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.

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Instructions for use in adult and pediatric Focal Segmental Glomerulosclerosis 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".

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 $\geq$ 300 mg/dL;

Group C. Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with LDL-C $\geq$ 70 mg/dL and either documented coronary artery disease or documented peripheral artery disease; and

Group D. Clinically diagnosed Familial Hypercholesterolemic Heterozygotes with lipoprotein(a) [Lp(a)] $\geq$ 60 mg/dL (or 130 nmol/L) 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.

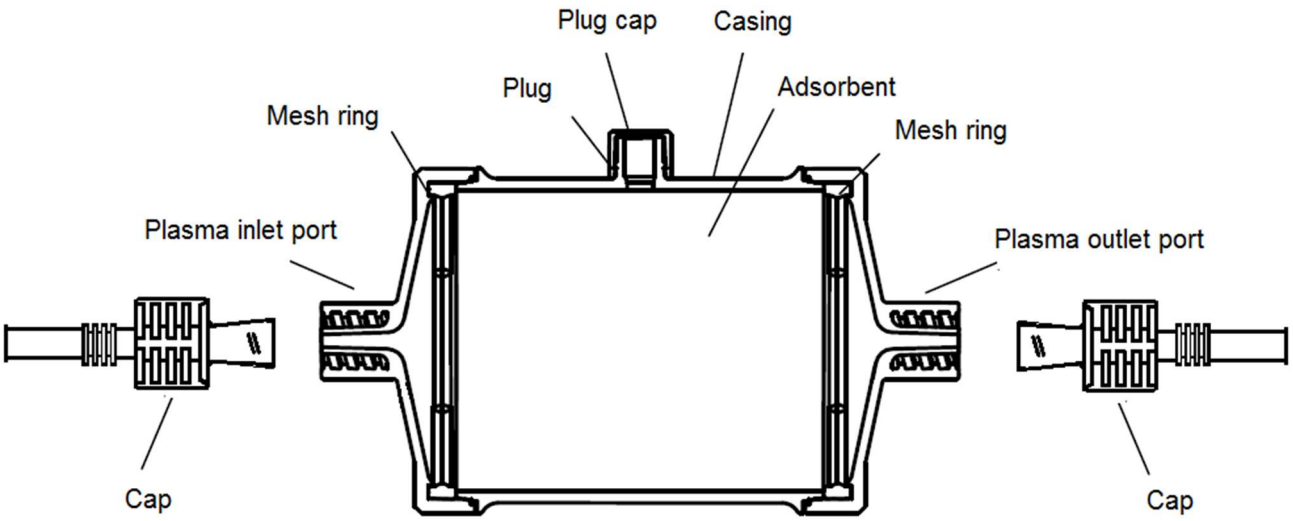
Documented peripheral artery disease (PAD) includes PAD diagnosed by symptoms and/or physical exam (e.g., using the Rutherford classification), ankle-brachial index (ABI), ultrasound exam, pulse volume recording (PVR), or peripheral vascular angiography, or documented by a history of peripheral vascular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

FH

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	*Adsorbent:* Dextran sulfate cellulose gel (150 mL each) *Casing:* Polypropylene
Filling Liquid	Sodium citrate/citric acid solution
Sterilization Method	Steam autoclave at 121°C for 20 minutes

FH

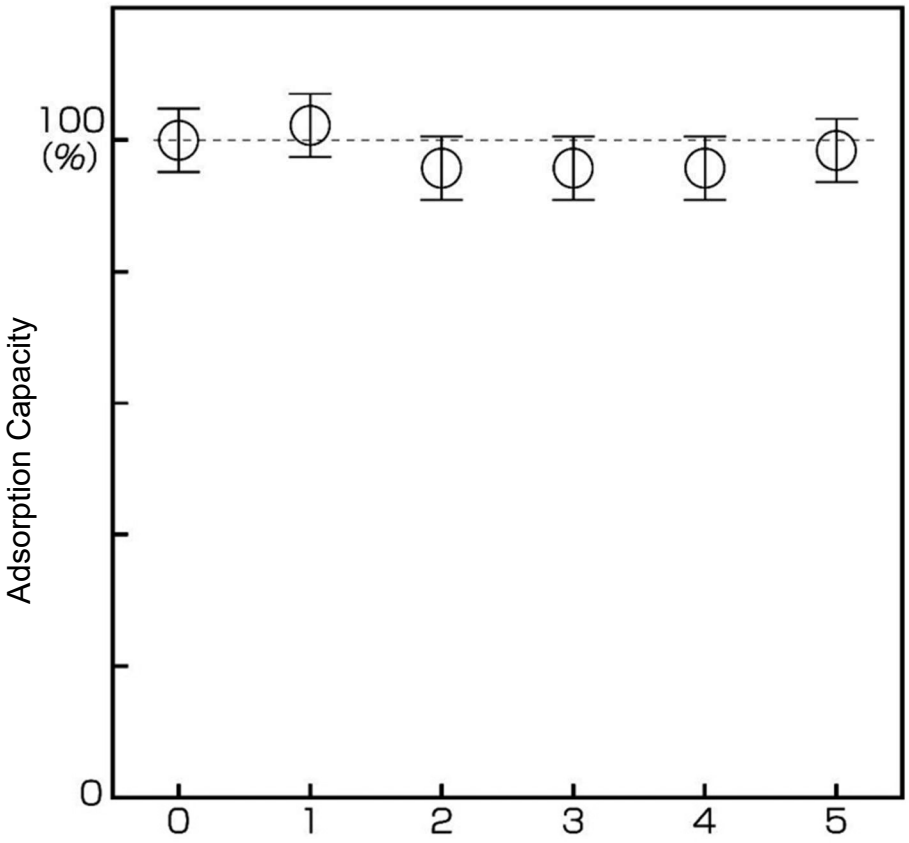
IV. Performance Characteristics

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)



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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 are being treated with angiotensin-converting enzyme (ACE) inhibitors ;**

   Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER® LA-15 LDL Adsorption Column under concomitant ACE inhibitor medication. Temporal ceasing of ACE inhibitor intake to remove its bioactivity from the patient's blood may not always be sufficient to avoid such adverse reactions. The ACE inhibitors should be switched to another antihypertensive medication (for example, angiotensin II receptor blockers (ARBs)) at the medical discretion of the treating physician.

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 may cause hypotension in such patients (for ACE inhibitors, see VI. Contraindications).** When clinically feasible, patients should not receive antihypertensive drugs prior to undergoing the LDL-apheresis procedure on the day of receiving the apheresis. 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 ≤ 5th percentile for age, gender and height.

FH

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 ⅔ to ¾ 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 handing 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 ºC. It is recommended that the blood warmer be set at a temperature between 36-38 ºC 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.

FH

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, **patients who are being treated with any ACE inhibitor should not be treated with the LIPOSORBER® LA-15 (See VI. 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** prior to undergoing the LDL-apheresis procedure on the day of receiving the apheresis, 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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