FDA Executive Summary

Prepared for the

Spring 2020, Meeting of 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 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 familial hypercholesterolemia (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 focal segmental glomerulosclerosis (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.

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. Since each Liposorber LA-15 system treatment regmen includes 12 treatments/patient, the total ADN is 96,000.

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. 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 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.

Table 1 below provides the number of device components distributed by the firm for the calendar year 2019 in the United States.

Table 1. Annual Distribution Number-Calendar Year Jan-Dec 2019

Device	Total Sales
MA-03 Apheresis Machine	2
Liposorber® LA-15 LDL Adsorption Column (2 columns/shipment)	504
Sulflux® KP-05 Plasma Separator	552
NK-M3R (U) Tubing System for Plasmapheresis	570

*Each shipment of adsorption columns contains two columns. Therefore, 504 shipments would include 1008 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 two reports: The six year interim post-approval study report (H120005/R015), received at the FDA on September 12, 2019, and the six year annual report, received at the FDA on December 27, 2019. The sponsor reported that Institutional Review Board (IRB) approval had been obtained for seven clinical sites, and, seventeen subjects had been enrolled (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 (R001)	7/8/14	0	0	Study Pending	
12-month (R002)	10/2/14	0	0	Progress Adequate	
18-month (R004)	4/6/15	3	0	Progress Adequate	
24-month (R005)	10/1/15	3	4	Progress Adequate	
36-month (R007)	10/4/16	3	9	Progress Inadequate	• Worked with sponsor to revise study timeline • Provided recommendations for enrollment strategies
39-month (R008)	12/28/16	4	9	Progress Adequate	
48-month (R010)	10/13/17	6	14	Progress Inadequate	• Deficiency letter issued to request plan from sponsor for improving enrollment
60-month (R013)	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 (R015 and R016)	09/12/2019 and 12/25/2019	7	17	Progress Adequate	

Since the last report, there have been 3 new patients entered into the study:

1) One patient received full treatment course but then withdrew from study follow-up after treatments complete
2) One patient was undergoing treatment at the time of development of this document.
3) One patient received full treatment course but then withdrew from study after 1 month follow-up visit

The distribution of subjects' demographics is presented in Table 3 below.

Table 3. Demographics of Subjects (n=17)

	n	%
Age (years)		
6 - 8	5	29.4
9 - 11	3	17.6
12 - 14	7	41.2
15 - 17	0	0
18 - 20	2	11.8
Sex		
Male	8	47.1
Female	9	52.9
Race/ethnicity		
Caucasian	9	52.9
African American	4	23.5
Hispanic/Latino	2	14.3
Unknown	2	14.3

Source: Constructed based on data from H120005/R013 and R015

Follow-up is ongoing; its status per study visit is shown in Table 4 below. Of the 17 subjects enrolled in the study, there have been nine withdrawals before the final protocol visit, including two in the current reporting period. The reasons for withdrawal are listed in Table 5 below. Two subjects are in active follow-up. 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 one subject who withdrew and then underwent a second round of treatment.

Table 4. Subject Follow-up per Study Visit

Study Visit	Completed	Withdrawn	Active
~9 weeks Apheresis Procedures	12[a, b]	2	0
1-month	10[b]	4	0
3-month	7[b]	1	0
6-month	6[b]	1	0
12-month	5[b]	1	1
24-month	3	0	0

[a] One subject did not start treatment due to thyroid disease; [b] Including two protocol deviations;
Source: Constructed based on data from H7120005/R013 and R015

Table 5. Reasons for Withdrawal/Exclusion

Anonymized Subject	Status	Reason
A	Withdrew after 6M	Subject moved to another hospital and had further treatment off the study.
B	Withdrew after 3M	Subject relapsed and had another treatment series off the study.
C	Withdrew after final apheresis treatment	Subject dropped out and was lost to follow-up.
D	Exclusion (treatment not started)	Subject was revealed to have thyroid disease after enrollment (Medical Exclusion Criteria #8)
E	Withdrew after final apheresis treatment	Unknown
F	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.
G	Withdrew after 12M	Unknown
H	Exclusion (continuing active follow-up)	The reported Up/c of ACH004 at baseline was 0.08, which indicated that the patient achieved complete remission before treatment and was considered be inappropriate for treatment.
I	Withdrew after 1M (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.
J	Withdrew after 1M (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.
K	Withdrew after 1M	Unknown
L	Withdrew after 1 M	Unknown

Source: Constructed based on data from H120005/R013 and R015

Interim Results

Probable Benefit

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

At one month follow-up, three of eight subjects in whom Urine Protein/Creatinine Ratio (Up/c) data was available had achieved partial remission. Two subjects had missing Up/c data at one month and therefore remission status was uncertain; both of these patients had nephrotic syndrome 3 months after the final Liposorber LA-15 treatment. Four of seven patients who were followed for three or six months had complete or partial remission at the three or six month follow-up periods, while three other patients had no remission (nephrotic syndrome, or NS,

persisting). At 12-month follow-up, two patients had complete remission, one had partial remission, while two had persistent NS.

These outcomes and current status are shown in Table 6 below. Subjects C and D are not included in the table bacause they withdrew after the last treatment without follow-up labs (C) or were ineligible for inclusion (D). Subject F (baseline glomerular filtration rate 39.8 ml/min) and H (urine protein-to-creatinine ratio not consistent with nephrotic syndrome) are not included in the table because they did not meet study inclusion criteria and therefore are considered protocol deviations and excluded from the probable benefit results; however these subjects continued follow-up visits. Subject F met criteria for nephrotic syndrome at 1, 3, 6, and 12-month follow-up. Subject H met criteria for complete remission at 1, 3, 6, and 12-month follow-up.

Table 6. Remission Status Based on Urine Protein/Creatinine (Up/c) Ratio

Anonymized Subject	1-month	3-month	6-month	12-month	24-month	Status
A	Partial	Partial	Partial			Withdrew after 6 mo visit
B		NS				Withdrew after 3 mo visit
M	NS	Partial	Complete	Complete	Complete	Completed study
N	Partial	Complete	Partial	Complete	Complete	Completed study
G	NS	NS	NS	NS		Withdrew after 12 mo visit
I	NS					Withdrew after 1 mo visit
J	NS					Withdrew after 1 mo visit
O	Partial	Partial	Partial	Partial	Partial	Active
P	Not done	NS	NS	NS		Active
L	NS					Withdrawal

NS=Nephrotic Syndrome; [a] Gray shading indicates that data will not be collected (i.e., missing data or subject withdrew), and absence of shading indicates that data were or will be collected; [b] No subjects had reached 24 mo visit window.
Source: Constructed based on data from H120005/R015 and R016

Safety

Primary safety endpoint: device-related and procedure-related serious adverse events (SAEs): The most common or serious adverse events with the Liposorber LA-15 system are listed in Table 7 below:

Table 7. 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 six year report, seventy-six adverse events have been reported. Table 8 shows the most serious events that have been observed. The events include nausea/vomiting/diarrhea/abdominal pain/ache, fever/infection, upper respiratory symptoms, headache, lightheadedness/fainting, hypotension, anemia, malaise, and weakness. The sponsor posits and the agency agrees that these events are most likely related to the patients' underlying conditions and/or the requirement for a central venous catheter for vascular access.

Table 8. Summary Table of Major Adverse Events

Adverse Event Type	Number of Events	Relationship to Device
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	9	None
Fever/Infection	16	2 (Possible)
Upper Respiratory (Congestion/Pharyngitis)	8	None
Headache	7	None
Lightheadedness/Dizziness	3	None
Malaise	3	None
Hypotension	2	None
Leg cramps	2	None
Allergic reaction (mild)	2	None
Pancreatitis	2	None
Hyponatremia	1	None
Dehydration	1	None
Worsening of Nephrotic Syndrome	1	None
Pneumonia	1	None
Bacteremia	1	None
Anemia	1	None

Source: Based on data from H120005/R013 and R015

Secondary probable benefit endpoint: laboratory values, including eGFR. Laboratory values including estimated glomerular filtration rate (eGFR) by study visit are shown in Table 9 below. The table shows that among the ten subjects who completed full device treatment and had at least one post-treatment visit with laboratory results, eGFR was stable or increased in all but one subject. All but two subjects displayed either stabilization or decline of urine protein (assessed by urine protein-to-creatinine ratio). The evidence for these subjects shows a trend towards stabilization or improvement of laboratory indices.

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

Table 9. Trends in Laboratory Values

Anonymized Subject	Baseline eGFR	Last eGFR	Trend in eGFR	Baseline U p/c	Last U p/c	Trend in U p/c
A	62	84	Increase	44	18	Decrease
B	89	79	Stable	8	6	Stable
M	85	100	Increase	6	0.4	Decrease
N	171	132	Stable	2	0.2	Decrease
G	60	34	Decrease	2	4	Increase
I	85	130	Increase	5	4	Stable
J	153	161	Stable	4	5	Stable
O	78	72	Stable	1	0.3	Decrease
P	60	191	Increase	5	3	Decrease
L	216	131	Stable	28	38	Increase

Source: Constructed from Table 2 of H120005/R013 and R015 and Table 2 of H120005/R010/A001

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 probable benefit, at the one month follow-up period, three of seven subjects (43%) had achieved partial 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 (9/10; 90%) of patients, albeit a brief follow-up period for 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 two 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

The sponsor did not include a literature review for this reporting period. FDA conducted a literature search on January 13, 2020 including all publications between January 1 to December 31, 2019 in PubMed and Embase without any additional filters. The following search terms were used: Kaneka, Liposorber, Drug-resistant Pediatric Primary Focal Segmental Glomerulosclerosis, and LDL-Apheresis as search terms. After reading the titles, abstracts, and full-texts, three pertinent articles were found. A summary of the articles is included below.

Krishnappa et al (2019) Liposorber LA-15 System for LDL Apheresis in drug resistant primary focal segmental glomerulosclerosis patients: interim results from a prospective, multicenter, single-arm intervention study (SUN-034) Kidney International Reports 2019 4:7 Supplement (S166-S167).

The objective of this prospective, multicenter, single-arm intervention study was to examine the safety and probable benefit at 1, 3, 6, 12 and 24 months following completion of apheresis treatment using Liposorber LA-15 system in patients with NS due to refractory primary FSGS, or primary FSGS associated NS in post renal transplant children. Children with drug resistant or drug intolerant NS secondary to primary FSGS with glomerular filtration rate (GFR) 60 ml/min/1.73m^2 or post renal transplant children with recurrent FSGS associated NS were included in the study. Each patient will have a total of 12 apheresis sessions over a period of 9 weeks. As of October 2017, 14 patients from 6 sites have been enrolled into the study. A total of 11 patients completed 12 apheresis treatments over a period of 9 weeks. At one-month follow-up, 1 of 4 patients (25%) attained partial remission of NS. Furthermore, 2 of 3 subjects (33.3%) and 2 of 2 subjects (100%) had partial/complete remission at 3- and 6-months follow-up respectively. Only one patient who was followed up for 12 months had complete remission of NS. These interim results did not include any safety data.

Raina et al (2019) Dextran-Sulfate Plasma Adsorption Lipoprotein Apheresis in Drug Resistant Primary Focal Segmental Glomerulosclerosis Patients: Results from a Prospective, Multicenter, Single-Arm Intervention Study. Front. Pediatr., 03 December 2019
https://doi.org/10.3389/fped.2019.00454

This is a prospective, multicenter, single-arm intervention study including Liposorber® LA-15 system in children (≤21 years old) with drug resistant or drug intolerant NS secondary to primary FSGS with glomerular filtration rate (GFR) ≥60 ml/min/1.73 m^2 or post renal transplant children with primary FSGS associated NS. The objective is to examine the safety and probable benefit at 1, 3, 6, 12, and 24-months following completion of apheresis treatment using Liposorber® LA-15 system. Each patient had 12 dextran-sulfate plasma adsorption lipoprotein apheresis sessions over a period of 9 weeks. Of 17 patients enrolled, six were excluded from the outcome analysis (protocol deviations). Of the remaining 11 patients, all but one completed apheresis treatments. Three patients were lost to follow-up immediately after completion of apheresis and excluded from outcome analysis. At one-month follow-up, 1 of 7 patients (14.3%) attained partial remission of NS while 2 of 4 subjects (50%) and 2 of 3 subjects (66.7%) had partial/complete remission at 3- and 6-months follow-up, respectively. One of two patients followed up for 12 months had complete remission and one patient had partial remission of NS after 24months. Improved or stable eGFR was noted in all patients over the follow-up period. Reported side effects were nausea, vomiting, diarrhea, abdominal pain, fever/infection, pharyngitis, headache, lightheadedness, malaise, hypotension, leg cramps, allergic reaction, pneumonia, bacteremia, and anemia. However, the frequency and severity of these adverse events is not reported. The small sample size, protocol deviations and high dropout rate are important limitations of this study.

Shah et al: LDL-apheresis-induced remission of focal segmental glomerulosclerosis recurrence in pediatric renal transplant recipients. Pediatr Nephrol 34:2343-2350, 2019 doi: 10.1007/s00467-019-04296-6.

This retrospective case-series study described Liposorber LA-15 therapy applied to 7 selected patients in four centers in the USA and the UK using a common protocol that included LDL-apheresis (LDL-A) in combination with various immunomodulatory drugs (corticosteroids, Rituximab, Calcineurin inhibitors, Mycophenolate mofetil) to treat recurrent FSGS that presented as nephrotic-range proteinuria and occurred immediately after transplantation in seven patients. Patients received a minimum of 9 weeks of therapy of Liposorber LA-15 therapy. Liposorber LA-15 and immunomodulatory therapy resulted in at least a ten-fold reduction in urinary protein-to-creatinine ratios consistent with partial or complete remission. All patients but one demonstrated improvement in their renal function at last follow-up (4-25 months) after Liposorber LA-15 discontinuation. No safety results are reported. According to the authors: the "Limitations of this case-series include the small number of patients, the relatively short duration of observation following LDL-A, and the inability to standardize the timing of LDL-A across patients. The cases in this retrospective review included the most refractory patients who showed no improvement with more conventional treatment. The authors admit to the inherent positive reporting bias given the retrospective nature of this paper."

Summary of the Literature Review

The three articles found in this search show efficacy results that are consistent with prior information provided by the sponsor in annual reports for the intended use popualtions. However, important limitations were found in this literature review as follows:

1. The three publications include small number of study patients. The total number of patients treated and evaluated in the three articles is 24 after excluding those lost to follow-up. Additionally, it is not clear if the Krishnappa et al and Raina et al publications are related to the same study and same patients at two different points in time, thus reducing the number of patients under study to 18. The publication by Shah et al is a retrospective case-series including 7 patients in which the authors "admit to the inherent positive reporting bias given the retrospective nature of this paper."

2. Krishnappa et al publication was an abstract from a meeting and does not include safety data.

3. Raina et al publication does not provide the frequency or severity of the reported adverse events.

4. Shah et al publication does not report safety data.

Conclusions from the Literature Review

Although the efficacy findings in the publications are consistent with that provided in the annual reports, there are important limitations in the articles found, including a small number of patients

(as is true for the post-approval study), the absence of any safety data in two of the three articles, and incomplete safety data in the only article which included safety.

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 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

The MDR Database was searched on January 2, 2020 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, 2019 and December 31, 2019.

The search resulted in three (3) MDRs (3002808904-2018-00023, 3002808904-2019-00005, and 3002808904-2019-00009) for the Liposorber® LA-15 system. One MDR involves a pediatric patient. The other two MDRs involve adult patients. The three MDRs were serious injury events. The pediatric event occurred within the US, while the other two events occurred in Japan and Italy. Summary level information is provided below.

MDR #1: 3002808904-2018-00023:
An 88-year-old male from Japan sustained a hypotensive event fifteen minutes after the start of treatment with the Liposorber device system. The patient became unconscious for several seconds, treatment was discontinued, and the patient recovered with 400 ml of saline infusion. The report stated that the patient was administered an angiotensin converting enzyme inhibitor (ACEi; Perindopril) three days prior to receiving treatment on the Liposorber® LA-15 system.

While it is possible that the ACEi therapy three days prior to Liposorber LA-15 therapy may have precipitated and/or exacerbated the hypotension, ACEi therapy in patients receiving Liposorber LA-15 therapy is a known contributor to bradykinin-release syndrome, which can present as hypotension. Patients are instructed to discontinue ACEi therapy within 24 hours of Liposorber LA-15 therapy. While this event occurred in a patient who had received the ACEi about 72 hours prior to Liposorber LA-15 therapy, it is possible that other factors (age, cardiac function) may have contributed to the reduction in blood pressure.

The agency will discuss this event with the sponsor, specifically regarding the occurrence of apparent bradykinin release syndrome in a patient who received an ACEi more than 24 hours prior to the Liposorber LA-15 treatment. At this time, we believe that no labeling change is required as bradykinin release syndrome and hypotension are known side effects of Liposorber LA-15 therapy.

MDR #2: 3002808904-2019-00005:
A 15-year-old boy with recurrent focal segmental glomerulosclerosis (FSGS) that occurred after renal transplant was receiving plasmapheresis until the day of the event. The patient's estimated glomerular filtration rate (eGFR) was <60 and he was receiving ACEi (Enalapril). One of the catheter ports, per his mother, was not working well. Only one of the ports was used for the plasmapheresis. Vital signs were stable at start of the treatment. Sixteen minutes into treatment the patient complained of chest pain, thrashed in the bed with lips cyanotic despite pulse oximetry of 100%. Oxygen was applied and 100 ml of normal saline was rapidly infused. A code was called, during which the patient received intravenous Solumedrol. Within five minutes, the patient improved and was transferred to the emergency department. There, he became stable after 30-40 minutes.

The events were most likely caused by bradykinin-release syndrome caused by an interaction between the ACEi and the LA-15 column. The current label requires withholding ACEi use within 24 hours of Liposorber LA-15 device therapy. While this period is usually adequate to reduce the likelihood of bradykinin-release and hypotension, the medication half-life in this patient may have been longer due to reduced (eGFR <60 ml/min) renal function.

The agency will discuss this event with the sponsor, specifically regarding the occurrence of apparent bradykinin release syndrome in a patient who received an ACEi more than 24 hours prior to the Liposorber LA-15 treatment. At this time, we believe that no labeling change is required as bradykinin release syndrome and hypotension are known side effects of Liposorber LA-15 therapy.

MDR #3: 3002808904-2019-00009:
A 62-year-old male from Italy had hyper-Lp(a) and polygenic hypercholesterolemia, requiring treatment with the Liposorber LA-15 system every other week for 5 months. The treatments had proceeded without any problems. One month prior to the next LA-15 treatment, the patient developed an episode of TakoTsubo cardiomyopathy. This was reported by Dal Pino et al ("Recent takotsubo syndrome and lipoprotein apheresis: an alert for a safe procedure. Eur J Prevent Cardiol, 2019). The TakoTsubo syndrome was apparently triggered by a sexual act, with mid-to-apical hypokinesia in the anterior septum and anterior wall. Thereafter, Bisoprolol, 1.25 mg once a day, was started. One month after the TakoTsubo episode, the patient developed systemic malaise, characterized by sweating and presyncope while receiving LA-15 therapy. The patient immediately received 600 ml plasma volume and an intravenous bolus of 500 mg methylprednisolone. His blood pressure, which was normal before the start of LA-15 therapy, was low and poorly responsive to administration of fluids. His symptoms were severe as to require the discontinuation of the Liposorber LA-15 therapy. Two months after the episode, echocardiography showed the resolution of hypercontractility and of the left ventricular outflow tract obstruction. Therefore, LA therapy was started again without problems, but, with the precaution of limiting the blood flow to 65 ml/min and administering a bolus of physiological solution (150-200 ml) at the beginning of treatment to reduce the risk of hypovolemia.

The symptoms of systemic malaise, characterized by sweating and presyncope, while receiving LA therapy were most likely related to the development of severe hypotension during apheresis. This episode was very likely related to the patient's history of TakoTsubo cardiomyopathy one month earlier. It is likely that the patient's TakoTsubo cardiomyopathy had not fully resolved when his apheresis was first resumed. The apheresis was thus resumed too soon.

The agency will request the complete published case report for this patient, which could not be accessed. The main information that is required is whether an echocardiogram was done just before the apheresis was resumed and, if so, what the echocardiogram showed with regard to the status of the patient's cardiomyopathy.

Since TakoTsubo cardiomyopathy is a rare condition, it is very unlikely that other patients undergoing apheresis (with the Kaneka device or any other brand device) would likely develop hypotension due to TakoTsubo cardiomyopathy.

The review team believes that restricting Liposorber LA-15 therapy to patients with cardiac disease associated with low left ventricular ejection fraction, heart failure, reduced ejection fraction and certain cardiomyopathies would unnecessarily result in reducing the availability of a vital therapeutic option for patients with severe hypercholesterolemia and high risk for cardiac disease and death. Therefore, the review team does not believe that a labeling change regarding this event is required since hypotension is a known risk associated with Liposorber LA-15 therapy. However, the team will discuss this event with the Kaneka team.

VII. SUMMARY

FDA recommends:

1. Continued surveillance and will report the following to the PAC in 2021:
   - Annual distribution number
   - PAS follow-up results
   - Literature review
   - MDR review

2. Discussion with the sponsor about the occurrences of two adverse events:
   a. Hypotension in patients while receiving Liposorber LA-15 therapy after receiving ACEi therapy more than 24 hours before the device treatment;
   b. Hypotension and syncope during Liposorber LA-15 therapy in a patient who had developed cardiomyopathy at least one month prior to the Liposorber treatment

   The review team does not believe that a labeling change regarding these events is necessarily required since hypotension is a known risk associated with Liposorber LA-15 therapy. However, the team will collaborate with Kaneka's team about these events.