



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 ©2010 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 and 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:

- diet therapy
- drug therapy
- LDL apheresis
- orthotopic liver transplant

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.

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 to 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 (FDA)

The 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 \geq 300 mg/dL, or heterozygous FH with LDL levels \geq 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.

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, both nonrandomized and randomized trials and technology assessments. 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 (Kroon, et al., 1996; Donner, et al., 1997; Gordon, et al., 1998; Moga, Harstell, 2004; Sachais et al., 2005; Ontario Health Technology Advisory Committee [OHTAC], 2007). Several clinical trials have demonstrated that lipid apheresis is associated with a greater reduction in LDL levels when compared to medication alone and 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; Thompson and Thompson, 2006). Additionally, when evaluating long-term safety and efficacy of LDL apheresis in children, studies have also demonstrated efficient lowering of baseline LDL cholesterol levels (Coker, et al., 2009; Palcoux, et al., 2008; Hudgins, et al., 2008). There is sufficient evidence in the medical literature to support that in both homozygous and heterozygous patients, there is overall clinical benefit of LDL apheresis.

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®*	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®) ©2010 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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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.