Liposorber® LA-15 System
Humanitarian Device Exemption (HDE) H120005

Pediatric Advisory Committee
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Renal Devices Branch

Office of Device Evaluation

Indications for Use for Pediatric HDE

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

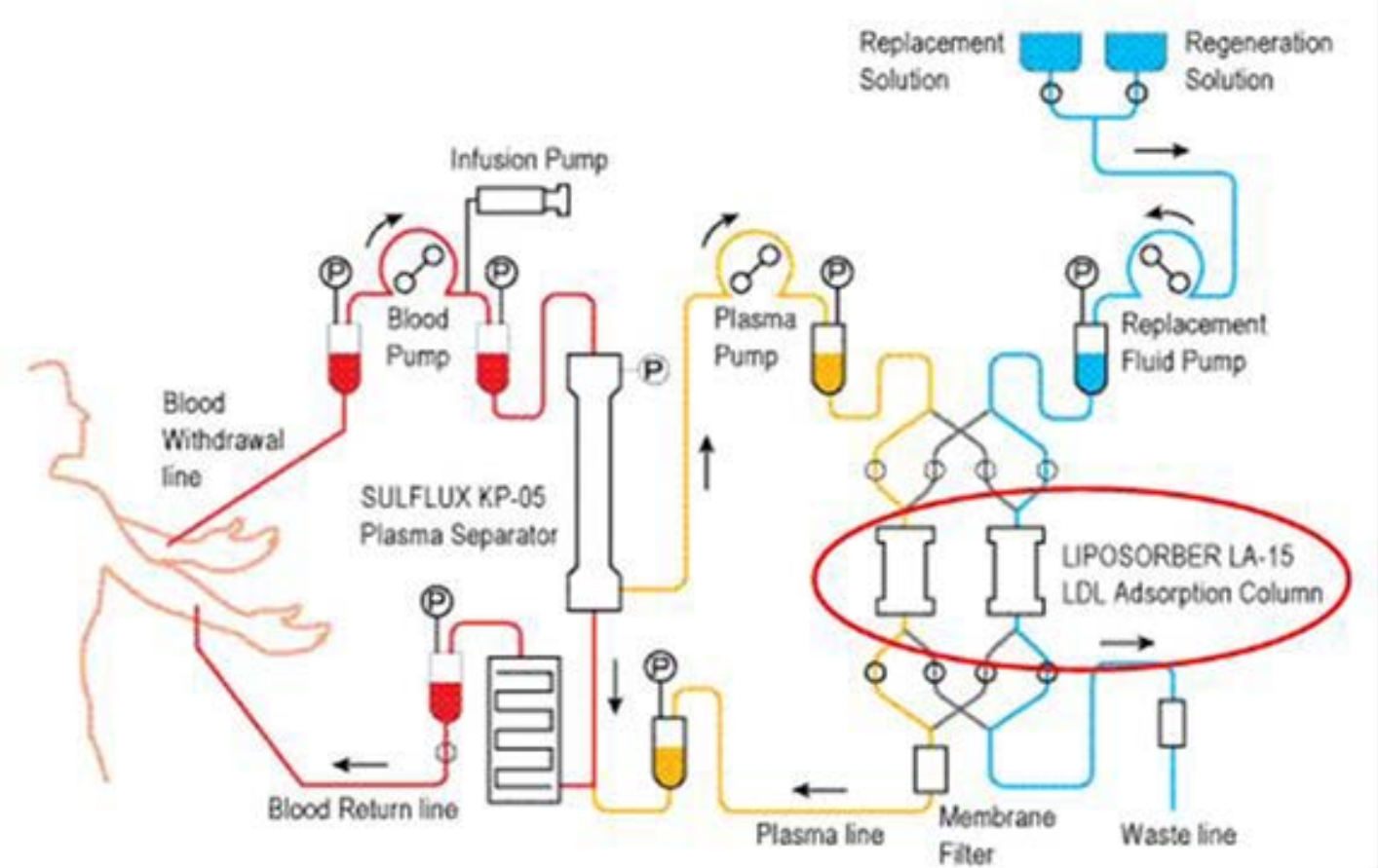
- **Standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated and the patient has a GFR ≥ 60 ml/min/1.73m^2 or**
- **The patient is post renal transplantation**

GFR=Glomerular Filtration Rate, a measure of kidney function

Background

- **FSGS is a kidney disease resulting in severe proteinuria and usually, nephrotic syndrome (NS). The majority of patients reach end-stage (dialysis-dependent) renal failure within 10 years of initial diagnosis.**
- **Previous reports show probable benefit and safety for adults and children with FSGS treated with the Liposorber LA-15 system.**
- **The HDE for Liposorber therapy for FSGS in children was approved in 2014.**
- **This is an annual update of the post-approval study.**

Device Description



Post-Market Study

Objectives	• Safety: Adverse events during and 1 month after final Liposorber treatment
	• Probable benefit:
	  • Achievement of complete or partial remission of NS 1 month after final Liposorber treatment
	  • GFR

Criteria	• Age: ≤ 21 years (all ages approved with FH) • Body weight: ≥ 18 kg at baseline • FSGS and persistent NS • Resistant to or intolerant of medical therapy • Reasonably good (GFR ≥ 60 ml/min/1.73m^2) renal function

Treatment Schedule	• 12 uses in 9 weeks of therapy
	  • Twice weekly for 3 weeks
	  • Weekly for 6 weeks

Collected Information	• 32 patients allowed in PAS: 8 Treated • Adverse events • Device malfunction • Degree of proteinuria (after final therapy) • Renal function (after final therapy)

Interim Results-Probable Benefit

8 patients treated
6 Patients with 3-6 Month Follow-Up Data

Remission Status	I Month After Final Treatment	3 Months After Final Treatment	6 Months After Final Treatment
Complete	*0*	*1*	*1*
Partial	*2*	*2*	*2*
None	3	3	3
Uncertain	1	Not Available	Not Available

*** Table adapted from that provided by the sponsor**

Definitions:

Complete Remission: Urine protein:creatinine ratio (Up/c) < 0.2 (g/g) on first morning urine sample.

Partial Remission: ≥ 50% reduction in Up/c compared to the value at screening or Up/c between 0.2 and 2.0 (g/g) with first morning urine sample.

Interim Results-Probable Benefit

Patient	Baseline eGFR	3 or 6 Month eGFR	Baseline Up/c	3 or 6 Month Up/c	Baseline LDL-C (mg/dL)	3 or 6 Month LDL-C (mg/dL)	Baseline suPAR (ng/mL)	3 or 6 Month suPAR (ng/mL)
1	62.2	83.9	44.3	17.5	60	498	290	782.5
2	89.4	78.7	8.1	6.3	212	189	226	722
3	84.9	98.3	6.3	0.2	345	78	297	544
4	39.8	30.2	1.1	3.5	165	194	302	1048
5	170.7	130.1	1.9	0.4	126	115	452	412
6	60.0	60.9	1.8	2.1	96	86	854	Not Done

- **Table adapted from that provided by the sponsor**
- **eGFR (ml/min/1.73m2) stable or improved in all 6 patients**
- **Values in red font show clinically significant decline in U p/c**

Safety: Children with FH Treated with the Liposorber LA-15 System

Potential Adverse Event As Per PMA	Prevalence Rate in FH 36 children; >1000 treatments
Death	Not reported to occur
Cardiac (arrhythmia, bradycardia, tachycardia, MI)	Not reported to occur
Thrombocytopenia	Not reported to occur
Infection	Occurred in 2 of 20 patients
Hypersensitivity	Not reported to occur
Nausea and vomiting	0.3-2.5% of treatments
Low Vitamin E level	Not reported to occur
Temporary decrease in blood protein level	Not reported to occur
Hypotension	2.0-2.5% of treatments
Flushing/blotching of skin	Not reported to occur
Angina	0.2-0.3% of treatments
Fainting/lightheadedness	Not reported to occur
Anemia	Not reported to occur
Prolonged bleeding at intravenous or catheter site	Not reported to occur
Hemolysis	Not reported to occur
System	Not reported to occur
Vertigo	0-0.3% of treatments
Diaphoresis	Not reported to occur
Urticaria	Not reported to occur
Shivering	0-0.3% of treatments
Headache	0-0.5% of treatments

Stefanutti et al, Transf Apheresis Sci, 2004; Hudgins et al, Amer J Cardiol, 2008

8

Interim Results-Safety

Occurrence During 9 Week Treatment Period	Description of AE/SAE	Severity	Require hospitalization	Relationship to Liposorber device
Yes	Fever/Diarrhea/ Abdominal Pain/Vomiting	Moderate	Yes	Not related
Yes	Fever/Possible Infection/Viral Illness	Moderate	No	Not related

- Table adapted from that provided by the sponsor to delete patient identifiers
- These events were determined to be not reportable by the manufacturer
- The FDA deemed that adverse events were related to the patients' underlying disease or use of a catheter and not the Liposorber device

Systematic Literature Review Update

- Search Strategy:
  - Liposorber OR (LDL AND apheresis)
  - Date range: January 31, 2016 – December 5, 2016
- Results:
  - 109 articles were found. Reasons for exclusion:
    - Non-clinical study (n=47)
    - No use of Liposorber LA-15 (n=42)
    - No pediatric patients (n=19)
    - Indication other than FSGS (n=1)
- No new information regarding probable benefit or safety for pediatric patients with FSGS

Medical Device Report Review

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Medical Device Report (MDR) Database MDR Search Criteria:

Product Codes:

MMY (Lipoprotein, Low Density, Removal)

PBN (Apheresis for Focal Glomerulosclerosis in Pediatric Patients),

Date Report Entered:

January 1 through December 31, 2016

Search Results: 6 total MDRs

1 pediatric

(14 years old)

5 adults

(age range 50 to 82 years)

***All 6 events reported by device manufacturers**

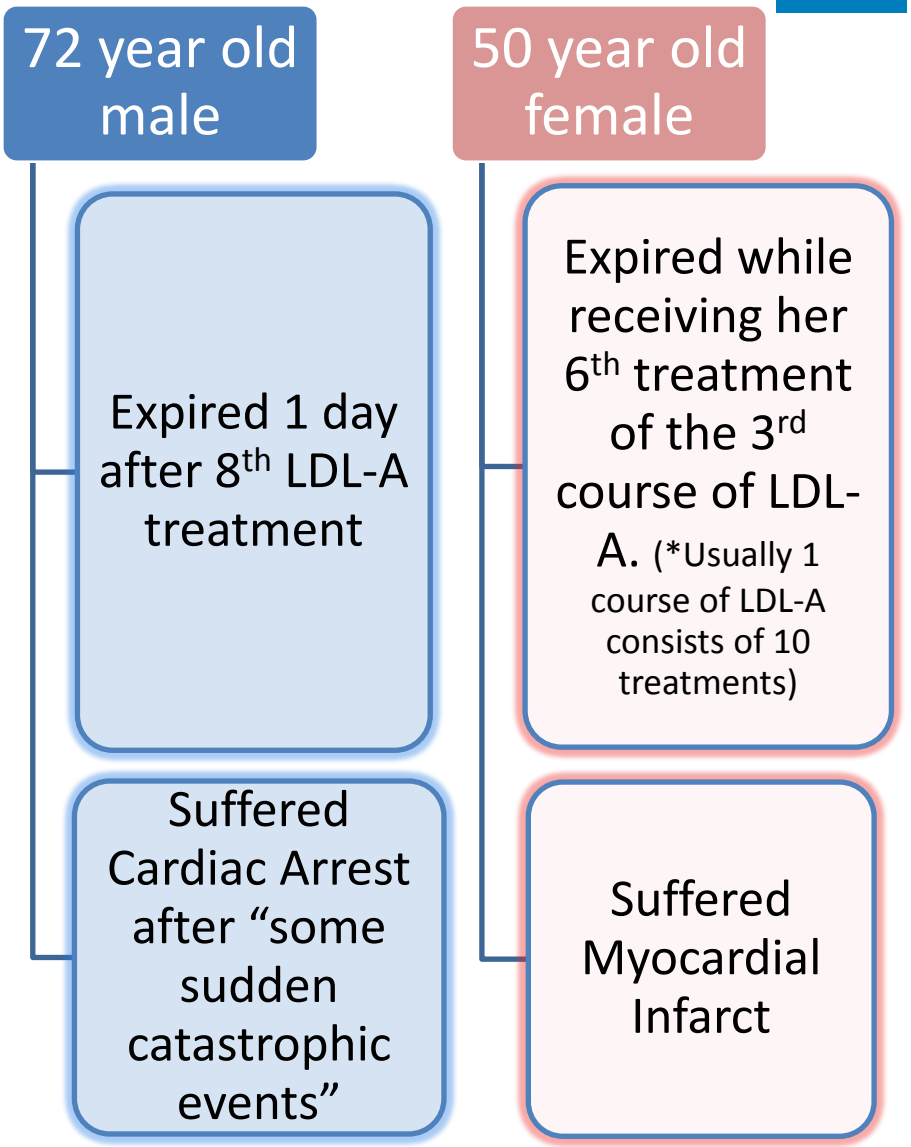
Reported Adverse Events

Pediatric Report –Serious Injury

- 14 year old male
- recurrent nephrotic syndrome associated with FSGS after renal transplantation
- Developed Grade 3 anemia after his 17th Liposorber treatment
- Labeling addresses the possibility of anemia with LDL-Apheresis (LDL-A) procedures and the manufacturer narrative of this report cites this could be secondary to:
  - "cumulative blood loss by the residual blood in the extracorporeal circuit" and
  - "blood sampling for chemistry" in each LDL-A procedure

Reported Adverse Events

- 2 Adult Reports- **Death**
- Suffered from a cardiac arrest and myocardial infarct respectively
- No clearly stated device causality in either report
  - the manufacturer notes in the report of Myocardial Infarct that the LDL-A treatment may have been relevant to the patient's sudden change.



Reported Adverse Events

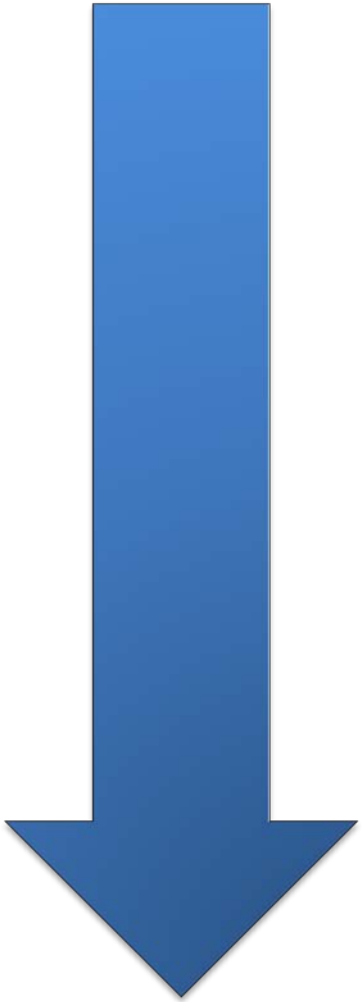
- 3 Adult Reports-**Serious Injury**
  - All events involved the patient experiencing severe hypotension, with either loss of consciousness (n=1) or shock (n=2).
  - LDL-A was discontinued and patient recovered with treatment (i.e. oxygen, saline, adrenaline) in all events
  - No clearly stated device causality

82 y.o. female	82 y.o. male	Unidentified patient
• Hypotension post 1st LDL-A treatment & loss of consciousness • No clearly stated device causality	• Hypotension & shock 30 minutes post LDL-A treatment • LDL-A treatment followed a HD treatment on the same day • Manufacturer suggests "the event was due to the patient's intolerance to the combination procedure"	• Hypotension & shock 15 minutes post LDL-A treatment • Patient was prescribed a ACE inhibitor at another hospital

Conclusions from MDR Review

- In 2016, a total of six (6) MDRs significant adverse events were received. (2 Death, 4 Serious Injury)
- There was no mention of specific device-related issues, however manufacturer investigations could not completely exclude the relevance of LDL-A treatment to the outcomes.
- Known inherent risks with the use of this device (i.e. anemia, shock, hypotension, and dyspnea), are addressed in the IFU's for this device.
- Concomitant medications (i.e. angiotensin-converting enzyme (ACE) inhibitors, anti-hypertensive drugs and the use of an anticoagulants) need to taken into consideration by physicians prescribing LDL-A treatment.

Considerations from MDR Review



Items that May Benefit from Modified Labeling:

- The increased potential for the development anemia during **repetitive LDL-A treatments** secondary to:
  - cumulative blood loss by the residual blood in the extracorporeal circuit and
  - blood sampling for chemistry in every LDL-A procedure.
- **Combination treatment of HD and LDL-A** on the same day could increase the risk of hypovolemia due to:
  - the extracorporeal volume of the LDL-A system being larger than that of the HD system and
  - the patient already losing a certain amount of circulating blood volume.

CDRH Recommendations

- CDRH believes that the device labeling could potentially be enhanced related to issues of:
    - Causes of anemia with multiple LDL-A treatments
    - Risk for hypovolemia and hemodynamic changes in patients who receive LDL-A therapy and another extracorporeal therapy (e.g., HD) on the same day

  CDRH will discuss these issues with the sponsor

- Continue surveillance and report of the following to the PAC in 2018:
    - The outcome of the labeling review and discussions (including any labeling revisions)
    - Distribution numbers
    - MDR review results
    - Literature review results

Question to the PAC

- Does the Committee agree with CDRH's conclusions and recommendation?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Annual Distribution

Total Sales: Calendar Year

(Jan-Dec, 2016)

(1) MA-03 Apheresis Machine: 3 machines

(2) Disposables:

a) **LIPOSORBER® LA-15 LDL Adsorption Column: 270 pcs**

b) **Sulflux® KP-05 Plasma Separator: 264 pcs**

c) **NK-M3R (U) Tubing System for Plasmapheresis: 264 sets**

FDA Conclusions

- **As of January, 2017, eight pediatric patients have received a full course (9 weeks, 12 treatments) of therapy for FSGS with the Liposorber® LA-15 system.**
- **Of the 8 patients that finished a complete course of therapy, 6 have 3-6 month follow-up data:**
  - **3 exhibited either a compete or partial remission, with reduction in urine protein/creatinine**
  - **All showed stabilization or improvement in GFR**
- **While some adverse events were not insignificant, none were thought to be device-related, but rather consistent with that observed in the underlying disease or with associated devices (catheter).**

FDA Recommendations and Panel Question

- **FDA concludes that the benefit-risk profile to date supports continuation of the PAS and recommends continued surveillance. FDA will report the following to the PAC in 2018:**
  - **Annual distribution number**
  - **PAS follow-up results**
  - **Literature review**
  - **MDR review**

- ***Question:*** **Does the Committee agree with FDA's conclusions and recommendations?**


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