FDA Executive Summary

Prepared for the
Spring 2022 review by the
FDA's Pediatric Advisory Committee

H120005
Liposorber® LA-15 System

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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 (hereafter referred to as Liposorber LA-15) from Kaneka in pediatric patients for the treatment of nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) 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.

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.

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

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 (FDA).

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) 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. Since each Liposorber LA-15 system treatment regimen includes 12 treatments/patient, the total ADN is 96,000.

Section 613(b) of the Food and Drug Administration Safety and Innovation Act (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. On 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 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 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.

Table 1 below provides the number of device components distributed by the firm for the calendar year 2020 in the United States

Table 1. Annual Distribution Number-11/01/2021-10/30/2021

Device	Total Sales
MA-03 Apheresis Machine	0
Liposorber® LA-15 LDL Adsorption Column (2 columns/shipment)*	180
Sulflux® KP-05 Plasma Separator	186
NK-M3R (U) Tubing System for Plasmapheresis	198

*Each shipment of adsorption columns contains two columns. Therefore, 180 shipments would include 360 columns.

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

a. PAS Conditions of Approval:

The Liposorber HDE (H120005) was approved on October 10, 2013

The purpose of the PAS 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 an estimated Glomerular Filtration Rate (eGFR) ≥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 FSGS.

This is 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.

b. PAS Study Status:

PAS study data was available from the eight year interim post-approval study report, received at the FDA on October 6, 2021.

The sponsor reported that Institutional Review Board (IRB) approval had been obtained for six clinical sites, and twenty-three subjects had been enrolled since study inception (Table 2). The study was anticipated to have enrolled 20 subjects by September 2017, and enrollment was anticipated to be completed in August 2018.

Table 2. PAS Study: Patient Enrollment and Study Status

Interim Report	Date Received	Sites Enrolled	Patients Enrolled	Study Status	Actions Taken by FDA
6-month	7/8/14	0	0	Study Pending	
12-month	10/2/14	0	0	Progress Adequate	
18-month	4/6/15	3	0	Progress Adequate	
24-month	10/1/15	3	4	Progress Adequate	
36-month	10/4/16	3	9	Progress Inadequate	• Worked with sponsor to revise study timeline • Provided recommendations for enrollment strategies
39-month	12/28/16	4	9	Progress Adequate	
48-month	10/13/17	6	14	Progress Inadequate	• Deficiency letter issued to request plan from sponsor for improving enrollment
60-month	10/09/18	7	14	Progress Inadequate	• A teleconference will be scheduled with the sponsor to identify current enrollment barriers and alternatives to improve it.
72 month	09/12/2019 and 12/25/2019	7	17	Progress Adequate	
84 month	10/07/2020 and 12/28/2020	7	23	Progress Adequate	
96 month	10/06/2021	10	25	Progress Adequate	

Since the last report:

- Two (2) new patients (Patient X and Patient Y) were enrolled
  - One (1) patient (Patient X) reached the 1-month F/U
  - One (1) patient (Patient Y) withdrew after the final treatment before the 1-month F/U.
- Two (2) patients (Patient V and Patient W)reached the12-month F/U

The sponsor also reports an error in prior reporting of patient status in 2019, as detailed in Table 3 below:

Table 3

Patient ID	Status Incorrect	Status Correct
Patient G	Reached the 6 month follow-up period	Withdrew after treatment without follow-up
Patient H	Excluded from the study	Withdrew after treatment without follow-up
Patient N	Excluded from the study	Withdrew after treatment without follow-up
Patient R	Reached the 6 month follow-up period	Withdrew after treatment and 1 month follow-up visit

The distribution of subjects' demographics is presented in Table 4 below.

Table 4. Demographics of Enrolled Subjects (n=25)

	N	%
Age (years)		
6 - 8	7	28.0
9 - 11	6	24.0
12 - 14	7	28.0
15 - 17	2	8.0
18 - 20	3	12.0
Sex		
Male	12	48.0
Female	13	52.0
Race/ethnicity		
Caucasian	15	60.0
African American	6	24.0
Hispanic/Latino	2	8.0
Unknown	2	8.0

Source: Constructed based on data from H120005 annual reports

Patient enrollment and status and the reasons for withdrawal are exhibited in Table 5 below. Since study inception, there have been two protocol deviations (two patients who should have been excluded from study entry due to not meeting inclusion criteria). Those two subjects are still undergoing follow-up visits, as well as two subjects who withdrew and then underwent a second round of treatment.

Summary of the report to date: Twenty-five (25) patients have been enrolled since study inception. Among those:

- Three (3) patients were excluded from the study due to protocol deviations
- Seven (7) patients withdrew from the study after completing all device treatments without any further follow-up. Since the primary probable benefit endpoint required data one month after the final device treatment, these patients had unevaluable benefit data.
- One (1) patient withdrew during the device treatment period

- There is evaluable probable benefit follow-up data for fourteen (14) patients. Among those patients:
  - Four (4) subjects completed all 24 month follow-up visits
  - Three (3) subjects are in active follow-up. Among those patients:
    - One (1) patient has completed the one month visit
    - Two (2) patients completed the twelve month visit
  - Four (4) patients withdrew after the one month, post-treatment visit
  - One (1) patient withdrew after the three month, post-treatment visit
  - One (1) patient withdrew after the six month, post-treatment visit
  - One (1) patient withdrew after the twelve month, post-treatment visit

These results are also displayed in tables 5 and 6 below.

Table 5. Patient Enrollment and Status

Subject/Patient ID	Completed All Apheresis Treatments?	Follow-up Status	Reason for Withdrawal/Comment
Patient A	Yes	Withdrew after 6 month follow-up visit	Subject moved to another hospital and had further treatment off the study.
Patient B	Yes	Withdrew after 3 month follow-up visit	Subject relapsed and had another treatment series off the study.
Patient C	Yes	Completed 24 month post-treatment follow-up	
Patient D	Yes	Withdrew after final apheresis treatment	Subject dropped out and was lost to follow-up.
Patient E	No	Exclusion (treatment not started)	Subject was revealed to have thyroid disease after enrollment (Medical Exclusion Criteria #8)
Patient F	Yes	Withdrew after final apheresis treatment	Unknown
Patient G	Yes	Withdrew after final apheresis treatment	Moved to another location
Patient H	Yes	Withdrew after final apheresis treatment	Required second series of device treatments-Major protocol deviation
Patient I	Yes	Withdrew after final apheresis treatment	Unknown
Patient J	Yes	Exclusion (continuing active follow-up)	The reported eGFR level at baseline was 39.8 ml/min/1.73m^2, which fell out of the inclusion criteria of an eGFR > 60 ml/min/1.73m^2.
Patient K	Yes	Completed 24 month post-treatment follow-up	None
Patient L	Yes	Withdrew after 12 month follow-up visit	None
Patient M	Yes	Exclusion (continuing active follow-up)	The reported Up/c of Patient M at baseline was

			0.08, which indicated that the patient achieved complete remission before treatment and was considered be inappropriate for treatment.
Patient N	No	Withdrew during apheresis treatment period	None
Patient O	Yes	Withdrew after 1 month follow-up visit (continuing active follow-up after second round of treatment)	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment.
Patient P	Yes	Withdrew after 1 month follow-up visit (continuing active follow-up after second round of treatment)	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment.
Patient Q	Yes	Completed 24 month post-treatment follow-up	None
Patient R	Yes	Withdrew after 1 month follow-up visit	None
Patient S	Yes	Withdrew after final apheresis treatment	Unknown
Patient T	Yes	Completed 24 month post-treatment follow-up	None
Patient U	Yes	Withdrew after 1 month follow-up visit	Unknown
Patient V	Yes	Completed 12 month post-treatment follow-up	None
Patient W	Yes	Completed 12 month post-treatment follow-up	None
Patient X	Yes	Completed 1 month post-treatment follow-up	None
Patient Y	Yes	Withdrew after final apheresis treatment	None

Source: Constructed based on data from H120005 annual reports

Table 6. Follow-up Visits Completed

*Study Visit Completed**	*Number of Patients*
1-month	5
3-month	1
6-month	1
12-month	3
24-month	4

*Seven patients withdrew after the final treatment without a one month follow-up visit, three patients were excluded due to protocol deviations and one patient withdrew during the treatment period

Interim Results

Probable Benefit

Primary probable benefit endpoint for evaluable subjects: The primary probable benefit endpoint is the percent of patients who show complete or partial remission at 1 month after the final apheresis treatment.

- At the one month follow-up visit, six of fourteen (43%) subjects in whom Up/c data was available at baseline and at the 1 month visit had achieved either partial (four subjects) or complete (two subjects) remission.

Further U p/c data:

- At either the 3 month or 6 month visit (whichever they were able to achieve), six of eight (75%) subjects had complete or partial remission at the three or six month follow-up periods, while the other subjects (25%) had no remission (nephrotic syndrome, or NS, persisting).
- At the 12-month follow-up, five of seven (71%) subjects displayed either partial (3 subjects) or complete (2 subjects) remission, while two of seven (29%) subjects had persistent NS.
- At the 24-month follow-up, three of four (75%) subjects displayed either partial (3 subjects) or complete (2 subjects) remission, while one of four (25%) subjects had persistent NS.

Secondary probable benefit endpoint: Percentage of patients who show complete or partial remission at the 3, 6, 12, and 24 month follow-up visits after the final apheresis treatmentDetailed information regarding remission status for each patient is displayed in Table 7.

Table 7. Remission Status Based on Up/c Ratio

Patient ID	1-month	3-month	6-month	12-month	24-month	Status
Patient A	PR	PR	PR			Withdrew after 6 mo visit
Patient B	N/A	NS				Withdrew after 3 mo visit
Patient C	NS	PR	CR	CR	CR	Completed study
Patient F	NS					Withdrew after the final device treatment
Patient H	NS					Withdrew after the final device treatment
Patient K	PR	CR	PR	CR	CR	Completed study
Patient L	NS	NS	NS	NS		Withdrew after 12 mo visit
Patient O	NS					Withdrew after 1 mo visit
Patient P	NS					Withdrew after 1 mo visit

Patient Q	PR	PR	PR	PR	PR	Active
Patient R	NS					Withdrew
Patient T	N/A	NS	NS	NS	NS	Active
Patient U	NS					Withdrawal
Patient V	CR	CR	CR	PR	(-)	Active
Patient W	PR	NS	PR	PR	(-)	Active
Patient X	CR	(-)	(-)	(-)	(-)	Active
Patient Y	NS					Withdrew after the final device treatment

NS=Nephrotic Syndrome; PR=Partial Remisssion; CR=Complete Remission; N/A=Data Not available or Reported; (-)=Not Yet Followed-Up; [a] Gray shading indicates that data was not collected (i.e., missing data or subject withdrew), and absence of shading indicates that data were or will be collected;
Source: Constructed based on data from H120005 annual reports

Eleven of thirteen subjects (85%) displayed either stabilization or decline of urine protein (assessed by urine protein-to-creatinine ratio), while one subject does not have a follow-up value to assess. The evidence for these subjects shows a trend towards stabilization or improvement of laboratory indices (Table 8).

Table 8. Up/c Values By Study Visit

Subject	Baseline Up/c	Last Up/c	Trend in Up/c
1	44	18	Decrease
2	8	6	Stable
3	6	0.4	Decrease
4	2	0.2	Decrease
5	2	4	Increase
6	5	4	Stable
7	4	5	Stable
8	1	0.3	Decrease
9	27	15	Decrease
10	5	3	Decrease
11	28	38	Increase
12	8	0.5	Decrease
13	29	0.6	Decrease

Source: Constructed based on data from H120005 annual reports

While not a secondary endpoint, the Agency also conducted analysis of change in eGFR as a measure of renal function. For patients that completed the device treatment and had at least one follow-up visit, the changes in eGFR from baseline (pre-device treatment) to the most recent follow-up study visit are also shown in Table 9 below. The table shows that among the thriteen subjects who completed full device treatment and had at least one post-treatment visit with laboratory results, eGFR was stable or increased in 12/13 (92%) subjects.

Table 9. Renal Function (measured by estimated glomerular filtration rate) and other laboratory values by study visit

Subject	Baseline eGFR	Last eGFR	Trend in eGFR
1	62	84	Increase
2	89	79	Stable
3	85	100	Increase
4	171*	109	Stable
5	60	34	Decrease
6	85	130	Increase
7	153*	161	Stable
8	78	72	Stable
9	159	160	Stable
10	60	191	Increase
11	216*	131*	Stable
12	16	36	Increase
13	58	152	Increase

Source: Constructed based on data from H120005 annual reports
*Baseline or last eGFR value was falsely elevatedfor age. These values were defaulted to be normal for age.

The Agency also conducted an analysis of the outcomes of data for the eleven (11) subjects who either did not attend the visit immediately after the last device (five subjects), or, only attended the visit after the last treatment (6 subjects) treatment but did not attend any of the 1, 3, 6, 12 or 24 month follow-up visits, to ascertain if the exclusion of the data from those subjects may have skewed the results. Table 10 below shows those results:

Table 10. Outcomes of Subjects Who Withdrew Early or Were Excluded From the Study

Urine Protein and eGFR	Number of Subjects	Interpretation of Effect of Device on Disease Status
Labs Not Available After Last Apheresis Treatment	5	Cannot Determine

Decrease in Urine Protein with Increase in eGFR	1	Positive Response
Urine Protein not Available with Increase in eGFR	2	Likely Positive Response
Increase in Urine Protein with Decrease in eGFR	1	Disease Progression
No Change in Urine Protein with Decrease in eGFR	1	Likely Disease Progression
Urine Protein not Available with Decrease in eGFR	1	Likely Disease Progression

These outcomes (three subjects with positive response and three with disease progression) are generally similar to that of the subjects for whom follow-up data is available.

Safety

Primary safety endpoint: device-related and procedure-related SAEs: The most common or serious adverse events with the Liposorber LA-15 system are listed in Table 11 below:

Table 11. Known Adverse Events Observed with the Liposorber LA-15 System

1. Death
2. Cardiac (including myocardial infarction)
3. Thrombocytopenia
4. Infection/bacteremia
5. Hypersensitivity (anaphylactoid) reaction
6. Nausea and vomiting
7. Reduction in Vitamin E level
8. Transient decrease in serum protein and albumin level
9. Hypotension
10. Flushing/blotching
11. Angina/chest pain
12. Fainting/lightheadedness
13. Anemia
14. Prolonged bleeding (at cannulation site)
15. Hemolysis
16. Device malfunction
17. Vertigo
18. Diaphoresis
19. Urticaria

As of the eight year report, 89 adverse events have been reported, with nine events reported during the most recent reporting period. Table 12 shows the most serious adverse events that have been observed. The events include gastrointestinal (nausea/vomiting/diarrhea/abdominal pain/ache), fever/infection, upper respiratory symptoms, headache, edema/anasarca, lightheadedness/fainting, hypotension, anemia, malaise, and weakness. The sponsor posits and the agency agrees that a great majority of these events are most likely related to the patients' underlying conditions and/or the requirement for a central venous catheter for vascular access.

Table 12. Summary Table of Adverse Events

Adverse Event Type	Number of Events	Relationship to Device
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	10	None
Fever/Infection	16	2 (Unknown)
Upper Respiratory (Congestion/Pharyngitis)	8	None
Headache	7	None
Edema/Anasarca (Exacerbation)	8	None
Lightheadedness/Dizziness	3	None
Malaise	3	None
Hypotension	2	None
Leg cramps	2	None
Allergic reaction (mild)	2	None
Pancreatitis	2	None
Transplant rejection (in subject treated after renal transplantation)	2	None
Hyponatremia	1	None
Dehydration	1	None
Worsening of Nephrotic Syndrome	1	None
Pneumonia	1	None
Bacteremia	1	None
Anemia	1	None
Hematuria	1	None
Acute Kidney Injury	1	Possible

Source: Constructed based on data from H120005 annual reports

FDA Conclusions About Probable Benefit and Safety:

Conclusions remain limited due to the small number of subjects and a limited period of follow-up in many patients. For the primary probable benefit (percentage of patients who show complete or partial remission by measuring the Up/c at the 1 month follow-up visit after the final

apheresis treatment), six of fifteen (40%) of subjects had achieved either partial or complete remission one month after the last device therapy. However, 67-75% of the patients that reached either the 3, 6, 12 or 24 month follow-up visit achieved either a partial or complete remission. In comparison, seven of eleven (64%) pediatric patients in the study by Hattori et al. (Amer J Kidney Dis, 2003) showed either complete or partial remission one month after device therapy. Overall, the data show stabilization or improvement of eGFR over the follow-up period in the vast majority (92%) of patients. While the follow-up period was brief for some patients, the stabilization or improvement in eGFR suggests amelioration of progression may have occurred in some patients. The rates and severity of adverse events have been relatively low considering the underlying patient risk profiles (chronic kidney disease with nephrotic syndrome) and the known risks associated with any extracorporeal therapy. The review team believes that the vast majority of adverse events were unrelated to the device, while three were possibly related. Enrollment has improved slightly; therefore, the study status has been changed to "Progress Adequate." In summary, 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. FDA has worked interactively with the sponsor and study investigators to identify barriers to study enrollment that may be ameliorated by changes in study design.

LITERATURE REVIEW

Purpose

The purpose of this literature review is to keep current the knowledge published regarding the safety and effectiveness of Liposorber in pediatric patients for the treatment of nephrotic syndrome associated with primary (FSGS).

Methods

FDA conducted a literature review of the pediatric use of Liposorber by Kaneka on January 4, 2022 including all publications written in English between January 1 to December 31, 2021 in PubMed, Embase and Google Scholar. Without any additional filters, three groups of search terms were used:

1. Kaneka, Liposorber, Drug-resistant Pediatric Primary Focal Segmental Glomerulosclerosis, and Low-Density Lipoprotein (LDL)-Apheresis, or LDL-A.
2. Liposorber, Child, Focal Segmental Glomerulosclerosis
3. Apheresis, Child, Focal Segmental Glomerulosclerosis

After reading the titles, abstracts, and full-texts, 6 articles were selected.

Results

Summaries of the selected articles are included below.

1. Reddy RL: This was a chapter review of Therapeutic Apheresis in *Transfusion Medicine (*Fifth Edition. Edited by Jeffrey McCullough; 2021 John Wiley & Sons Ltd. Published 2021 by John Wiley & Sons Ltd.). The review included a discussion about LDL-A. The main points regarding LDL-A were:

a. Specialized procedures, such as low-density lipoprotein (LDL) apheresis or Staph-A columns, remove specific plasma components, such as LDL or immunoglobulin, and do not require replacement fluids.
b. LDL-A results in the selective removal of abnormal components for diseases such as familial hypercholesterolemia.
c. The Kaneka Liposorber requires an approximate extracorporeal blood volume of about 400 ml

Lead Reviewer Comment: This review chapter provides an excellent summary of therapeutic apheresis. The discussion about LDL-A is limited and does not specifically describe the benefits and risks for patients with FSGS.

2. Al-Mousily M, et al., Liposorber® LA-15 system for LDL apheresis in resistant nephrotic syndrome patients. Pediatr Nephrol, 2021 (DOI: 10.1007/s00467-021-05211-8). This is a case series report of five children with steroid-resistant nephrotic syndrome (SRNS) who were treated with 12 sessions of LDL-A. They report that among the five children, one achieved complete remission (CR) while three achieved partial remission (PR). LDL-A also resulted in a significant reduction in lipids (total cholesterol and triglyceride).

   Lead Reviewer Comment: This article describes the treatment of children with SRNS (three with minimal change disease, or MCD, and two with FSGS). Therefore, there seems to be some possible inclusion of patients with FSGS in the PAS described herein with two patients included in this study. Regardless, the general outcomes (remission of NS) seem better in this case series than those described in this executive summary. That is most likely due to the fact that three patients in this case series had MCD, which even if SR, is a milder form of NS. Unfortunately, the authors did not report if adverse events were observed for or occurred. This article suggests that LDL-A may at least temporarily induce either PR or CR in children with two forms of SRNS.

3. De Souza L, et al., Recurrent glomerulonephritis after kidney transplantation: a practical approach. Curr Opin Organ Transplant 26:360-380, 2021 (DOI:10.1097/MOT.0000000000000887): This was a review article describing treatment options for patients with primary glomerulonephritides (GN) being considered for kidney transplantation and the risk for recurrence of the original disease and deterioration of renal function after kidney transplantation. The authors report some novel therapies for patients who develop recurrent disease after kidney transplantation based on renal histology and the pathophysiology of recurrent glomerulonephritis. They report that there is an ongoing trial for LDL-A with the Liposorber device. Specific outcomes in patients with recurrent FSGS after transplantation treated with the Liposorber device are not provided.

   Lead Reviewer Comment: This is an excellent review article describing recurrent renal disease after renal transplantation. The relevance for this executive summary and therapy are minimal, since specific outcomes in patients with recurrent FSGS after transplantation treated with the Liposorber device are not provided.

4. Shah, S et al.: Role of therapeutic apheresis in the treatment of pediatric kidney diseases. Pediatr Nephrol 36:621-629, 2021 (DOI: 10.1007/s00467-020-04744-8) This is a review article describing the utility and experience of therapeutic apheresis (TA, including therapeutic plasma exchange, or TPE), for children with kidney diseases. They report that while TA/TPE are employed frequently in children with kidney disease, most experiences are extrapolated from adult studies. They state that registries are needed to better understand the role of apheresis modalities in children with kidney disease. They report that treatment options for children with FSGS are limited and do not frequently result in improved outcomes. They refer to studies showing that LDL-A can reduce proteinuria in FSGS and may be beneficial in drug-resistant nephrotic syndrome in FSGS patients. They report the results of the study by Hattori et al. showing that 2 out of 11 patients had partial remission and 5 had complete response after 4 weeks of LDL-A for FSGS.

   Lead Reviewer Comment: This is an excellent review article describing the benefits and unknown factors of TA and TPE for children with renal disease. The review contains no new information regarding treatment of children with FSGS.

5. Muso E, et al.: Favorable therapeutic efficacy of low-density lipoprotein apheresis for nephrotic syndrome with impaired renal function. Ther Apher Dial, 2021 (DOI: 10.1111/1744-9987.13694): This is a post-hoc analysis of the Prospective Observational survey on the Long-Term Effects of the LDL-Apheresis on the Drug Resistant Nephrotic Syndrome (POLARIS) performed in patients with estimated mildly decreased (GFR ≥60 ml/min/1.73 m2), moderately impaired (≥30 to <60 ml/min/1.73 m2), and severely impaired (<30 ml/min/1.73 m2) renal function. They report significant improvements of proteinuria and renal function in patients with higher and some with moderately impaired GFR. Risks were not comprehensively studied or reported.

   Lead Reviewer Comment: This is a good follow-up study of a large cohort (uncontrolled) of patients with FSGS and reduced GFR. The results are somewhat predictable and consistent with other therapies for patients with renal disease: Higher pre-treatment GFR predicts better outcomes, likely due to underlying (pre-treatment) slower disease progression, earlier diagnosis, and greater renal reserve. This analysis does pertain to the HDE for children with FSGS, since the approval required GFR of at least 60 ml/min for study inclusion to optimize the likelihood for benefit that outweighs the risk. The absence of safety data is a major limitation of this study.

6. Ge et al., Use of Lipid-Modifying Agents for the Treatment of Glomerular Diseases, J Personalized Med, 11:820-835, 2021 (DOI: 10.3390/jpm11080820): This is a review article describing dyslipidemia is associated with chronic kidney disease (CKD) and therapies thereof. They mention that LDL-A has been used as an alternative therapy for patients with FSGS and is currently under investigation for its safety and efficacy in drug-resistant pediatric primary FSGS.

   Lead Reviewer Comment: This is a good review article describing the occurrence of dyslipidemia and renal disease. The authors mention the current HDE PAS but do not

provide any specifics or results. The review contains no new information regarding the effectiveness or safety of the treatment of children with FSGS with LDL-A.

Lead Reviewer Summary Comments: The literature review provides few new insights that are relevant for the ongoing HDE PAS. The one encouraging outcome was from the Muso et al. analysis showing that higher GFR (equivalent to the cutoff for the HDE PAS) predicts the best outcomes.

OVERVIEW OF MEDICAL DEVICE REPORTS (MDR) DATABASE

Strengths and Limitations of MDR Data
Each year, the FDA receives several hundred thousand 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 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 caused a specific event can be difficult based solely on information provided in each 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

Joann Fujikawa conducted the MDR search.

MDR #1:
Report Number: 2435151
Event Date: 10/12/2017
Date Entered: 04/08/2021
FDA Received Date: 04/08/2021
Procode: PBN

Report: "On October 11 [a treatment with the device] was conducted without any problem in out-patient basis. Since the patient had fever on the next day of 9th LDL-apheresis [LDL-A], she was admitted to the hospital for further examination and medication. Her WBC was 34200/microliter and the result of the blood culture was Escherichia Coli positive, which was found to become negative after administration of antibiotics. The 12th LDL-apheresis, the final session, on October 25th was over without any problem. The attending physician was planning to discharge the patient after removing the catheter."

Lead Reviewer Comment: While this event occurred in 2017, it was identified in our current MDR search. This patient was receiving a series of LDL-A treatments and developed a fever and infection, presumably (not stated in the report) due to a catheter-related bloodstream infection (CRBSI). CRBSI are not uncommon in patients with an indwelling catheter. This is a device-related adverse event (AE), but due to the catheter, not the Liposorber device. This event raises no concerns about the Liposorber device or therapy.

MDR #2:
Report Number: 2435151
Event Date: 11/20/2015
Date Entered: 06/24/2021
FDA Received Date: 06/24/2021
Procode: PBN

Report: The patient is a 14 year old boy who has been treated by the LDL-apheresis with Liposorber LA-15 system approved as a humanitarian use device (HUD) for his treatment of recurrent nephrotic syndrome associated with focal segmental glomerulosclerosis (FSGS) post renal transplantation. He has developed anemia and received exogenous erythropoietin [Epo] but this was not optimally effective. After his 17th treatments with the LDL-apheresis, his anemic

condition worsened into grade 3 anemia (his hemoglobin level fell below 7g/dl) and required a PRBC transfusion."

Lead Reviewer Comment: While this event occurred in 2015, it was identified in our current MDR search. This patient was receiving a series of LDL-A treatments and developed worsening anemia. He had been previously diagnosed with anemia and was receiving Epo. The most likely cause of his anemia was chronic kidney disease (CKD), since patients with FSGS often develop CKD and are allowed in the PAS with a GFR of at least 60 ml/min (stage 3 CKD). The anemia may have been exacerbated by some blood loss during LDL-A treatments and is known AE associated with any extracorporeal therapy, including LDL-A, but that was not reported in this MDR. This is most likely an underlying disease-related AE, with a possible contribution from treatments with the Liposorber device. This event raises no new concerns about the Liposorber device or therapy.

The Manufacturer and User Facility Device Experience (MAUDE) Database was also searched on January 4, 2022 utilizing the following search criteria:

- Product codes: MMY (Lipoprotein, Low Density, Removal) and PBN (Apheresis for Focal Glomerulosclerosis in Pediatric Patients).
- Report Create Date: Between January 1, 2021 and December 31, 2021

MAUDE #1:

Mfr#: 9614654-2015-00015
Date Report Received: 06/24/2021:
MAUDE Adverse Event Category: Adverse Event Without Identified Device or Use Problem
Report: "The patient is a 6 year old boy who has been treated by the LDL-apheresis with Liposorber LA-15 system approved as a humanitarian use device (HUD) for his treatment of recurrent nephrotic syndrome associated with focal segmental glomerulosclerosis (FSGS) post renal transplantation. He has developed anemia and received exogenous erythropoietin but this was not optimally effective. After his 17th treatments with the LDL-apheresis, his anemic condition worsened into grade 3 anemia (his hemoglobin level fell below 7g/dl) and required a PRBC transfusion."

Lead Reviewer Comment: This event seems to be the same event reported in MDR #2 above, although the patient age in the MDR was 14 years while this report shows the patient age to be 6 years. If this is not the same patient as reported in the MDR, the basic conditions are the same. This patient was receiving a series of LDL-A treatments and developed worsening anemia. He had been previously diagnosed with anemia and was receiving Epo. The most likely cause of his anemia was chronic kidney disease (CKD), since patients with FSGS often develop CKD and are allowed in the PAS with a GFR of at least 60 ml/min (stage 3 CKD). The anemia may have been exacerbated by some blood loss as with any extracorporeal therapy, including LDL-A, treatments, and is a known AE associated with LDL-A, but that was not reported in this MDR. This is most likely an underlying disease-related AE, with a possible contribution from

treatments with the Liposorber device. This event raises no new concerns about the Liposorber device or therapy.

MAUDE #2:

Mfr#: 3002808904-2017-00005
Date Report Received: 04/08/2021:
MAUDE Adverse Event Category: Adverse Event Without Identified Device or Use Problem
Report: "A pediatric patient developed focal segmental glomerular sclerosis (FSGS) with steroid resistant nephrotic syndrome. A tunneled catheter for blood withdrawing was placed at right internal jugular vein on (b)(6) 2017 for commencing LDL-apheresis using the Liposorber LA-15 system. The LDL-apheresis up to 9th on (b)(6) was conducted without any problem in out-patient basis. Since the patient had fever on the next day of 9th LDL-apheresis, she was admitted to the hospital for further examination and medication. Her WBC was 34200/microliter and the result of the blood culture was Escherichia Coli positive, which was found to become negative after administration of antibiotics. The 12th LDL-apheresis, the final session, on (b)(6) was over without any problem. The attending physician was planning to discharge the patient after removing the catheter."

Lead Reviewer Comment: This event seems to be the same event reported in MDR #1 above. This patient was receiving a series of LDL-A treatments and developed a fever and infection, presumably (not stated in the report) due to a catheter-related bloodstream infection (CRBSI). CRBSI are not uncommon in patients with an indwelling catheter. This is a device-related adverse event (AE), but due to the catheter, not the Liposorber device. This event raises no concerns about the Liposorber device or therapy.

Lead Reviewer Summary: In summary, the two MDRs and two MAUDE reports do not raise any new safety concerns about the Liposorber device or LDL-A therapy.

VII. SUMMARY

FDA recommends:

1. Continued surveillance and will report the following to the PAC in 2023:
   - Annual distribution number
   - PAS follow-up results
   - Literature review
   - MDR review