

LIPOSORBER[®] LA-15

LDL ADSORPTION COLUMNS

Instructions for use in Familial Hypercholesterolemia (FH)

FH

Caution: Federal law restricts this device to sale by or on the order of a physician.

Carefully review the “LIPOSORBER[®] LA-15 System Operator’s Manual” and use only under the direction of a licensed physician with appropriate training.

KANEKA

Distributed by
KANEKA MEDICAL AMERICA LLC
623 Fifth Avenue, New York, NY 10022

Manufactured by
KANEKA CORPORATION
2-3-18, Nakanoshima Kita-ku, Osaka 530-8288, Japan

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I. Introduction

The LIPOSORBER® LA-15 LDL Adsorption Column set is one of three disposable device components of the LIPOSORBER® LA-15 System. It is comprised of two LIPOSORBER® LA-15 LDL Adsorption Columns, each containing 150 mL of dextran sulfate cellulose adsorbent.

The technical characteristics of the LIPOSORBER® LA-15 LDL Adsorption Columns are explained in Section III of this instructions for use.

Before using the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review this instructions for use and the “LIPOSORBER® LA-15 System Operator’s Manual”.

II. Indication

The LIPOSORBER® LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has been either ineffective or not tolerated:

- Group A. Clinically diagnosed Familial Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dL;
- Group B. Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dL;
- Group C. Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 100 mg/dL and either documented coronary artery disease or documented peripheral artery disease; and
- Group D. Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C ≥ 100 mg/dL, lipoprotein(a) [Lp(a)] ≥ 60 mg/dL and either documented coronary artery disease or documented peripheral artery disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had a trial of diet and maximum tolerated combination drug therapy to reduce LDL-C according to the current professional guidelines on the management of blood cholesterol.

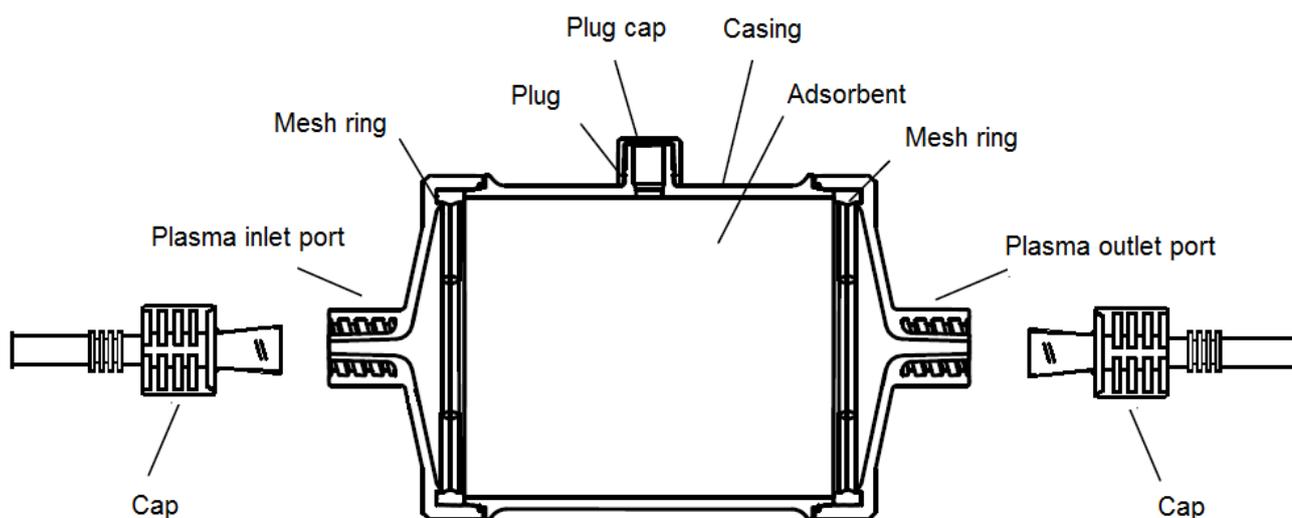
Documented coronary artery disease (CAD) includes CAD diagnosed by invasive or computed tomography (CT) coronary angiography, or by electron beam (ultrafast) CT (EBCT), or documented by a history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery.

Documented peripheral artery disease (PAD) includes PAD diagnosed by symptoms and/or physical exam (e.g., using the Rutherford classification), ankle-brachial index (ABI), ultrasound exam, pulse volume recording (PVR), or peripheral vascular angiography, or documented by a history of peripheral vascular intervention, peripheral vascular bypass surgery, or minor or major amputation.

Baseline lipid levels are to be determined after stabilization on diet and drug therapy by making two measurements during a 2- to 4-week period. (Note: The two values should be within 10% of each other, indicating a stable condition.)

III. Technical Characteristics

LIPOSORBER® LA-15 LDL Adsorption Column



	LIPOSORBER® LA-15 LDL Adsorption Column (2 pieces)
Material	<u>Adsorbent:</u> Dextran sulfate cellulose gel (150 mL each) <u>Casing:</u> Polypropylene
Filling Liquid	Sodium citrate/citric acid solution
Sterilization Method	Steam autoclave at 121°C for 20 minutes

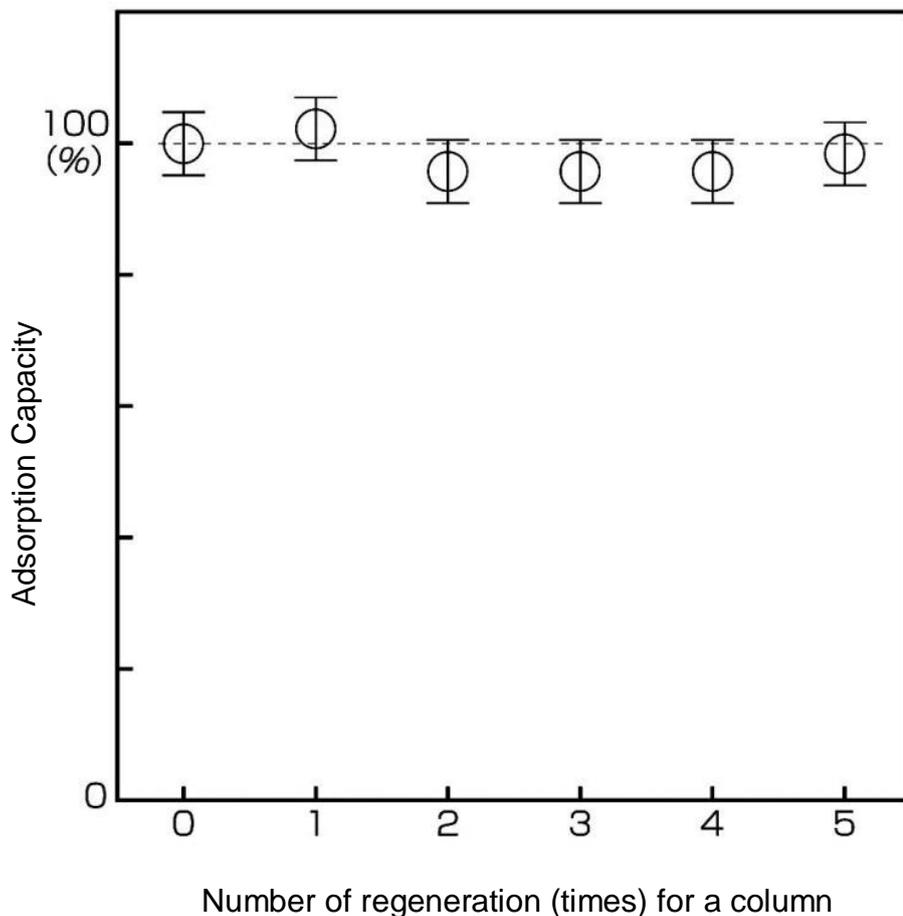
IV. Performance Characteristics

A. Acute Percentage Reductions in Lipids, Lipoproteins and Serum Components Achieved During the Study Period of the Clinical Trial of the LIPOSORBER® LA-15 System

Lipid/Lipoprotein	Acute Percentage Reduction (%)
Total Cholesterol	61 – 71
LDL-C	73 – 83
HDL-C	3 – 14
Lp(a)	53 – 76
Triglycerides	47 – 68
Serum Component	Acute Percentage Reduction (%)
Vitamin E (α -tocopherol)*	63
Vitamin E (γ -tocopherol)*	55
Albumin	14

* Data for the acute reductions in these serum components also included limited data from follow-up treatments.

B. Relationship of Adsorption Characteristics by Regeneration Numbers (In Vitro)



V. Operations

Carefully review the “LIPOSORBER® LA-15 System Operator’s Manual” and use only under a physician’s direction. **Do not reuse.**

Use of the LIPOSORBER® LA-15 System in patients with FH is recommended to occur once every week for Groups A and B and once every two weeks for Group C and D.

VI. Contraindications

The LIPOSORBER® LA-15 System must not be used in:

1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual’s renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
3. patients for whom extracorporeal circulation therapy with the LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

VII. Warnings

1. **Before using the LIPOSORBER® LA-15 System, including the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review the instructions for use provided for each of the disposables and the “LIPOSORBER® LA-15 System Operator’s Manual”. Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program.** Users should follow all operating or maintenance procedures published by Kaneka Medical America LLC and use only the disposable device components recommended by Kaneka Medical America LLC. Failure to do so may result in injury or loss of life.

2. **LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients.** When clinically feasible, patients should not receive antihypertensive drugs during the 24 hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.
3. **The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Medical America LLC or the use of disposable device components not recommended by Kaneka Medical America LLC may result in serious patient injury or loss of life.** The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the Operator's Manual.
4. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. **Using the incorrect solution may result in serious injury or possible death.**
5. The LIPOSORBER® LA-15 LDL Adsorption Column is disposable and is **intended for use in a single use only. Never reuse.** Discard this disposable after each use.
6. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
7. **Rinsing and subsequent priming of the fluid pathway of the LIPOSORBER® LA-15 LDL Adsorption Columns with appropriate solutions are necessary before commencing the procedure.** Because air bubbles in the LDL Adsorption Columns may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the columns during rinsing and priming.
8. While operating, the differential pressure across the LIPOSORBER® LA-15 LDL Adsorption Column must be **under 100mmHg**. If the differential pressure across the column rises extremely, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.
9. **Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant.** Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual at Section **1.6 Adverse Events**). **In some patients the potential for development of a coagulopathy extending several days post-therapy may exist.** In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual at Section **1.8.3 Instructions for Use regarding "Determining Heparin Dosage"**).
10. **To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.**
11. No chemicals or solvents are to be used either inside or outside of this disposable device.

12. Due to the risk of reduction of blood pressure with the LIPOSORBER® LA-15 System, extra caution should be exercised in use of the system in patients with systolic and/or diastolic blood pressure \leq 5th percentile for age, gender and height.
13. Use special caution in patients where the extracorporeal volume of approximately 400 mL potentially will exceed 10% of the patient's total blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.
14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in Section **7.6 Manual Blood Return** of the Operator's Manual.
15. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than once a week or for treated volumes larger than two patient plasma volumes in FH has not been established.
16. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. This device is designed for perfusion of plasma only.
17. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 LDL Adsorption Column.

VIII. Precautions

1. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions (See Operator's Manual at Section **1.6 Adverse Events**).
2. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
3. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. **Do not reuse.**
4. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.
5. Drip chambers in the extracorporeal circuit should be kept at least $\frac{2}{3}$ to $\frac{3}{4}$ full and monitored at all times in order to decrease the risk of air embolism.
6. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the LIPOSORBER® LA-15 Column Set to ensure that it is intact and undamaged. Do not use the LIPOSORBER® LA-15 LDL Adsorption Column if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bags containing the LIPOSORBER® LA-15 LDL Adsorption Column until immediately prior to use.
7. The safety and effectiveness of LDL-apheresis using the LIPOSORBER® LA-15 System in FH have not been established for: (1) patients less than 15 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with renal or thyroid disease or liver abnormalities.

8. The safety and effectiveness of LDL-apheresis using the LIPOSORBER® LA-15 System in FH have not been established for pregnant women or for women during the lactation period, e.g. the effect of treatments on folic acid levels has not been determined.
9. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.
10. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in the Operator's Manual. The amounts of heparin outlined in the Operator's Manual are intended as general suggestions. **The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.**
11. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases, however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
12. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
13. In transporting and storing the disposables, handle with care. Store the disposable in a clean and secure area at room temperature (5-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. **Handle the LIPOSORBER® LA-15 LDL Adsorption Column with care to avoid dropping or other sudden impacts and never allow it to freeze. Do not use an LDL Adsorption Column that may have been dropped, damaged or frozen.**
14. The expiration date of the LIPOSORBER® LA-15 column is 4 years from the sterilization date. The LIPOSORBER® LA-15 column must never be used after the expiration date.
15. High density lipoprotein cholesterol (HDL-C) may be acutely reduced by up to 14% post-treatment. Epidemiologic studies have shown that both low HDL-C and high LDL-C are independent risk factors for coronary artery disease. The risk of acutely lowering HDL-C while lowering LDL-C with this device is unknown.
16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40 °C. It is recommended that the blood warmer be set at a temperature between 36-38 °C in order to avoid significant decreases in blood temperature during extracorporeal circulation.
17. LDL-apheresis in FH should be considered a lifetime therapy since, upon discontinuation of therapy, lipid levels will return to pre-treatment levels or higher. Diet and drug therapy must be maintained during the treatment period as the rate of rebound will accelerate if lipid-lowering drug therapy is discontinued.
18. Patient's cholesterol levels (TC, LDL-C, HDL-C, etc.) should be monitored every 3 months during the course of long-term FH therapy.
19. The long-term safety and effectiveness of LDL-apheresis using the LIPOSORBER® LA-15 System for FH have not been established (See Operator's Manual at Section **1.7 Clinical Experience**).
20. Anemia may be minimized by the appropriate use of iron supplements.

IX. ADVERSE EVENTS

During the course of the clinical study from December 1988 through June 1995, 74 patients* had received 4,936 treatments using the LIPOSORBER® LA-15 System. Prior to enrollment in the clinical study, 76% of the patients had documented coronary artery disease, and 26% of all patients previously had a myocardial infarction. Upon enrollment in the clinical study, 74% of the patients had LDL-cholesterol levels exceeding 200 mg/dL after diet and maximum drug therapy. Patients who were receiving or had received LDL-apheresis therapy with the LIPOSORBER® LA-15 System experienced the following adverse events:

Adverse Events Experienced During LDL-Apheresis Procedures

Patients in the clinical study experienced the following adverse events during LDL-apheresis procedures using the LIPOSORBER® LA-15 System:

Table 1.1.

Adverse Event	Episodes		Patients	
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

Single incidents of the following adverse events also occurred: Arrhythmia; vasovagal reaction; bleeding (prolonged); chills; diaphoresis; and blood loss.

* Included in this patient total are one emergency use patient treated for nephrotic syndrome (FSGS) and one patient with coronary artery disease treated under a special IDE supplement for an elevated Lp(a) level.

Deaths

Six patients who had been enrolled in the clinical study died:

Forty-four year old male died on September 30, 1992 from congestive heart failure resulting from preexisting supravalvular aortic stenosis and coronary artery disease. Patient had ceased receiving LDL-apheresis treatment more than a year earlier.

Seventeen year old male, who had received 226 LDL-apheresis treatments, died on May 14, 1995 from blunt trauma to the head suffered as a result of an accidental fall from a window after consuming alcohol.

Seventy-two year old male, who had received 150 LDL-apheresis treatments, died on January 13, 1996, apparently from a heart attack resulting from severe, preexisting coronary artery disease, including two prior myocardial infarctions, a stroke, and two coronary artery bypasses.

Sixty-one year old male, who had received 14 LDL-apheresis treatments, died in the spring of 1990, from a malignant glioma of the brain.

Sixty-one year old male who had received 96 treatments and had multiple risk factors, including cerebrovascular disease with prior ischemic injury to brain, left ventricular mural thrombus, and hypertension, died on September 22, 1994 of cerebral hemorrhage.

Fifty year old male, who had smoked two packs of cigarettes per day for more than 30 years, died on April 22, 1990 of lung cancer with metastases to the liver.

None of these deaths occurred during an LDL-apheresis treatment, and the clinical investigators for the patients did not identify LDL-apheresis as a causal factor. However, it cannot be concluded with certainty, due to the small size of the patient groups and the lack of a control group, whether any of the deaths were treatment related.

Myocardial Infarctions

During the course of the clinical study, three MIs occurred: Two occurred in patients who were no longer receiving treatment. No MI occurred during an actual LDL-apheresis procedure, and the clinical investigators for the patients did not identify LDL-apheresis as a causal factor. The possibility that there is an increased risk of angina or MI in patients receiving this therapy cannot be totally excluded.

Other Potential Adverse Events

Although patients participating in the clinical study did not experience the following adverse events during the reported 4,936 treatments, such events may occur in procedures involving extracorporeal circulation: uncontrolled bleeding; infectious disease transmission, including hepatitis; sepsis due to circuit contamination; air embolism, and hypersensitivity reactions.

Other complications may include: plasma loss from circuit leaks; coagulopathy potentially extending several days post treatment; and volume shifts. Equipment malfunction or user error may result in fluid volume abnormalities which may require acute medical intervention.

Patients on antihypertensive drugs, such as diuretics, calcium antagonists, beta blockers and ACE inhibitors, are at increased risk of hypotensive reactions occurring during therapy. ACE inhibitors have been associated with severe hypotension associated with flushing, dyspnea, and bradycardia. Therefore, **ACE inhibitors should not be administered for 24 hours or longer preceding each apheresis procedure. (See Contraindications.)** In order to minimize the potential risks which also may be associated with other anti-hypertensive medications, it is recommended that patients refrain from taking antihypertensive drugs at least the day before the LDL-apheresis procedure, when clinically feasible. Before each treatment, patients should be requested to advise the attending physician when they last took a dose of such medication. One of the hypotensive events reported in Table 1.1 was attributed to the administration of ACE inhibitors. The administration of ACE inhibitors in conjunction with therapy with the device also has been associated with the occurrence of tachycardia, and three of the reported tachycardia events (two in an emergency use patient) were attributed to the administration of ACE inhibitors.

Reduction in Blood Components

LDL-apheresis is known to decrease the selected blood components listed below. The long-term effects of such reduction have not been established.

Table 1.2.

Blood Component	Acute Percentage Reduction (%)
Hemoglobin	1.4
Vitamin E (α -tocopherol) *	63
Vitamin E (γ -tocopherol) *	55
Albumin	14
Fibrinogen	29
Platelets	17

* Data for the acute reductions in these blood components also included limited data from follow-up treatments.

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LIPOSORBER[®] LA-15

LDL ADSORPTION COLUMNS

Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis (FSGS)

FSGS

Humanitarian Use Device

Authorized by Federal (USA) law for use in the treatment of adult and 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) \geq 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.

Caution: Federal law restricts this device to sale by or on the order of a physician.

Carefully review the "LIPOSORBER[®] LA-15 System Operator's Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)" and use only under the direction of a licensed physician with appropriate training.

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Instructions for use in Familial Hypercholesterolemia start from the back cover

I. Introduction

The LIPOSORBER® LA-15 LDL Adsorption Column set is one of three disposable device components of the LIPOSORBER® LA-15 System. It is comprised of two LIPOSORBER® LA-15 LDL Adsorption Columns, each containing 150 mL of dextran sulfate cellulose adsorbent.

The technical characteristics of the LIPOSORBER® LA-15 LDL Adsorption Columns are explained in Section III of this instructions for use.

Before using the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review this instructions for use and the “LIPOSORBER® LA-15 System Operator’s Manual for use in the treatment of adult and pediatric patients with primary focal segmental glomerulosclerosis (FSGS)” (hereinafter referred to as “Operator’s Manual for FSGS”).

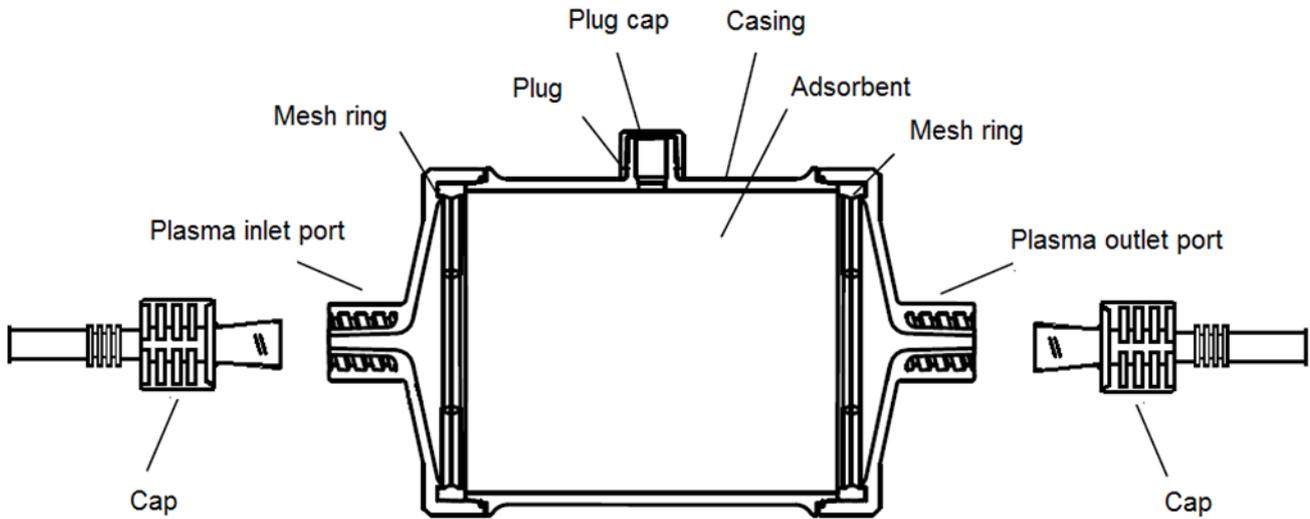
II. Indication

The LIPOSORBER® LA-15 System is indicated for use in the treatment of adult and pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) when:

- standard treatment options, including corticosteroids and/or calcineurin inhibitor, treatments 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.

III. Technical Characteristics

LIPOSORBER® LA-15 LDL Adsorption Column



	LIPOSORBER® LA-15 LDL Adsorption Column (2 pieces)
Material	<u>Adsorbent:</u> Dextran sulfate cellulose gel (150 mL each) <u>Casing:</u> Polypropylene
Filling Liquid	Sodium citrate/citric acid solution
Sterilization Method	Steam autoclave at 121°C for 20 minutes

IV. Operations

Carefully review the "Operator's Manual for FSGS" and use only under a physician's direction. **Do not reuse.**

Use of the LIPOSORBER® LA-15 System in adult and pediatric patients with FSGS is recommended to occur twice weekly for 3 weeks followed by once per week for six weeks.

V. Contraindications

The LIPOSORBER® LA-15 System must not be used in:

1. patients who have been treated with angiotensin-converting enzyme (ACE) inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE inhibitor currently in use. If required, ACE inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

2. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
3. patients for whom extracorporeal circulation therapy with the LIPOSORBER® LA-15 System cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
4. patients with hypersensitivity to dextran sulfate cellulose, heparin or ethylene oxide.

VI. Patient Selection

The following patients may benefit from the LIPOSORBER® LA-15 System. The following are intended only as **guidelines** for appropriate patient selection:

- Adult and pediatric patients with GFR ≥ 60 mL/min/1.73 m² and a history of primary FSGS accompanied by refractory or recurrent nephrotic syndrome defined as:
 - Patients unresponsive to standard corticosteroid and/or calcineurin inhibitor therapy for at least 8 weeks resulting in failure to achieve complete or partial remission.
 - or*
 - Patients intolerant to standard therapies due to severe side effects which negatively affect quality of life without providing an acceptable level of clinical benefit.
 - or*
 - Patients in whom standard therapies are contraindicated.

OR

- Adult and pediatric post renal transplantation patients with nephrotic syndrome associated with primary FSGS.

VII. Warnings

1. **Before using the LIPOSORBER® LA-15 System, including the LIPOSORBER® LA-15 LDL Adsorption Column, carefully review the instructions for use provided for each of the disposables and the “Operator’s Manual for FSGS”. Persons performing the procedures must be qualified to perform extracorporeal procedures, and have completed the required training program.** Users should follow all operating or maintenance procedures published by Kaneka Medical America LLC and use only the disposable device components recommended by Kaneka Medical America LLC. Failure to do so may result in injury or loss of life.
2. **LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients.** When clinically feasible, patients should not receive antihypertensive drugs during the 24-hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.
3. **The storage and use of this disposable device other than in accordance with the instructions published by Kaneka Medical America LLC or the use of disposable device components not recommended by Kaneka Medical America LLC may result in serious patient injury or loss of life.** The manufacturer and distributor(s) of this device will not be responsible for patient safety if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified in this instructions for use and the Operator’s Manual for FSGS.

FSGS

4. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. **Using the incorrect solution may result in serious injury or possible death.**
5. The LIPOSORBER® LA-15 LDL Adsorption Column is disposable and is **intended for use in a single use only. Never reuse.** Discard this disposable after each use.
6. The LIPOSORBER® LA-15 System may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure.
7. **Rinsing and subsequent priming of the fluid pathway of the LIPOSORBER® LA-15 LDL Adsorption Columns with appropriate solutions are necessary before commencing the procedure.** Because air bubbles in the LDL Adsorption Columns may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the columns during rinsing and priming.
8. While operating, the differential pressure across the LIPOSORBER® LA-15 LDL Adsorption Column must be **under 100 mmHg**. If the differential pressure across the column rises extremely, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.
9. **Citrate preparation (ACD) should never be used as an anticoagulant in the system. The LIPOSORBER® LA-15 System is designed solely for treatment using heparin as an anticoagulant.** Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped (See Operator's Manual for FSGS at Section **1.7 Adverse Events**). **In some patients the potential for development of a coagulopathy extending several days post-therapy may exist.** In addition to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used (See Operator's Manual for FSGS at Section **1.9.2 Instructions for Use regarding "Determining Heparin Dosage"**).
10. **To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.**
11. No chemicals or solvents are to be used either inside or outside of this disposable device.
12. Due to the risk of reduction of blood pressure with the LIPOSORBER® LA-15 System, extra caution should be exercised in use of the system in patients with systolic and/or diastolic blood pressure \leq 5th percentile for age, gender and height.
13. Use special caution in patients where the extracorporeal volume of approximately 400 mL potentially will exceed 10% of the patient's total blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.
14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in Section **7.6 Manual Blood Return** of the Operator's Manual for FSGS.

15. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than twice a week or for treated volumes larger than 60mL/kg patient plasma volumes in FSGS has not been established.
16. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. This device is designed for perfusion of plasma only.
17. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 LDL Adsorption Column.

VIII. Precautions

1. The need for the administration of angiotensin receptor blockers (ARBs) prior to the treatment on the day of the apheresis treatment should be determined by the treating physician. If the treating physician determines that it is not necessary, the patient should not take ARBs on the day of the apheresis treatment until the apheresis treatment is completed in order to minimize the risk of a hypotensive reaction during the extracorporeal therapy.
2. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions (See Operator's Manual for FSGS at Section **1.7 Adverse Events**).
3. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.
4. The transducer protectors must be attached and locked to the machine and tubing lines. Strict aseptic technique should be used during this and all procedures. After the completion of the procedure, properly dispose of all used and unused transducer protectors. **Do not reuse.**
5. Each tubing line must be properly connected and cleared of air, prior to the start of Rinse. Do not allow air to be trapped in the set. Puncturing tubing lines may cause air embolism.
6. Drip chambers in the extracorporeal circuit should be kept at least $\frac{2}{3}$ to $\frac{3}{4}$ full and monitored at all times in order to decrease the risk of air embolism.
7. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Prior to use, carefully examine the packaging of the LIPOSORBER® LA-15 Column Set to ensure that it is intact and undamaged. Do not use the LIPOSORBER® LA-15 LDL Adsorption Column if the package, sterile bag, protective cap or the product itself is not intact or is damaged. Do not open the bags containing the LIPOSORBER® LA-15 LDL Adsorption Column until immediately prior to use.
8. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS have not been established for: (1) patients less than 21 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with thyroid disease or liver abnormalities.
9. The safety and probable benefit of LDL-apheresis using the LIPOSORBER® LA-15 System in FSGS has not been established for pregnant women or for women during the lactation period, e.g. the effect of treatments on folic acid levels has not been determined.

10. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.
11. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in the Operator's Manual for FSGS. The amounts of heparin outlined in the Operator's Manual for FSGS are intended as general suggestions. **The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.**
12. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.
13. When disposing of the disposable device components and wastes, comply with all local requirements and the policies of the facility regarding precautions for and prevention of infection and environmental pollution.
14. In transporting and storing the disposable, handle with care. Store the disposable in a clean and secure area at room temperature (5-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. **Handle the LIPOSORBER® LA-15 LDL Adsorption Column with care to avoid dropping or other sudden impacts and never allow it to freeze. Do not use an LDL Adsorption Column that may have been dropped, damaged or frozen.**
15. The expiration date of the LIPOSORBER® LA-15 column is 4 years from the sterilization date. The LIPOSORBER® LA-15 column must never be used after the expiration date.
16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40 °C. It is recommended that the blood warmer be set at a temperature between 36-38 °C in order to avoid significant decreases in blood temperature during extracorporeal circulation.
17. Anemia may be minimized by the appropriate use of iron supplements.

IX. Clinical Data

Clinical data to support the safety and probable benefit of LIPOSORBER® LA-15 System for FSGS can be divided to pre-transplant FSGS and post-transplant FSGS.

1. Adults

Published Clinical Studies of LIPOSORBER® LA-15 System Treatment for Patients with Nephrotic Syndrome (NS) and FSGS in adults are summarized in the table below.

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre-transplant or Post-transplant
Muso 2015 [1] Muso 2015 [2]	44 (26 with FSGS)	Prospective Multicenter Single arm	Immediate to 2 years after treatment	Urinary Protein (UP) decreased from 6.28 ± 2.96 to 3.46 ± 3.34 g/day. 21/44 patients (48%) had a favorable 2-years outcome.	Pre-transplant
Muso 2001 [3] Muso 1999 [4]	17 (14 with FSGS)	Prospective Multicenter Controlled	Immediate to 2 years after treatment	UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day. The rate of achieving complete or incomplete remission was 71%. As for the 2-years outcomes, 13/17 patients (76%) maintained UP <1.0 g/day.	Pre-transplant
Yokoyama 2002 [5]	6 (2 with FSGS; 1 treated with LIPOSORBER®)	Prospective Single Center	Unknown	This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.	Pre-transplant
Nakamura 2006 [6]	8 FSGS	Prospective Single Center	2 weeks	UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.	Pre-transplant
Muso 2007 [7]	41 FSGS	Retrospective	5 years	At 1 month after LDL apheresis UP was significantly decreased. Remission of nephrotic syndrome was observed in 18/29 patients (62%) followed at 2 years and 13/15 patients (86%) followed at 5 years.	Pre-transplant and Post-transplant

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre-transplant or Post-transplant
Case Studies					
Masutani 2005 [8]	1 FSGS	Case Report	1 year	LIPOSORBER® in conjunction with drug treatment resulted in reduction of UP from 6.8 g/day to 2.0 g/day. Incomplete remission had been maintained for more than 1 year.	Post-transplant
Miura 2009 [9]	1 FSGS	Case Report	40 days	Six cycles of hemodialysis were performed in conjunction with 4 cycles of LIPOSORBER® treatment. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment.	Pre-transplant
Miyazono 2008 [10]	1 FSGS	Case Report	Unknown	After 6 treatment sessions, the patient's UP decreased to non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to normal. Although the patient experienced a relapse of nephrotic syndrome, 6 more sessions of LIPOSORBER® treatment brought the UP down to 0.8 g/day.	Pre-transplant
Tsukada 2006 [11]	1 FSGS	Case Report	Unknown	The patient underwent 8 sessions of treatment using LIPOSORBER®, which resulted in the reduction of the UP level and improvement of renal functions.	Post-transplant
Haikal 2016 [12]	1 FSGS	Case Report	5 months	Partial remission sustained 5 months post therapy	Pre-transplant

1) Pre-transplant FSGS

- (i) **Muso et al. (2001) [3]:** This study describes the comparison of efficacy between the treatment with the LIPOSORBER® LA-15 System in combination with steroids (LDL-A group) and that with steroids only (steroid monotherapy (SM) group) for patients with nephrotic syndrome who did not respond to full-dose (prednisolone, daily 1 mg/kg b.w.) therapy of 1-month duration under the fixed treatment protocol. The LDL group consisted of 17 patients (FSGS: 14, minimal change nephrotic syndrome (MCNS): 3) who were treated with the LIPOSORBER® LA-15 System. Treatments were performed twice a week for 3 weeks followed by weekly treatment for 6 weeks. The SM group included 10 patients (FSGS: 9, MCNS: 1) who were treated only with continuous full-dose steroids.

Results

Effectiveness:

- Total cholesterol (TC) level in the LDL-A group was significantly decreased after the treatment (337 ± 118 to 242 ± 45.2 mg/dL, $p=0.006$), whereas decrease of TC level in the SM group was not significant (448 ± 106 to 366 ± 159 mg/dL, $p=0.169$).
- Hypoalbuminemia significantly improved in the LDL-A group (2.7 ± 0.7 to 3.1 ± 0.7 g/dL, $p=0.014$), while almost no change was noted in the SM group (2.8 ± 0.4 to 2.9 ± 0.7 g/dL, $p=0.822$).
- Proteinuria was significantly ameliorated in the LDL-A group (6.2 ± 3.3 to 2.7 ± 2.7 g/day, $p=0.0008$), while significant amelioration of proteinuria was not observed in the SM group (8.7 ± 4.0 to 8.2 ± 7.7 g/day, $p=0.85$).
- Average duration needed for a decrease of urinary protein to <3.5 g/day was significantly shorter in the LDL group than in the SM group (14.7 ± 19.6 days vs 47.8 ± 6.9 days, $p=0.002$).
- At the end of the treatment period, 9 patients (52%) in the LDL-A group achieved urinary protein level <1.0 g/day, whereas only 1 patient (10%) showed the same level in the SM group.
- As for the long-term outcomes (2 years after the end of the treatment period), 13 out of 17 patients (76%) maintained urinary protein level <1.0 g/day in the LDL-A group, compared to only 2 in 9 patients (22%) in the SM group.

Safety:

- The incidence of adverse events was not reported.

Conclusion

Superiority of therapeutic efficacy of the treatment with the LIPOSORBER® LA-15 System in combination with steroids to that with steroids alone was demonstrated in controlled study.

This study was a follow-up of the multicenter study reported by Muso et al (Kidney Int) in 1999. In this study, the authors did not report any adverse events.

Summary: Among the 17 patients with FSGS, short-term and medium-term efficacy data were provided compared to controls. Adverse events were not mentioned in the report.

- (ii) **Nakamura et al. (2006) [6]:** This study investigated the effect of LIPOSORBER® LA-15 System in treating FSGS as part of a larger study to determine whether the levels of urinary liver-type fatty acid-binding protein (L-FABP) are associated with the severity of nephrotic syndrome. At the beginning of the study, all FSGS patients received 60 mg/day prednisone for 6 months, followed by either cyclophosphamide or mizoribine for another 6 months. Treatment with LIPOSORBER® LA-15 System was performed in 8 patients with drug-resistant FSGS twice a week for 3 weeks, then once a week for 6 weeks. In each 3-hour treatment session, 3000-4000 mL of plasma were treated. Renal function in terms of daily urinary protein excretion and serum creatinine levels were measured before the start of treatment and 2 weeks after the final treatment session.

Results

Effectiveness:

- Comparing the clinical parameters before and after the treatment, urinary protein and serum creatinine decreased significantly from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day ($p < 0.01$) and from 123.8 ± 26.5 $\mu\text{mol/L}$ to 97.2 ± 17.7 $\mu\text{mol/L}$ ($p < 0.05$), respectively, and total protein increased from 40 ± 8 g/L to 60 ± 9 g/L ($p < 0.01$).
- In addition, serum level of L-FABP decreased from 122.6 ± 78.4 $\mu\text{g/gCr}$ to 64.4 ± 43.8 $\mu\text{g/gCr}$ ($p < 0.05$).

Safety:

- The article did not report any adverse events associated with LIPOSORBER® LA-15 System.

Conclusion

This study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorated proteinuria, hypoproteinemia, and renal function in drug-resistant FSGS.

This was a prospective study. Among the 8 patients with FSGS, encouraging short-term efficacy data were provided. A control arm was not included in this study. Adverse events were not mentioned in the report.

- (iii) **Muso et al. (2015) [11]:** The investigators conducted a prospective, observational, multi-center cohort study (POLARIS study). In the POLARIS study, patients with nephrotic syndrome who did not respond to primary medication were registered before starting the treatment with LIPOSORBER® LA-15 System and clinical effectiveness and safety were examined. A total of 58 patients (who underwent 64 treatments) were registered in the study. Of the 64 treatment regimens, 17 were excluded for various reasons, leaving 47 treatment regimens for 44 patients available for analysis. As for FSGS, 23 patients were registered and underwent a total of 26 treatments. Clinical data were collected at baseline and after treatment with LDL-apheresis based on 24-hour urinalysis. Lipid profiles and clinical parameters were compared between before and after the treatment.

Results

Effectiveness:

- TC and LDL cholesterol (LDL-C) levels were significantly decreased after the treatment (331.10 ± 113.25 to 210.38 ± 77.4 mg/dL; $p < 0.01$, 205.86 ± 100 to $84.92.37 \pm 56.64$ mg/dL; $p < 0.01$, respectively), whereas the changes of triglyceride (TG) and HDL-cholesterol (HDL-C) were not significant (262.74 ± 155.17 to 241.30 ± 182.14 mg/dL; n.s., 69.49 ± 22.58 to 73.64 ± 23.40 mg/dL; n.s.).
- Hypoproteinemia (serum protein), hypoalbuminemia (serum albumin), and proteinuria (urinary protein) were significantly ameliorated immediately after treatment (4.42 ± 0.69 to 4.68 ± 0.81 g/dL; $p < 0.05$, 2.15 ± 0.63 to 2.63 ± 0.79 g/dL; $p < 0.01$, and 6.28 ± 2.96 to 3.46 ± 3.34 g/day; $p < 0.01$, respectively). In addition, renal function (creatinine clearance) significantly improved immediately after treatment (58.59 ± 41.35 to 65.11 ± 41.39 mL/min; $p < 0.05$).
- Serum levels of fibrinogen and thrombin-antithrombin III complex (TAT) level were significantly reduced (374.46 ± 130.04 to 297.92 ± 108.87 mg/dL; $p < 0.01$, 16.39 ± 33.60 to 12.21 ± 34.10 ng/mL; $p < 0.05$, respectively) suggesting that treatment with LIPOSORBER® LA-15 System exerts anticoagulation activity.

Safety:

- The incidence of adverse events was not reported.

Conclusion

LDL apheresis therapy with LIPOSORBER® LA-15 System rapidly ameliorated symptoms of nephrotic syndrome i. e. proteinuria and hypoproteinemia in more than half of the patients who failed to respond to primary medication.

This was a short-term study.

The endpoints were:

- Complete remission: Urinary Protein (UP) = undetectable
- Incomplete Remission I: $UP < 1.0$ g/day
- Incomplete Remission II: $1.0 \text{ g} \leq UP < 3.5$ g/day
- No effect: $UP \geq 3.5$ g/day

In this study, complete or incomplete remission were considered favorable outcomes.

The average number of apheresis sessions was 9.6/patient. An average of 3.5 L of plasma was treated per session. Among the 44 patients, FSGS was the diagnosis in 23 (52.3%) of the patients.

- (iv) **Muso et al. (2015) [2]:** The long-term (2 years) outcome of the POLARIS cohort was investigated for the 44 subjects. Of the 58 patients who were registered in the POLARIS study, 5 were excluded from the study because of protocol violation or inadequate data collection, 6 were lost to follow up, and 3 died during the follow-up period, thus leaving 44 subjects eligible for analysis at two years. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%).

Results

Effectiveness:

- Twenty-one (21) of the 44 subjects (47.7%) had a favorable outcome, with 11 subjects (25%) in complete remission (defined as urinary protein undetectable) and 10 subjects (22.7%) in incomplete remission I (defined as urinary protein level < 1.0 g/day). Twenty-three (23) subjects (52.3%) had an unfavorable result, with 11 (25%) in incomplete remission II (defined as $1.0 \text{ g/day} \leq$ urinary protein < 3.5 g/day) and 12 (27.3%) with no effect (defined as urinary protein level \geq 3.5/day).
- An analysis was performed of the factors affecting outcome. The authors found that the urinary protein level post-treatment was strongly associated with 2-year outcome ($p < 0.001$). For subjects with favorable outcomes, the urinary level after treatment was $1.68 \pm 1.76 \text{ g/day}$ compared to $6.18 \pm 3.24 \text{ g/day}$ for subjects with unfavorable outcomes.
- Improvement of parameters representing disease conditions of nephrotic syndrome, including serum albumin, eGFR, urinary protein and total and LDL cholesterol were all significantly associated with favorable outcome. This suggests that an early rapid alleviation of nephrotic syndrome by LDL-apheresis contributes to a favorable outcome.

Safety:

- No adverse event associated with LIPOSORBER® LA-15 System was reported in this report.

Conclusion

The POLARIS study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorates nephrotic conditions and that the therapeutic efficacy of LDL apheresis was largely maintained for two years.

During the time from the short- to long-term POLARIS study, 3 subjects died of diseases unrelated to NS (cerebral infarction, lung cancer and pneumonia). Given the variety of histological diagnoses in the patients included in the study, it was challenging to ascertain the outcomes for patients with FSGS versus those with other diseases. That said, the study does report that urine protein levels decreased significantly and similarly for patients with/without FSGS and this study provides reasonable assurance of efficacy of the device in about 50% of patients with FSGS.

2) Post-transplant FSGS

Muso et al. (2007) [7]: This study describes 41 patients with refractory FSGS. The study population included a sub-set of 7 patients who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The study included the change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after LIPOSORBER® treatment. Although the investigators did not indicate that any of the patients included in the analysis were children, the results can be used to assess effectiveness in children as the course of the disease is sufficiently similar in both adults and children.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
 - Complete remission
 - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL
 - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin < 3.0 g/dL

Results

Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.
- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).
- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven post-transplant patients were included in the 41 patients analyzed at 1 month. The authors did not analyze the data collected from pre- and post-transplant patients separately. Instead, the authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 years follow-up.

Safety:

- The incidence of adverse events was not reported.

Conclusion

The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

This was a retrospective study. Patients had drug-resistant (persistence of proteinuria ≥ 1.0 g/day after the initial treatment for at least 4 weeks) NS and FSGS. Of the 41 cases of NS due to FSGS, 20 were new-onset. The device treatment was provided in conjunction with standard medications for FSGS/NS: steroids,

cyclosporine A, or other immunosuppressive medications. Each patient received 3-12 treatments with the device.

Adverse events (safety) were not assessed.

In summary, among the 41 patients, encouraging two-year efficacy data were provided for 29 patients (assuming constant enrollment) and five-year data were available for 15 patients. This may be due to steady enrollment throughout the study period.

Safety Assessment

The studies above did not report reliable adverse event data. However, the safety data from adults with functional hypercholesterolemia (FH) treated with the device can be extrapolated to safety for adults with FSGS treated with the LIPOSORBER® LA-15 System. The table below demonstrates the rates of various adverse events in adults with FH treated with the LIPOSORBER® LA-15 System:

Adverse Event	Episodes		Patients	
	Count	Percentage	Count	Percentage
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

2. Pediatrics

Hattori et al. (2003) [13]: This study describes the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the LIPOSORBER® LA-15 System, none of the patients had received a renal transplant (“pre-transplant”). At the start of the 7th apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., GFR), degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
 - Complete remission: reduction in urinary protein ($< 4 \text{ mg/m}^2/\text{h}$) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
 - Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein $< 40 \text{ mg/m}^2/\text{h}$) with normal serum albumin
- Renal Function (as GFR, in mL/min/1.73m²)
- Proteinuria (g/m²/day).

Results

Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).
- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).
- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

Safety:

- Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

Conclusion

The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS.

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X. ADVERSE EVENTS

Adverse events that may be associated with the use of the LIPOSORBER® LA-15 System in FSGS include, but are not limited to, those listed in the following paragraphs. If a patient experiences an adverse reaction during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition stabilized. The physician should determine all medical responses to adverse reactions based upon the individual patient's physical condition.

- 1) Death
- 2) Cardiac: Various abnormal heart rhythms may develop including bradycardia, tachycardia, and other arrhythmias. Myocardial infarction is another potential adverse cardiac event. If these are detected by vital sign monitoring, physical examination, or electrocardiography, immediate assessment and continued monitoring is essential.
- 3) Thrombocytopenia
- 4) Catheter-related adverse events: Use of the device requires a central venous access (catheter) for children and for some adults given their small venous caliber. Infection of the catheter may occur due to exit site infection, catheter-related bloodstream infection (CRBSI), improper use of the catheter, or internal catheter infection. Aseptic technique is required for catheter use. If an infection or bacteremia is suspected, culture of the catheter ports, in conjunction with peripheral culture (optional), is required. Antibiotic therapy should be provided according to physician discretion. Also, there are other adverse events associated with catheter use (e.g., hemothorax, pneumothorax, blood loss, arterial puncture, superior vena cava syndrome, arrhythmia, central venous stenosis, thrombosis and loss of potential fistula access).
- 5) Hypersensitivity (anaphylactoid) reaction: Use of ACE inhibitors within 24 hours of therapy with the device can cause an increase in bradykinin levels, resulting in severe hypotension. ACE inhibitors should not be taken within 24 hours of therapy with the device.
- 6) Nausea and Vomiting. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).
- 7) Reduction in Vitamin E level
- 8) Transient decrease in serum protein and albumin level
- 9) Hypotension: The procedure should be stopped, and the patient should be placed in the Trendelenburg position and/or receive a fluid challenge. If the hypotension persists, the procedure should be terminated. Note: For an "anaphylactoid" reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, anti-histamines, and/or calcium have been reported by clinicians as effective interventions.
- 10) Abdominal symptoms. Patients may exhibit nausea, vomiting abdominal discomfort. These events should be addressed with conservative management and supportive care. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g., hypotension).

- 11) Flushing/blotching: Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of diphenhydramine (e.g., Benadryl).
- 12) Angina/chest pain: The procedure should be stopped and medical therapy instituted at the discretion of the physician. If the angina persists, the procedure should be terminated.
- 13) Fainting/lightheadedness: See hypotension.
- 14) Anemia: May be minimized by the appropriate use of iron supplements.
- 15) Prolonged bleeding (at cannulation site after removing venous cannulae): Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that, during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). Repetitive LDL apheresis treatment may affect the patient's clotting time. Therefore, a periodic check, of other relevant coagulation parameters is recommended, including the number of thrombocytes and the fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.
- 16) Hemolysis: as evidenced by discoloration of plasma or hemolysis as Indicated by activation of the blood leak detector alarm of the MA-03. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.
- 17) Device malfunction: The system contains various components, including LDL adsorption columns (2), plasma separator, tubing system, and an electronic control unit. System malfunction may occur due to any of these components. If system malfunction occurs, the patient's vital signs and clinical status should be monitored immediately and repeatedly. It may be necessary to suspend treatment if the patient develops symptoms or if the problem cannot be readily solved.
- 18) Vertigo
- 19) Diaphoresis
- 20) Urticaria: Mild discomfort may occur requiring supportive care. Vital signs and physical examination of the patient are required in order to assess if urticaria is a component of a more severe, generalized reaction to the therapy. Specific associated symptoms, including, but not limited to, difficulty breathing, chest pain, and dizziness should be addressed by the physician.
- 21) Shivering
- 22) Headaches