowering cholesterol levels, and studies that compared the DSC system and/or HELP system with other apheresis systems. The controlled studies did have methodological weaknesses; however, the reported results suggest that aggressive cholesterol lowering therapy, defined as LDL apheresis (LDL-A) combined with drugs, was an effective and safe treatment for patients with homozygous FH and severely ill heterozygous FH patients with coronary artery disease (CAD). The level of reduction that must be achieved by the addition of LDL-A or plasmapheresis to drug therapy in order to show a clinical benefit is not clearly defined. In addition, further studies are needed to evaluate safety and efficacy in other categories of patients such as pregnant women, women during the lactation period, and children.

In October 2007, the Ontario Health Technology Advisory Committee (OHTAC) published an evidence based analysis evaluating low-density lipoprotein apheresis using the H.E.L.P. system for the treatment of patients with refractory homozygous and heterozygous FH. The committee identified 398 articles published between January 1998 and May 2007, eight of which met inclusion criteria (five case series, two case series nested within comparative studies, and one retrospective review). A technology assessment conducted by the Alberta Heritage Foundation and the FDA reviews were also included. Based upon the analysis of available evidence, the group reported that the mean acute relative decrease in LDL cholesterol ranged from 53 to 77%. The mean chronic relative decreases in LDL cholesterol and total cholesterol ranged from 9 to 46% and 5 to 34%, respectively. The chronic mean relative increase in HDL cholesterol ranged from 12 to 27%. In general, the

studies were of low quality. An economic analysis to forecast future costs was also conducted. The evidence for the safety and effectiveness of HELP for patients with homozygous FH was limited; however, since it is such a rare condition, obtaining better-quality evidence is unlikely. The committee did not identify any studies that assessed long-term outcomes such as survival rates and cardiovascular events. The conclusions of the committee's analysis was that for homozygous FH patients, the benefits of LDL apheresis clearly outweigh the risks and burdens; in both homozygous and heterozygous patients, there is evidence of overall clinical benefit of LDL apheresis from case series studies; and in contrast to homozygous patients, there remains a lot of uncertainty in the social/ethical acceptance of this technology for the treatment of refractory heterozygous patients due to uncertainty in the estimate of benefits, risks, and burdens (OHTAC, 2007).

Summary

Familial hypercholesterolemia (FH) is an inherited low-density lipoprotein (LDL) receptor abnormality in which extremely high levels of low-density lipoprotein cholesterol lead to the early development of atherosclerotic disease. Patients who are unresponsive to or who cannot tolerate conventional lipid-lowering agents and diet therapy have limited treatment options. LDL apheresis has been shown to effectively reduce LDL levels. The available, published scientific literature is sufficient evidence to support the use of LDL apheresis in the treatment of elevated cholesterol demonstrated in patients with severe, refractory FH.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT ^{®*} Codes	Description
36516	Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion.

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

ICD-9-CM Diagnosis Codes	Description
272.0	Pure hypercholesterolemia

*Current Procedural Terminology (CPT[®]) ©2008 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2008	0010	Apheresis for Familial Hypercholesterolemia
Great-West Healthcare	4/23/07	95.286.05	Plasmapheresis, Plasma Exchange, Therapeutic Apheresis

9/19/07

05.324.02

Plasmapheresis, Therapeutic LDL
Apheresis for Severe
Hypercholesterolemia

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