

A PATIENT GUIDE TO THE LIPOSORBER® LA-15 SYSTEM

Humanitarian Use Device

Authorized by Federal (USA) law for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors, are unsuccessful or not well tolerated and the patient's glomerular filtration rate (GFR) ≥ 60 ml/min/1.73 m² or
- The patient is post renal transplantation.

The effectiveness of this device for this use has not been demonstrated.

Notes: The Liposorber® LA-15 System is approved for pediatric patients with focal segmental glomerulosclerosis (FSGS). All references to “you” in this booklet refer to “you”, if you are legally allowed to give your own consent (i.e., if you are age 18-21 years old). If you are providing consent on behalf of a child under the age of 18 “you” refers to your child.

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I. Key medical terms

The following terms are used in this guide or may be used by your physician in discussing your condition and possible treatments for your condition.

Air embolism: entry of air into your bloodstream

Anemia: not enough iron in your blood or loss of blood

Anticoagulation: blood thinning

Anti-hypertensive medications: medications for lowering high blood pressure

Arrhythmia: irregular heartbeat

Bolus : a rapid injection

Calcineurin inhibitor: Medications used to treat FSGS that reduce the effect of certain parts of the immune system

Extracorporeal: blood taken outside the body

Flushing/blotching: flushing is a temporary feeling of your body being hot or your skin, especially your face, become redder; blotching is when your skin has patches where it is redder.

Glomerular filtration rate: a measure of the function of the kidney

Hemolysis: breakdown of red blood cells

Hypersensitivity reaction: allergy

Hypotension: low blood pressure

Infection: damage to your body, usually caused by bacteria or viruses.

Myocardial infarction: a heart attack: complete or partial blockage of one of the arteries in your heart.

Prolonged bleeding (at blood access site(s)): bleeding at the site where the intravenous device or catheter is placed that continues in excess of 20 minutes after removal of the needle.

Plasma: the liquid part of the blood which does not contain the blood cells

Serum albumin: a particular type of protein in your blood. There are many types of proteins in your blood. A brief decrease in serum albumin does not usually cause serious adverse effects, but if it needs to be treated, your doctor will add an albumin solution to your blood.

Serum protein: proteins in your blood. There are many types of proteins in your blood. A brief decrease in serum proteins does not usually cause serious adverse effects, but if it needs to be treated, your doctor can provide these by an intravenous route or change your diet.

Thrombocytopenia: a persistent decrease in the platelets in your blood. Platelets help your blood clot.

Transient: temporary, brief.

Vitamin E: Vitamin E is one of many vitamins essential to your health. A significantly low level of Vitamin E can lead to problems with your nervous system. Vitamin E supplements (pills) usually help return Vitamin E to acceptable levels.

II. How this guide can help you

This Patient Guide provides basic information to respond to general questions which you are likely to have about treatment with the Liposorber LA-15 system. During and after you read this guide, please feel free to discuss this with your doctor and ask any questions that you may have with your physician, who is familiar with your specific medical condition. Treatment with this medical device must be prescribed by a physician and used by medical professionals who have been trained in its specific use.

III. Why you are considered a candidate

You have primary focal segmental glomerulosclerosis (FSGS), a generally aggressive disease of the kidney that has no known cause and has resulted in you experiencing nephrotic syndrome. Nephrotic syndrome means that you have low blood protein due to excess loss of protein through the urine. The low blood protein prevents your blood vessels from holding onto water, so the water leaks out under your skin and results in swelling. That swelling is called edema. You also may have less than normal kidney function. To be eligible to receive treatment for your kidney disease with the Liposorber LA-15 system, you must have a level of kidney function, called the “glomerular filtration rate”, of at least 60 ml/min/1.73 m², a measurement that your doctor will calculate. (The normal level is 110-120 ml/min/1.73 m².) In order to receive treatment (called LDL pheresis) with the Liposorber LA-15 system, you must also not be responding to standard treatments for FSGS.

In summary, you are being considered as a candidate to receive therapy with the Liposorber LA-15 system because, even though you receive medications currently available, the nephrotic syndrome associated with your kidney disease, primary focal segmental glomerulosclerosis (FSGS), persists.

IV. Indications for Treatment with Liposorber LA-15 System

Below are the medical conditions and circumstances that would allow your doctor to treat you with the Liposorber LA-15 system:

There are two approved uses of the Liposorber[®] LA-15 System related to FSGS. The Liposorber LA-15 System is indicated for use in the treatment of children with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) and:

- (1) Standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful or not well tolerated, and the patient’s glomerular filtration rate (GFR) \geq 60 ml/min/1.73 m², or
- (2) You have had a kidney transplant.

If you meet either of these above conditions (criteria) and, after reading this guide and discussing it with your physician, you choose this therapy, you will be closely followed by the medical team, including checking for various symptoms that can occur due to the kidney disease or those that may occur with the Liposorber LA-15 system therapy. You will also be required to provide blood for various laboratory tests during and after the time that you are being treated with the Liposorber LA-15 system.

V. Contraindications for Treatment with the Liposorber LA-15 System

Below are the medical conditions and circumstances that would not allow your doctor to treat you with the Liposorber LA-15 system:

- (1) your doctor is currently treating you with a medication called an angiotensin-converting-enzyme (ACE) inhibitor and believes that this medication cannot be stopped for at least a day before each treatment with the Liposorber[®].
- (2) your doctor believes that because you have certain conditions related to blood clotting (such as severe hemophilia, severe bleeding, severe stomach ulcers, or because you are receiving medications that reduce the amount of available vitamin K [an important blood clotting factor]) it will not be possible to give you medications that thin the blood (called anticoagulants) and prevent blood clotting during the procedure.
- (3) your doctor believes that you cannot tolerate therapy with a machine that temporarily removes large amounts of blood because you have a medical condition (such as poor heart function), current or recent heart attack (also called acute myocardial infarction), abnormal heart rhythm, recent or current stroke (acute apoplexy), or severe uncontrollable high blood pressure (hypertension) or low blood pressure (hypotension); or
- (4) you are allergic to parts of the Liposorber LA-15 system, including dextran sulfate cellulose, heparin (a blood thinner) or ethylene oxide (the chemical used to sterilize portions of the device).

VI. Alternatives

Treatment for nephrotic syndrome in patients with primary FSGS is very difficult due to many reasons, including the fact that the disease course is not the same in all patients. The goal of treatments that are currently being used is to control the symptoms (such as swelling, or edema, due to losses of excess protein through the urine), to slow down the disease and try to prevent the complete loss of kidney function (called End Stage Renal Disease, or ESRD). Once a patient develops ESRD, they must either start dialysis or receive a kidney transplant.

Currently available treatments include: 1) use of drugs that weaken the certain parts of immune system (immunosuppressives) such as corticosteroids (e.g., prednisone), medications that reduce the effect of other parts of the immune system (cyclosporine, tacrolimus), or mycophenolate mofetil, 2) use of medications that lower the blood pressure, 3) use of medications to slow down the leaking of protein through the urine, or 4) a combination of these treatments. In addition, providing the best nutritional therapy through the diet by reducing fat and fluid intake and using medications that remove excess water (diuretics) may be used to lessen or avoid symptoms. Among these treatment options, corticosteroids are usually most effective in causing remission (reduction of or complete disappearance) of nephrotic syndrome and are commonly used as the first treatment in combination with drugs that lower blood pressure. However, some patients do not respond well to this treatment. Other drugs that weaken the immune system may be used if corticosteroids do not provide improvement for the patient, but there are some patients who do not improve with the use of any current medication. Kidney transplantation can be effective in treating FSGS; however, the chance of survival of the kidney transplant may be severely reduced in many patients with FSGS. In children, FSGS is the leading cause of kidney transplant failure since the nephrotic syndrome and FSGS can return in the transplanted kidney.

There are many therapies for patients with FSGS and nephrotic syndrome. Not all patients need to receive the same treatments. As you consider the Liposorber LA-15 system therapy, you should discuss all other possible treatments for your disease with your physician.

VII. What is LDL-apheresis?

The Liposorber LA-15 system provides what is called “LDL-apheresis”. Treatment with the Liposorber LA-15 system requires the removal of blood from the body by inserting a large needle or catheter into a large vein (“intravenous insertion”), passage of that blood through the machine to remove LDL-cholesterol (a fat also called “bad cholesterol”), then returning the blood to your body through another catheter. Removal of large amounts of blood is called “extracorporeal” (outside the body) therapy. Excessively high blood LDL-cholesterol can build up to dangerous levels in some patients. The doctor will explain to you why this treatment may be helpful in patients with primary FSGS and nephrotic syndrome.

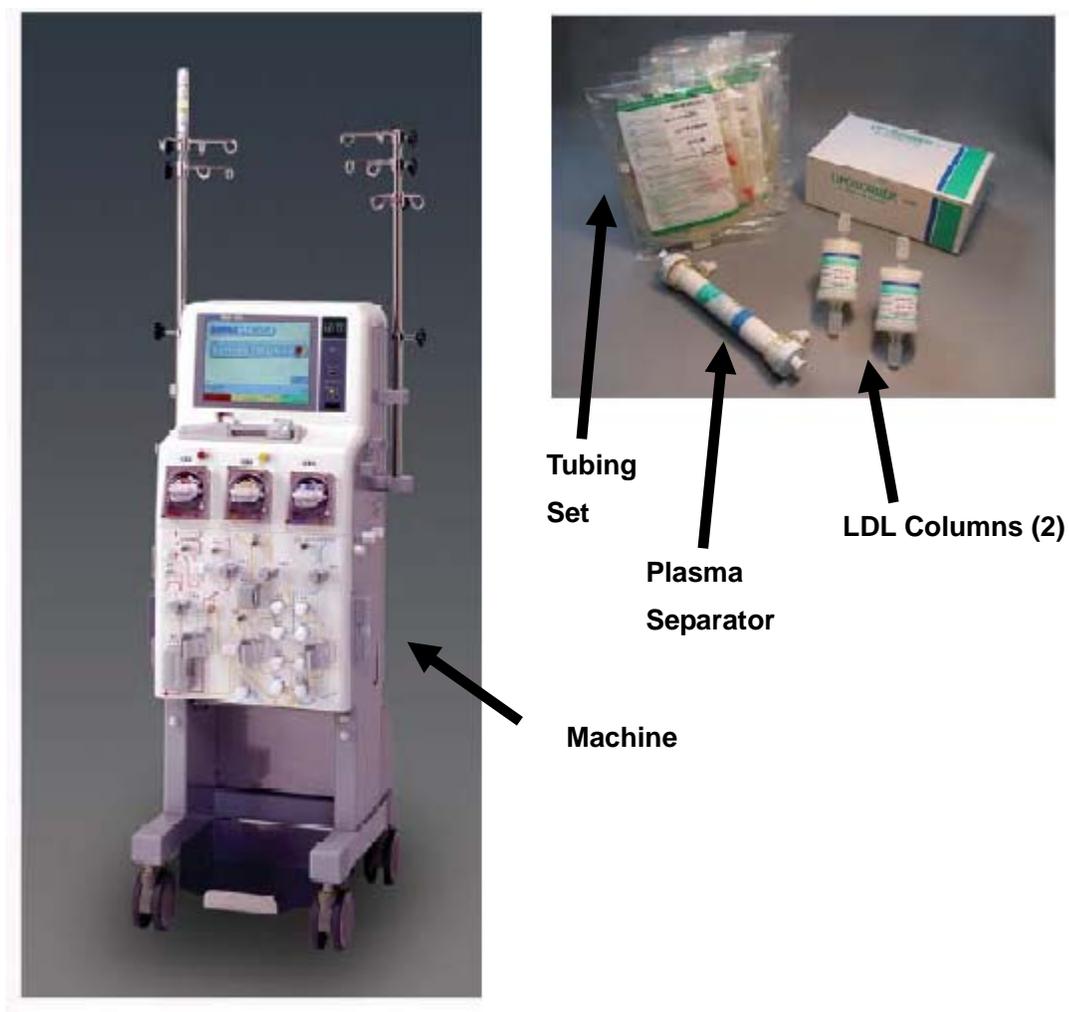
VIII. How is LDL-apheresis performed?

LDL-apheresis takes a portion of your blood and sends it through several parts of the Liposorber LA-15 system. That portion of your blood will be temporarily outside your body. The Liposorber LA-15 system has been approved in the United States since 1996 for use in patients with excessively high blood LDL-cholesterol levels who are not responding to diet and medical treatment. The blood, which contains blood cells (like white blood cells that fight infection), is removed from the body and first sent through the part of the system called the plasma separator. The plasma separator takes the blood cells out of the blood and leaves the liquid part (that contains the chemicals like salt, calcium, and LDL-cholesterol) to enter the rest of the LA-15 system (the columns). The blood cells are saved and eventually returned to you. Once the plasma enters the columns, it is cleansed of the LDL-cholesterol. The reason that your doctor is considering this treatment for you is that the system may also remove other substances in the plasma that may be involved in your kidney disease.

IX. What is the Liposorber[®] LA-15 System?

The Liposorber[®] LA-15 System consists of three parts that are used once then thrown away (disposables) along with a computerized machine that controls and checks the system’s mechanical functioning while you are undergoing the procedure. The disposable parts include the plasma separator, a

tubing set to move the blood around that is designed specifically for the Liposorber[®] LA-15 System, and two columns that contain a substance called dextran sulfate cellulose that traps and then removes LDL-cholesterol from the plasma.



LA-15 System

X. Use of the Liposorber LA-15 System for Nephrotic Syndrome and Primary FSGS

Although the system has been successful in lowering blood LDL-cholesterol levels in many patients with very high levels, your doctor believes that this system may also help relieve your nephrotic syndrome. This belief is based on studies that show that some children with nephrotic syndrome and primary FSGS who are not responding to drug therapy have benefited from treatment with the system. In one study of 11 children with FSGS who did not respond to medical therapy, Hattori and colleagues (published in the medical literature in the American Journal of Kidney Diseases in 2003) showed that the Liposorber[®] system, when used along with prednisone, caused remission of nephrotic syndrome in 7 of 11 patients within 9 weeks of starting treatment. Among the 7 children who had a remission, 5 had a complete (full) remission and as a group had normal kidney function over a period of 4.4 years. They only found that one patient had a problem (infection of a catheter) with the system treatment, which was not a severe infection. Although this offered some evidence of benefit for some patients with nephrotic syndrome and FSGS, to this day it is not known how the Liposorber[®] LA-15 system works to benefit patients with FSGS.

XI. What Happens with Treatment with the Liposorber[®] LA-15 System?

There are various steps involved with treatment with LDL-apheresis using the Liposorber[®] LA-15 System, including:

- (1) withdrawal of blood from a vein through a needle and entrance of the blood into the system. On occasion, the doctor may not be able to use a standard intravenous needle to obtain blood, and it will be necessary to insert a temporary catheter into a larger (chest) blood vessel;
- (2) a blood thinner called heparin that prevents your blood from clotting when it is outside your body will be added to your blood after it leaves your body;
- (3) Your blood will be passed through the Liposorber[®] LA-15 System.

Each part of the LDL-apheresis treatment is described in more detail below:

1. Access to Blood. The goal of the treatment is to have enough blood flowing through the device to allow the blood to be treated in a reasonable amount of time, but not have so much blood leaving your body that it would be considered unsafe. The proper amount of blood to remove at any time is based on your weight. With lower weight, a lower amount of blood should be removed at any one time. In order to remove and return blood to your body, needles attached to tubing will be inserted into a vein in your body. Usually, arm veins are big enough for the treatment to work; however, if your arm blood vessels are not adequate, your doctor may recommend that a catheter be placed in another place (for example, your upper chest). Insertion of the needles may be slightly painful, but once they are in place there should be little or no discomfort. The needles are attached to tubing and to a pump that moves the blood through the rest of the Liposorber LA-15 system and eventually through a part that adds a medication (called anticoagulants) that thins the blood to keep it from clotting while outside your body.

2. Anticoagulation. An anticoagulant (blood thinner) is necessary for all therapies where blood is removed from the body. Blood can easily clump (clot) while outside the body. If it clotted, treatment would have to be stopped. To prevent clotting, your doctor will add to the system a medication that prevents the blood from clotting while outside the body. Typically, you will first receive a large amount of heparin (called a bolus, or rapid injection) followed by a steady amount of heparin each hour. The blood thinning effects of heparin may continue for several hours after completing the procedure. The medical team will make sure that during this time, you are in a safe place to prevent you from trauma or other injury that could cause excessive bruising or bleeding.

3. LDL-Apheresis System (See Figure). After getting access to the blood and thinning it, the system pumps blood into the LDL-apheresis system, which includes the tubing, the plasma separator, the columns, and the machine. All parts of the system that come into contact with your blood and plasma are sterile (clean from bacteria and other harmful substances) and will be used only for one treatment.

Blood is continuously removed throughout the entire treatment. At the same time, once blood runs through the system, it is returned with the blood cells. Thus, the entire treatment involves the continuous removal and return of blood.

The Liposorber[®] LA-15 System has several built-in safety features, including a blood warmer,

filters, air detectors, and various alarms. The procedure takes approximately three hours to perform. Depending on how you are tolerating the treatments, you may receive up to a total of twelve treatments with the Liposorber LA-15 system over nine weeks.

4. Once the procedure is complete, the needles and tubing are removed from your blood vessels. Removal of the needles is not generally painful. Once the medical staff has made certain that the access sites in your blood vessels appear normal and that you are stable and able to leave, you will be released to go home.

XII. Safety of LDL-apheresis

Note: A detailed explanation of risks and adverse reactions associated with LDL-apheresis should be provided by your physician.

Adverse Reactions

The following potential adverse events (side effects) can be or have been associated with LDL-apheresis. These include:

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Death	Not reported to occur	Death
Cardiac (heart-related, including abnormal heart rhythm, slow heart rate, fast heart rate and heart attack)	Not reported to occur	Mild to serious
Thrombocytopenia (low count of platelets that help blood clot and prevent bleeding)	Not reported to occur	Mild to serious

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Infection (local or widespread)	Occurred in 2 of 20 patients	Mild to serious
Hypersensitivity (allergic-type reaction to a part of the system)	Not reported to occur	Mild to serious
Nausea and vomiting (abdominal symptoms)	0.3-2.5% of treatments (1/333 to 1/40 treatments)	Mild
Low Vitamin E level (which can cause muscle weakness, nausea and vomiting)	Not reported to occur	Mild
Temporary decrease in blood protein level (including albumin which holds water in the blood vessels)	Not reported to occur	Mild to moderate
Hypotension (low blood pressure)	2.0-2.5% of treatments (1/40 to 1/50 treatments)	Mild to severe
Flushing/blotching of skin	Not reported to occur	Mild
Angina (chest pain)	0.2-0.3% of treatments (1/500 to 1/333 treatments)	Mild to moderate
Fainting/lightheadedness	Not reported to occur	Mild to moderate
Anemia (low blood count)	Not reported to occur	Mild to serious
Prolonged bleeding at intravenous or catheter site	Not reported to occur	Mild to moderate
Hemolysis (breaking up of red blood cells)	Not reported to occur	Mild to serious
System (machine or its parts) malfunction	Not reported to occur	Mild to serious

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Vertigo (dizziness, unsteadiness)	0-0.3% of treatments (none to 1/333 treatments)	Mild to moderate
Diaphoresis (excess sweating)	Not reported to occur	Mild
Urticaria	Not reported to occur	Mild
Shivering	0-0.3% of treatments (none to 1/333 treatments)	Mild
Headache	0-0.5% of treatments (none to 1/333 treatments)	Mild

Some of the adverse events (side effects) are explained in greater detail below:

Hypotension or low blood pressure is the most common adverse reaction. If you have a hypotensive reaction during your treatment, it can be corrected by temporarily stopping your treatment, placing your head down and raising your legs, and, in some cases, giving you I.V. fluids. In most all cases, the hypotension will go away and your treatment can continue.

Stopping the procedure resolves most adverse reactions or complications that may occur during LDL-apheresis procedure.

Since certain medications, such as blood pressure medications called ACE inhibitors can cause severe medical problems if taken while you are receiving LDL-apheresis treatment and are therefore contraindicated (not allowed) while you are receiving a treatment (please see Section V above), your doctor will ask you if you have used these medications if you are scheduled for a Liposorber LDL-apheresis treatment.

Although no studies have been done to test the safety of the Liposorber for pregnant women or their unborn babies, there may be unknown adverse reactions for the woman or her unborn baby associated with the use of Liposorber LA-15 system during pregnancy.

XIII. What you can do to minimize adverse reactions

1. Do not have the procedure on an empty stomach. Make sure you eat and drink adequately before the procedure. If fasting blood samples are necessary, bring some food with you to eat while you are being treated.
2. Do not perform strenuous exercise on the day of your procedure.
3. If you are taking an ACE inhibitor medication, talk with your physician to consider a medication change.
4. Do not take other anti-hypertensive (for high blood pressure) medications on the day of treatment until after your LDL-apheresis procedure. Again, talk with your physician before stopping your medication.
5. Your physician may prescribe an iron supplement if you develop an iron deficiency anemia.
6. Avoid activities increasing the risk of physical injury for 24 hours after your treatment because of the blood thinning medication used.
7. Sexually active women of childbearing potential should use oral, implantable or barrier methods of birth control (e.g., birth control pills, intrauterine device, condoms) during treatment with the Liposorber LA-15 system to prevent pregnancy and any adverse reaction that may harm an unborn child.