FDA Executive Summary

Prepared for the
March 7, 2017 meeting of the
FDA's Pediatric Advisory Committee

H120005
Liposorber® LA-15 System

TABLE OF CONTENTS

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review provides a safety update based on the postmarket experience with the use of the Liposorber® LA-15 System from Kaneka in pediatric patients for the treatment of nephrotic syndrome associated with primary focal segmental glomerulosclerosis since approval in 2013. The Liposorber LA-15 System, a blood processing system that is used outside the body, includes disposable components and a control/monitor unit. The device works by removing certain lipoproteins from the patient's blood. The patient's blood is first passed through a plasma filter where the blood cells are separated from plasma (the liquid component of the blood). The plasma is then further passed through two adsorption columns, which are packed with a gel designed to capture the lipoproteins in the blood. The blood cells and the treated plasma are then returned to the patient via the blood return line.

The purpose of this review is to provide the Pediatric Advisory Committee with postmarket safety data, so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

II. INDICATIONS FOR USE

The Liposorber® LA-15 System is indicated for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis, when

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated, and the patient has a GFR $\geq$ 60 ml/min/1.73m^2, or

- The patient is post renal transplantation.

III. BRIEF DEVICE DESCRIPTION

The Kaneka Liposorber® LA-15 System is an integrated extracorporeal blood processing system that includes disposable components and a control/monitor unit.

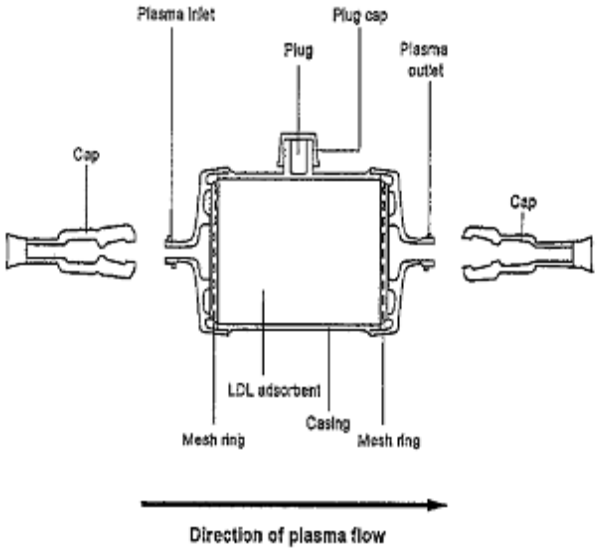
The components of the device are identical in material and design to the device currently approved via PMA P910018 (for subgroups of patients with familial hypercholesterolemia (FH)) and its supplements. The Liposorber® LA-15 System consists of four major components: the Sulflux KP-05 Plasma Separator, Liposorber® LA-15 Adsorption Columns, NK-M3R Tubing Set, and MA-03 Machine.

1. The Sulflux KP-05 Plasma Separator (approved on 6/27/2007 – Supplement 11) separates the plasma from whole blood. This component is comprised of porous hollow fibers made of polyethylene coated with an ethylene vinyl alcohol copolymer enclosed in a polycarbonate housing.

2. The Liposorber LA-15 Adsorption Columns (approved in original PMA 1996) (Table 1) are disposable. They adsorb apolipoprotein B-containing lipoproteins from a patient's plasma as it passes through the columns. The casing of the columns is polycarbonate.

Each column (they are used in pairs for a treatment) contains a microporous hydrophilic gel (with particle size of 64 – 160 µm) composed of 150 ml dextran sulfate cellulose (DSC) beads soaked in 0.04-0.08% (w/v) sodium citrate/citric acid solution.

Figure 1. Schematic of Liposorber LA-15 Adsorption Column



3. The NK-M3R Tubing Set (approved on 3/31/2009 – Supplement 12 and 6/18/2010 – Supplement 13) set is designed specifically for the Liposorber LA-15 System. The tubing is comprised primarily of polyvinyl chloride, but also contains polycarbonate, polypropylene, polyethersulfone, polytetrafluoroethylene, polyester, acrylic resin, isoprene rubber, and polyolefin elastomer. It is composed of the following:

    - Blood withdrawal line
    - Regeneration line
    - Plasma line
    - Blood return line
    - A set of five (5) connection lines (for connection to solution bags)
    - Membrane filter.

4. The MA-03 Machine (approved 3/31/2009 – Supplement 12) is a computer-controlled unit that controls the entire apheresis procedure.

While the Liposorber® LA-15 System (P910018) is labeled for either weekly or every other week use when used to treat familial hypercholesterolemia (FH) (depending on the patient's LDL-C levels), in the HDE, the Liposorber (H120005) is indicated for up to 12 uses in 3 months for treatment of focal segmental glomerulosclerosis (FSGS) (twice weekly for 3 weeks, then weekly for 6 weeks).

IV. REGULATORY HISTORY

The Liposorber LA-15 System received designation as a Humanitarian Use Device (HUD Designation) on September 28, 2012, and on October 10, 2013, the HDE application was

approved by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration.

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual.

Section 613(b) of the FDASIA states that an HDE holder of a HUD for which an HDE was approved prior to the enactment of FDASIA on July 9, 2012 may submit an HDE supplement (21 CFR 814.108) requesting an exemption from the profit prohibition for a HUD. In September 4, 2012, the firm requested a determination that the Liposorber® LA-15 System met the conditions of either subclause (I) or (II) under section 520(m)(6)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the FDASIA, so that the device might be sold for profit. The HDE supplement request was approved by the FDA on October 10, 2013.

As stated in section 520(m)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

The table below provides the number of device components distributed by the firm for the calendar year 2016 in the United States

Table 1. Annual Distribution Number

Calendar Year (Jan - Dec)	Total Sales
2016	240 Columns 234 Tubing Sets 234 Plasma Separators 2 Machines

VI. POSTMARKET DATA: POST-APPROVAL STUDY (PAS)

PAS Conditions of Approval:

The Liposorber HDE (H120005) was approved on October 10, 2013, with the following conditions of approval:

You have agreed to conduct a study as follows: The purpose of the study is to evaluate the long-term safety and probable benefit of the Liposorber LA-15 System for the treatment of pediatric

patients who have FSGS with a GER 60 ml/min/1.73 m^2 accompanied by nephrotic syndrome in which standard treatment options are unsuccessful or not well tolerated or for the treatment of pediatric post renal transplant patients with nephrotic syndrome associated with primary ESOS.

This will be a prospective, multicenter, single arm study with a total of 35 newly enrolled patients, treated at 3 to 10 clinical centers in the United States. The study participants will be followed for 24 months after the completion of the final apheresis procedure. The study visits will be as follows: Pre-procedural exams and laboratory tests, approximately 9 weeks of study apheresis procedures, and then for 1-, 3-, 6-, 12- and 24-month follow-up office visits after the last apheresis treatment.

The primary objectives of this study are to confirm the safety and probable benefit of the Liposorber LA-15 System in relieving nephrotic syndrome, defined as urine protein: creatinine ratio (Up/c) > 2.0 (gram protein per gram creatinine) with a first morning void urine sample, associated with refractory pediatric primary FSGS at 1 month after the final apheresis treatment.

The primary probable benefit endpoint is the percent of patients who show complete or partial remission at 1 month after the final apheresis treatment. Complete remission is defined as Up/c < 0.2 (g/g) with a first morning void urine sample. Partial remission is defined as at least 50% reduction in Up/c compared to the value at screening or Up/c between 0.2 and 2.0 (g/g) with a first morning void urine sample. A sample size of 30 patients is required for this analysis.

The Primary safety endpoint is the rate of device-related and procedure-related serious adverse events (SAEs) occurring during the treatment period and up to 1 -month follow-up visit. The rate of SAEs and corresponding 95% CI will be provided.

The secondary objectives are to evaluate safety and probable benefit of the Liposorber LA- 15 System in relieving nephrotic syndrome associated with refractory pediatric primary FSGS at 3 months, 6 months, 12 months, and 24 months after the final apheresis treatment. The secondary safety and probable benefit endpoints include: nephrotic condition (complete remission, partial remission, and nephrotic state) including the percentage of patients who obtain complete and partial remission at 3, 6, 12, and 24 months; incidence of adverse events encountered during the period in which apheresis treatments are given; incidence of all adverse events and SAEs occurring within 3, 6, 12, and 24 months after the final apheresis treatment; and laboratory values, including eGFR at baseline, after the last treatment, and at 1, 3, 6, 12, and 24 months after the final apheresis treatment, including percent change from baseline and percentage of patients showing an increase or decrease in each value.

PAS Study Status:

Site and Subject Enrollment

At the time of the three year interim report (H120005/R007), received at FDA on October 4, 2016, IRB approval has been obtained for three clinical sites and a total of nine subjects have been enrolled across the three study sites (Table 2). This represents an increase of five subjects in the past year.

Table 2. PAS Study: IRB Approvals and Patient Enrollment

	2016 PAC	2017 PAC
Number of IRB approvals	3	3
Number of patients enrolled	4	9

Source: Constructed based on data from H120005/R005 and H120005/R007

Distribution of subjects' demographics is presented in Table 3 below.

Table 3. Demographics of Subjects

	n	%
Age (years)		
6 to 8	3	33.33
9 to 11	1	11.11
12 to 14	4	44.44
15+	1[a]	11.11
Sex		
Male	6	66.67
Female	3	33.33
Race/ethnicity		
Caucasian	6	66.67
African American	1	11.11
Unknown	2	22.22

[a] 20 years old

Source: Constructed based on data from H120005/R007

Follow-up status per study visit is shown in Table 4 below. Of the nine enrolled subjects, eight completed the treatment course (approximately nine weeks of apheresis procedures), and one subject withdrew due to renal transplantation. Of the eight subjects who completed treatment course, three are no longer in the study (two due to renal transplantation) and five remain in the study. In total, six of the nine enrolled subjects have one month data for the primary study endpoint; the other three did not complete the one month visit due to subject withdrawal (n=2) and not completing the treatment course (n=1).

Table 4. Subject Follow-up per Study Visit

Study Visit	Completed	Withdrawn	Lost	Active
~9 weeks Apheresis Procedures	8[a]	1[b]	0	7
1-month	6	0	0	7
3-month	6	0	1	6
6-month	4	1[b]	0	5[c]
12-month	[d]			
24-month	[d]			

[a] One subject did not start treatment due to thyroid disease; [b] Had renal transplantation; [c] One completed the 1-month visit, one completed the 3-month visit, and three completed the 6-month visit; [d] None reached yet.
Source: Constructed based on data from H120005/R007

At the time of the 2016 PAC, the study status was reported as progressing adequately. However, enrollment for this study has been slow, due to IRB delays and the size of the intended pediatric patient population. Enrollment of 35 subjects was originally anticipated to be completed in April 2017. The study progress is not consistent with the FDA approved timeline; enrollment is lower than anticipated based on the intended use population and paucity of other available therapeutic options. Therefore, the study progress is now considered inadequate (for more information about study status determination, please see the FDA guidance document "Procedures for Handling Post-Approval Studies Imposed by PMA Order" at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm). On December 2, 2016, the FDA changed the study status to "Progress Inadequate" which means that the study progress is not consistent with the protocol timeline. The FDA advised the sponsor to consider strategies to increase site and subject enrollment, such as assistance from professional organizations, hiring a research coordinator or incentives for physicians or patients. During the review of the three year report (H120005/R007), FDA accepted a revised study timeline; subject enrollment is now projected to be completed in August 2018. The four year report is due on October 9, 2017, and the study status will be reassessed at that time.

Interim results

Primary probable benefit endpoint: percentage of patients who show complete or partial remission at 1 month after the final apheresis treatment
Secondary probable benefit endpoint: percentage of patients who show complete or partial remission at 3, 6, 12, and 24 months after the final apheresis treatment

Two subjects demonstrated partial remission and three showed no response at the one month follow-up visit. The remission status for subject (b) (6) was uncertain due to missing Up/c data

at one month. Therefore, the interim results showed that 2/6 or 33% of patients with one month data showed complete or partial remission, and 1/6 or 16.5% had unknown remission status.

One subject showed complete remission and two showed partial remission at the 3-6 month follow-up interval. The subjects who were in partial remission at one month were also in partial remission at six month follow-up (see Table 5, below). The subject with unknown status at one month was not in remission at three months.

Table 5. Remission Status Based on Urine Protein/Creatinine (Up/c)

Remission	F/U (1-month)		F/U (3, 6-month)		Note (Up/c level)
	Subject ID	#	Subject ID	#	
Complete		0	(b) (6)	1	3.33 (1M), 0.90 (3M), 0.18 (6M)
Partial	(b) (6)	2	(b) (6)	2	
	(b) (6)		(b) (6)		0.39 (1M), 0.10 (3M), 0.42 (6M)
No	(b) (6)	3		3	
			(b) (6)		
	(b) (6)		(b) (6)		
	(b) (6)		(b) (6)		2.67 (1M), 2.11 (3M)
Uncertain	(b) (6)	1			No data on Up/c
TOTAL		6		6	

Source: Table 2 from the Kaneka Pharma America's Three Year Interim Study Progress Report for New Enrollment Study for the Liposorber LA-15 System; The "Note" column denotes the Up/c level at the one month (1M), three month (3M), or six month (6M) visit.

Primary safety endpoint: device-related and procedure-related serious adverse events (SAEs):

As seen below in Table 6, there were two adverse events in the past year, since the previous report presented to the PAC in April 2016. The sponsor reports and the agency agrees that these events were not related to the treatment. One event (#(b) (6) was considered serious. At this time, there are no significant or new safety concerns based on the Post Approval Study interim results.

Table 6.: Reported AEs and SAEs since previous report presented in PAC 2016

AE/ SAE	Subject ID	Liposorber Treatment at Time of AE	Description of AEs/SAEs	Severity*	Hospitalization	Relationship to treatment**
AE	(b) (6)	Yes	Fever 103º, R/O line infection Neg culture	Moderate	No	Not related
SAE	(b) (6)	Yes	Fever max 100.7º, Diarrhea, Abdominal pain, Vomiting	Moderate	Yes	Not related

*Severity: Mild, moderate, severe, life-threatening, or fatal; **Relationship to treatment: Not related, unknown, or related.

Source: Table 4 from the Kaneka Pharma America's Three Year Interim Study Progress Report for New Enrollment Study for the Liposorber LA-15 System

Secondary probable benefit endpoint: laboratory values, including eGFR

Table 7. Renal function (measured by estimated glomerular filtration rate, or eGFR) and other laboratory values by study visit

Treatment	Parameter	Unit	Base-line	After final	1M F/U	3M F/U	6M F/U	Notes
[redacted] (b) (6)	Up/c	g/g·CRE	44 33	13.02	17.43	12.81	17.51	Withdrawal after 6M F/U
	s-CR	mg/dl	0.8	0.4	0.6	0.6	0.6	
	eGFR	ml/min/1.73 m^2	62.2	125.4	83.6	83.0	83 9	
	LDL-C	mg/dl	60	71	269	344	498	
	sUPAR	ng/ml	290		212.4	<LLOQ	782.5	
[redacted] (b) (6)	Up/c	g/g·CRE	8.11	3.84	–	6.27		Withdrawal after 3M F/U
	s-CR	mg/dl	0.7	0.7	0.7	0.8		
	eGFR	ml/min/1.73 m^2	89.4	91.0	89.7	78.7		
	LDL-C	mg/dl	212	30	181	189		
	sUPAR	ng/ml	226		198	722		
[redacted] (b) (5)	Up/c	g/g·CRE	6.33	<5.0	3.33	0.90	0.18	
	s-CR	mg/dl	0.8	0.4	0.6	0.6	0.7	
	eGFR	ml/min/1.73 m^2	84.9	172.2	112.9	114 3	98 3	
	LDL-C	mg/dl	345	23	96	70	78	
	sUPAR	ng/ml	297		791	540	544	
[redacted] (b) (6)	Up/c	g/g·CRE	1.05	0.68	3.99	8.18	3.51	eGFR ≃ 75, 2 months before LDL-A
	s-CR	mg/dl	1.9	1.8	1.9	2.7	2.5	
	eGFR	ml/min/1.73 m^2	39.8	42.0	39.6	27 9	30 2	
	LDL-C	mg/dl	165	37	150	316	194	
	sUPAR	ng/ml	302			1,048		
[redacted] (b) (6)	Up/c	g/g·CRE	1.98	0.71	0.39	0.10	0.42	
	s-CR	mg/dl	0.3	0.3	0.4	0.4	0.4	
	eGFR	ml/min/1.73 m^2	170.7	170.3	129.1	129.8	130.1	
	LDL-C	mg/dl	126	26	98	91	115	
	sUPAR	ng/ml	452		491	412		
[redacted] (b) (6)	Up/c	g/g·CRE	1.81	3.48	2.67	2.11		
	s-CR	mg/dl	1.2	1.2	1.4	1.2		
	eGFR	ml/min/1.73 m^2	60.0	60.0	51.9	60 9		
	LDL-C	mg/dl	96	21	98	86		
	sUPAR	ng/ml	854.0		NR	NR		

Up/c: Urine protein:creatinine ratio; s-CR: serum Creatinine; eGFR: estimated Glomular Filtration Rate; LDL-C: LDL-cholesterol; sUPAR: serum soluble Urokinase Plasminogen Activator Receptor;<LLOQ: less than Low Limit of Quantification; NR: Not Reported yet

Source: Table 3 from the Kaneka Pharma America's Three Year Interim Study Progress Report for New Enrollment Study for the Liposorber LA-15 System

This data shows stable eGFR in three patients and an increase over the follow-up period compared to baseline in three patients. For the four patients with six months of follow-up (reflecting perhaps approaching a steady state), eGFR increased slightly in two patients and was stable in two others (after determining that there was no real change in the serum creatinine and eGFR for patient (b) (6)

FDA Conclusions:

The interim results showed that 2/6 (33%) subjects showed partial or complete remission at the one month visit, although conclusions are very limited due to the small number of subjects with one month follow-up data. When multiple laboratory parameters were considered, there was evidence of probable benefit (reduction in proteinuria with stabilization or improvement in renal function) in 4/6 (67%) of patients). The Post-Approval Study has not raised any new concerns regarding safety or probable benefit at this time. The study progress will continue to be monitored.

2017 Update to the Systematic Literature Review on the Use of the Liposorber LA-15 Device in the Pediatric Population

Purpose

In preparation for the FDA PAC 2017 spring meeting, a systematic literature review was conducted to provide an update addressing the following question: *What use of the Liposorber LA-15 system is reported in the literature for the pediatric population (≤21 years old)?* This is an update from the literature review presented at the Pediatric Advisory Committee (PAC) meeting on April 24, 2016.

Methods

On December 5, 2016, a search was conducted using the PubMed (Medline) and EMBASE databases with the following search strategies:

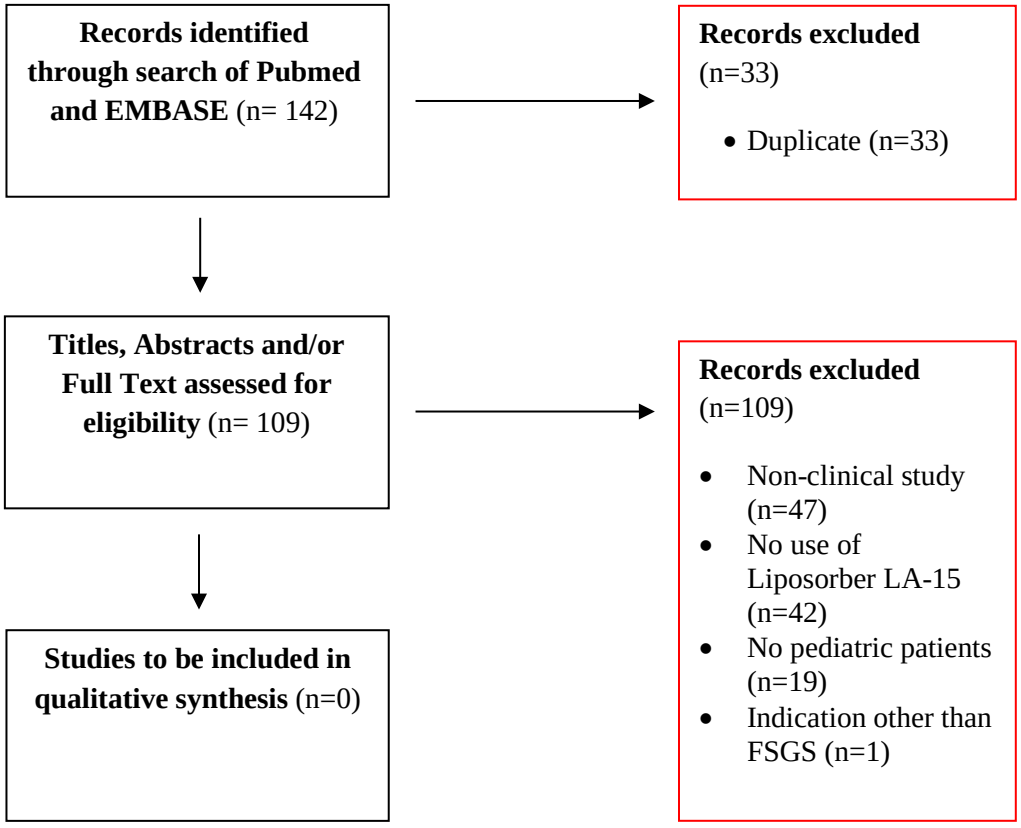
(Liposorber OR (LDL AND apheresis))

The search was limited to articles published between January 13, 2016 (last date of search included in the previous literature review presented in PAC 2016) and December 5, 2016 (see Figure 1). To determine the eligibility of the articles, the title, abstract, and/or full text were reviewed.

Results

The search yielded 42 records in PubMed, and 100 records in EMBASE (see Figure 2, below). After the exclusion of 33 duplicate records, there were a total of 109 articles for review. After review, one article was found to report use of the Liposorber LA-15 system in the pediatric population (Drouin Chartier, et al, 2016). However, this article was considered not relevant and excluded from review for the following reasons: 1) the study subjects had a diagnosis of Homozygous Familial Hypercholesteremia (HoFH) rather than FSGS, 2) no safety data were presented in the article, and 3) data were not presented separately for the adult and pediatric subjects. The reasons for exclusion of the remaining records were as follows: non-clinical study such as non-systematic review or bench study (n=47), no use of LA-15 or device not specified (n=42), or no pediatric patients (n=19).

Figure 2. Article Retrieval and Selection



Conclusions

A systematic literature review was presented to the Pediatric Advisory Committee (PAC) in 2016. For this year's PAC meeting, similar methodology was employed to determine if new information was available. The date range of the search was January 13, 2016 to December 5, 2016.

The search did not result in any new literature that reported on adverse events associated with the use of the device in the pediatric population, for the indication of FSGS. Therefore, the literature review update provided no new probable benefit or safety information.

Overview of MDR Database

Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues,

and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
    - rare, serious, or unexpected adverse events;
    - adverse events that occur during long-term device use;
    - adverse events associated with vulnerable populations;
    - off-label use; and
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs and FDA's internal MDR database include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Liposorber® LA-15 System

The MDR Database was searched on December 12, 2016 utilizing the following search criteria:

- Product codes MMY (Lipoprotein, Low Density, Removal) and PBN (Apheresis for Focal Glomerulosclerosis in Pediatric Patients),

- A date range of on or after January 1, 2016

The search resulted in zero (0) MDRs. Kaneka Pharma America was contacted in an effort to determine if the firm had submitted any MDR's during the relevant time period reference the

Liposorber® LA-15 System. The firm informed the FDA that they had mistakenly "sent MDRs to the FDA's test system since the initiation of the eMDR system." The firm "contacted the respective department in FDA" and resubmitted all 6 MDRs into the correct system, as of December 16, 2016. One (1) of the six (6) MDRs, based on the date of event and report, would have been included in the 2016 PAC presentation had it been submitted in 2015. The remaining five (5) MDRs are relevant to the current review period. All reports noted the patients to be undergoing apheresis treatment for focal segmental glomerulosclerosis (FSGS) or arteriosclerosis obliterans (ASO).

Pediatric MDR (n=1), Serious Injury

For the prior two (2) PAC meetings involving the Liposorber® LA-15 System, there were no pediatric MDRs submitted during those analysis periods. The firm did submit one (1) report on December 16, 2016 for an event which occurred in October 2015 (as noted above).

This report (MDR 9614654-2015-00015), involved a 14-year-old male in whom the LDL-apheresis (LDL-A) with the Liposorber® LA-15 System was being used as a humanitarian use device (HUD) for treatment of "recurrent nephrotic syndrome associated with FSGS after renal transplantation". The patient developed anemia and was treated with "exogenous erythropoietin" which was determined not to be "optimally effective". The patient's condition worsened to Grade 3 anemia after his 17th treatment and required a blood transfusion.

The manufacturer's narrative stated such an anemia is likely to be "multifactorial in etiology" and related to chronic disease, malnutrition, medications, and ongoing nephrosis. While rare, the manufacturer also states that anemia can occur during repetitive LDL-A procedures secondary to "cumulative blood loss by the residual blood in the extracorporeal circuit and blood sampling for chemistry" in each LDL-A procedure, which is also referred to in the labeling.

Adult MDRs (n=5), 2 Death, 2 Injury, 1 Malfunction

Five (5) MDRs were submitted from Japan, involving two (2) adult males, two (2) adult females, and one (1) adult patient of unknown gender. The patient problems reported included death, shock, anaphylaxis, hypotension, hypovolemia, loss of consciousness, and dyspnea. All five (5) reports indicated there was no known device problem associated with the patient events.

Deaths (n=2)

1. A 72-year-old male patient (MDR 9614654-2016-00001) on maintenance hemodialysis (HD) with new-onset FSGS was reported to have died one day after his 8th LDL-A treatment. The following day, after an uneventful HD treatment, he returned to his room

and later complained of feeling ill. He lost consciousness and suffered from cardiopulmonary arrest. The manufacturer narrative states, "It is speculated sudden death occurred after some catastrophic events". The physician in charge commented that the LDL-A "could not be relevant to the patient's death" but the manufacturer could not "completely exclude a possibility that LDL-apheresis is relevant to the catastrophic events".

2. A 50-year-old female patient (MDR 9614654-2016-00022) on HD, complicated with ASO and a history of diabetes and pacemaker placement, died while receiving her 6th LDL-A treatment of the 3rd course of LDL-A. It is reported that her physical condition changed suddenly and she exhibited signs of dyspnea, with oxygen saturation dropping from 98% at the start of LDL-A to 70% and her systolic BP (SBP) rising from 90 to 120 mmHg, requiring intubation, from which she did not recover. This patient was noted to have had "breathing difficulty during LDL-A under heparin"; therefore, "Futhan (or Nafamostat Mesilate), a protease inhibitor, was used as the anticoagulant of LDL-A since the 3rd LDL-A". The involved physician in charge reported the cause of death as "myocardial infarction" and that it "was not attributable to the LDL-A". However, the manufacturer noted the myocardial infarct "might have been relevant to a sudden change in her physical condition during the LDL-A such as dyspnea"; therefore, the events that occurred during the LDL-A cannot "be completely excluded".

Injuries (n=3)

1. This injury report (MDR 9614654-2016-00006) referenced an 82-year-old female on LDL-A and HD for FSGS, whose renal condition had been aggravated by the administration of Cyclosporin. On the day of her first LDL-A treatment the patient complained of feeling very tired and she began to shown signs of hypotension. On continued LDL-A treatment "her condition worsened and she lost consciousness". After intervention with saline and oxygen inhalation, her condition improved and LDL-A was discontinued. The manufacturer narrative noted that while the instructions for use (IFUs) provide information about the risks of hypotension with LDL-A treatment, this patient's "vital conditions on the day of the event might not be tolerable to this sort of extracorporeal treatment". The attending physician did note that the patient's renal functions had gotten worse rapidly and the timing of the initiation of the LDL-A treatment might have been "too late".

2. This injury report (MDR 9614654-2016-00020) involved an unidentified patient with hypercholesterolemia, on LDL-A for ASO, developed severe hypotension and went into shock approximately 15 minutes after starting LDL-A. The treatment was stopped, adrenaline was administered, and the patient stabilized. It was determined the patient was prescribed an angiotensin-converting enzyme (ACE) inhibitor at another hospital, which is contraindicated in the labeling with LDL-A treatment.

3. An 82-year-old male (MDR 9614654-2016-00009) on maintenance HD for ASO was placed on LDL-apheresis. Approximately 30 minutes after starting LDL-A (following HD treatment that same day) the patient became tired and hypotensive, (his SBP abruptly dropping down from over 100 mmHg to 53 mmHg) and went into shock. The patient was administered saline and LDL-A was discontinued. The patient's blood pressure resolved after 15 minutes (returning to130 mmHg). The manufacturer narrative states "the reported event was due to the patient's intolerance to the combination procedure" of HD and LDL-A, suggesting that LDL-A be provided first, followed by HD, in order to reduce the risk of hypovolemic shock if unable to avoid same day subsequent therapy. This report was initially reported as a malfunction event, and was reclassified based on the description of the event provided in the report.MDR Summary

The patient problems reported (anemia, shock, hypotension, and dyspnea), are known inherent risks with the use of this device, as indicated in the device IFUs. It is difficult to measure the role of patient co-morbidities in the outcomes following LDL-A treatment since patients with FSGS typically have cardiovascular disease. Based on the manufacturer's evaluations contained in the MDRs, consultation with the Office of Device Evaluation Medical Officer, and a review of the device's IFUs, it appears there may be certain factors to consider when treating with LDL-A including, but not necessarily limited to:

I. Consideration should be given to all <u>concomitant medications</u> the patient is taking such as:

   a. Use of an angiotensin-converting enzyme (ACE) inhibitor, which will activate bradykinin (a substance that causes vasodilation and hypotension), or

   b. Use of other anti-hypertensive drug which can exacerbate other causes of hypotension.

   c. Conversely, the use of an anticoagulant that can suppress the rise of bradykinin levels in patients, such as Nafamostat Mesilate (NM), a protease inhibitor has been reported to cause cardiac arrest in patients receiving dialysis (Kim et al. Kidney Res Clin Pract, 35:187-9, 2016)

II. <u>Combination treatment of HD and LDL-A</u> on the same day could exacerbate hypovolemia shock syndrome, given the extracorporeal volume of the LDL-A system is larger than that of the HD system and the patient has already lost a certain amount of circulating blood volume.

III. The increased potential for the development anemia during <u>repetitive LDL-A treatments</u> secondary to the cumulative blood loss by the residual blood in the extracorporeal circuit and blood sampling for chemistry in every LDL-A procedure.

Historically, the number of MDRs submitted each year has been relatively small (i.e. ranging from 0-8 MDRs received per year).

VII. SUMMARY

As of the October 2016 interim progress report provided by the sponsor, nine patients with FSGS were enrolled in the mandated post-approval study and eight completed treatment with the device. Two out of six (33%) showed partial or complete remission as defined by Up/c level at the one month follow-up visit. We also find probable benefit (reduction in proteinuria with stabilization or improvement in renal function as measured by different laboratory parameters) in 4/6 (67%) of patients. To date, no new safety concerns have arisen from the study. Our review of the published literature and received MDRs since the time of approval has identified limitations in the labeling of potential risks for both the pediatric and adult populations, which the FDA concludes needs to be addressed by the manufacturer to reduce the risk of illness or injury, despite the supposition that probable benefit to health continues to outweigh the risk of injury or illness.

Therefore, FDA recommends:

Review and discussion with the manufacturer related to strengthening the device labeling and determine if revisions of Instructions for Use (IFU's) are warranted as it relates to the issues of:

1. possible revision of Instructions for Use (IFU's) as it relates to the issues of:
    - the development anemia during repetitive LDL-A treatments
    - Exacerbation of hypovolemia and potential development of shock with combination treatment of HD and LDL-A on the same day

2. Continued surveillance and will report the following to the PAC in 2018:

    - Annual distribution number
    - PAS follow-up results
    - Literature review
    - MDR review