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

Pediatric Advisory Committee
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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

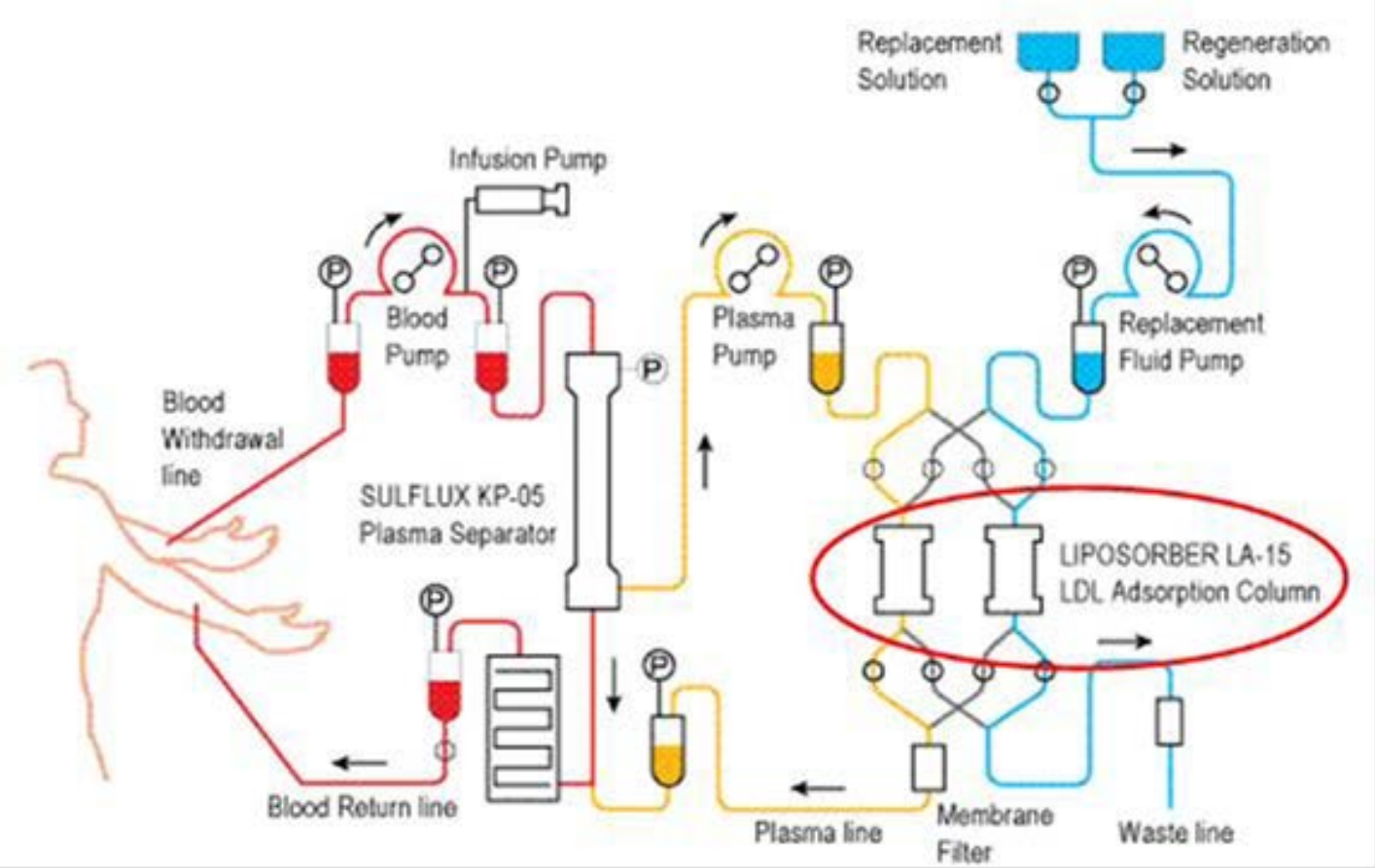
- **Standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated and the patient has a GFR ≥ 60 ml/min/1.73m^2 or**
- **The patient is post renal transplantation**

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 who were resistant to, or intolerant of, standard medical therapy.**
- **The HDE for Liposorber therapy for FSGS in children was approved in 2014.**
- **The sponsor is conducting a PAS to assess the probable benefit and safety of the device in children with NS and FSGS either before or after renal transplantation.**
- **The PAC was presented with a summary of the HDE in March, 2015. This is an annual update of the PAS.**

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 • Body weight: ≥ 21 kg at baseline (recently changed to ≥ 18 kg) • 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: 4 Treated • Adverse events • Device malfunction • Degree of proteinuria (after final therapy) • Renal function (after final therapy)

Interim Results-Probable Benefit

Treatment Dates		Urine Protein/Creatinine				Estimated Glomerular Filtration rate (Renal Function)			
Start	*End*	*BL*	*0*	*1*	*3*	*BL*	*0*	*1*	*3*
4/3/15	6/1/15	44.3	13.0	17.4	12.8	62.2	125.4	83.6	83.0
6/4/15	7/29/15	8.1	3.8	ND	6.3	104.3	91.0	89.7	78.7
8/5/15	9/30/15	6.3	ND	3.3	0.9	84.9	172.2	112.9	114.3
8/17/15	10/14/15	5.1	NA	NA	NA	95.8	NA	NA	NA

- Table adapted from that provided by the sponsor to delete patient identifiers
- BL-Baseline (pre-treatment)
- 0, 1, 3: Months after final treatment

Interim Results-Safety

Date of Occurrence	Description of AE/SAE	Severity	Require hospitalization	Relationship to Liposorber device
4/6/16	Leg cramps	Mild	No	Not related
4/7/15	Bacteremia	Mild	Yes	Not related
4/26/15	Diarrhea	Mild	No	Not related
5/6/15	L mandibular pain; r/o infection	Mild	Yes	Not related
6/4/15	L hip cellulitis	Moderate	Yes	Not related

- Table adapted from that provided by the sponsor to delete patient identifiers
- These adverse events all occurred in the same patient
- 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

Literature Review

1) **Two case reports (*Iwazu et al, Ther Apher Dial, 2015 and Araki et al, Intern Med, 2015):***
   - **Described two adult patients with confirmed or suspected FSGS treated with the Liposorber LA-15 system**
   - **Both patients demonstrated clinical improvement**
   - **Safety data was missing or minimal**

2) ***Muso et al, Nephron Extra, 5:58-66, 2015***
   - **Prospective study of 58 adult patients with refractory NS**
   - **Among 44 followed for 2 yrs:**
   - **Remission:**
     - **Complete remission-25%**
     - **Incomplete remission-47%**
     - **No remission-27%**
   - **Minimal safety data**

Medical Device Reporting (MDR)

- A search of the MDR database resulted in 2 MDRs for the analysis time period of November 1, 2014 to December 31, 2015
- There were **no MDRs for pediatric patients**
- The 2 MDRs (Death and Serious injury events) were submitted under the MMY product code that includes the Liposorber for adult patients who **were not** undergoing apheresis for focal glomerulosclerosis

Reported Adverse Events

Death Report

- 59 year-old female
- Multiple co-morbidities
- Death occurred after 6th apheresis procedure
- No clearly stated device causality

Serious Injury Report

- 83 year-old male
- Multiple co-morbidities
- Two adverse events during two treatments occurred, one resulting in hospitalization
- Manufacturer stated the events were related to concomitant medications

Annual Distribution

Total Sales: Calendar Year
(Jan-Dec, 2015)

(1) MA-03 Apheresis Machine: 3 machines

(2) Disposables:

a) **LIPOSORBER® LA-15 LDL Adsorption Column: 114 pcs**

b) **Sulflux® KP-05 Plasma Separator: 114 pcs**

c) **NK-M3R (U) Tubing System for Plasmapheresis: 114 sets**

FDA Conclusions

- **As of January, 2016, four pediatric patients have received therapy for FSGS with the Liposorber® LA-15 system.**
- **Of the three patients that finished a complete course of therapy, all exhibited reduction in urine protein/creatinine, while showing 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 2017:**
  - **Annual distribution number**
  - **PAS follow-up results**
  - **Literature review**
  - **MDR review**

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