Liposorber® LA-15 System

Humanitarian Device Exemption (HDE)  
H120005

Pediatric Advisory Committee  
March 24, 2015
Presentation Outline

Device Description, Regulatory History:
  Véronique Li
Pre-Market Clinical Data:
  Doug Silverstein, MD
Literature Review:
  Allison O’Neill, MA
Medical Device Reporting (MDR):
  Cynthia Bushee, RN, BSN
Device Description, Regulatory History

Véronique Li
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Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation
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.
The Liposorber® LA-15 System is an integrated extracorporeal blood processing system that contains the following components:

- Liposorber® LA-15 Adsorption Columns
- Sulflux® KP-05 Plasma Separator
- NK-M3R Tubing Set
- MA-03 Machine
Regulatory History

• February 21, 1996: PMA Approval for Familial Hypercholesterolemia (FH)
• September 4, 2012: Filing Date
• September 28, 2012: HUD Designation
• October 10, 2013: HDE Approval for Focal Segmental Glomerulosclerosis (FSGS)
Annual Distribution Number (ADN)

HDE: H120005 – Focal Segmental Glomerulosclerosis (FSGS)

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Outside of the US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columns</td>
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<td>0</td>
</tr>
<tr>
<td>Tubing Set</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Plasma Separator</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Machine</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Pre-Market Clinical Data

Doug Silverstein, MD
Medical Officer
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Office of Device Evaluation
FSGS: Background

• FSGS describes the histology on renal biopsy that may result from a variety of insults to the kidney.

• FSGS results in severe proteinuria and often, nephrotic syndrome (NS), featuring proteinuria and low serum albumin. Over time, kidney function declines.

• The majority of patients reach end-stage (dialysis-dependent) renal failure within 10 years of initial diagnosis.
Treatment of Pediatric FSGS

- **Corticosteroids:**
  - Mainstay of therapy for NS and most patients with FSGS
  - Response rate is about 20%
- **Calcineurin inhibitors** (Cyclosporine/Tacrolimus):
  - RCT: 27 children treated with high-dose CyA: Significantly higher remission rates and protein reduction with CyA
  - Many developed resistance and had severe side effects
- **Alkylating agents** (cyclophosphamide): limited data
- **Mycophenolate mofetil**: Best as adjunctive therapy
- **Plasmapheresis**:
  - Pre-transplant: very limited data with low (15-50%) response rate
  - Post-transplant: several small studies-response rates vary (40-80%)
Evidence for Probable Benefit: Liposorber LA-15 Treatment for Pre-Transplant Pediatric FSGS

Methods:
• Prospective study in 11 children with NS/medication-resistant FSGS
• Total number of LDL apheresis treatments: 132 (12/patient); 2X/wk for 3 wks, then 1X/wk for 6 wks
• Tapered prednisone

Results:
• 7/11 patients achieved remission of NS (5 complete; 2 partial) within 4 wks
• Among 5 with complete remission, renal function was normal during follow-up (median, 4.4 years).
• Among 2 with partial remission, 1 maintained stable renal function while other reached ESRD by 7.8 years

Liposorber Therapy for Pediatric Pre-Transplant FSGS

Evidence for Probable Benefit: Liposorber LA-15 Treatment for Post-Transplant FSGS/NS

Methods:
• Retrospective survey
• 5 years of data from 41 adults: 34 pre-tx and 7 post-tx (3-12 treatments/patient)
• Outcome indicators: serum total protein and albumin, degree of proteinuria 1 month after treatment, and achievement of long-term (2 years) remission of NS

Results:
• 1 month after LDL apheresis, serum total protein and albumin increased significantly and proteinuria was significantly decreased
• Remission of NS was observed in 62% of patients at 2 years
• Data for the 7 post-transplant patients was similar to the pre-tx patients

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

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

Post-Market Study

Objectives

• Safety and probable benefit of device in achieving remission of NS in 35 patients with refractory pediatric primary FSGS 1, 3, 6, 12 and 24 months after the final apheresis treatment

Criteria

• Age: ≤ 21 years
• Body weight: ≥ 21 kg
• FSGS and persistent NS
• Resistant to or intolerant of medical therapy
• Reasonably good (GFR ≥ 60 ml/min/1.73m²) renal function

Treatment Schedule

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

Collected Information

• Adverse events
• Device malfunction
• Degree of proteinuria (after final therapy)
• Renal function (after final therapy)
Post-Market Study: Endpoints

Primary:
• Probable benefit: Percent of patients who show complete or partial remission at 1 month after the final apheresis treatment
• Safety: Rate of device-related and procedure-related serious adverse events (SAEs) during the therapy and up to 1 month after

Secondary:
• Nephrotic condition (complete remission, partial remission)
• Incidence of all AEs
• Renal function (estimated GFR) compared to baseline

NOTE: The HDE was approved in 10/13, but as of 01/15, enrollment has not commenced.
Literature Review

Allison O’Neill, MA
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Office of Surveillance and Biometrics
What adverse events are reported in the literature since 1995, after treatment with the Liposorber LA-15 system for any indication in the pediatric population (≤21 years old)?
Article Retrieval and Selection

Records identified in Pubmed and Embase (n=2,263)

Number after duplicates removed (n=1,491)

Titles and abstracts reviewed (n=1,491)

Full-text articles reviewed (n=453)

Articles included in qualitative synthesis (n=15)

Articles excluded (n=1,038)

Articles excluded (n=438)
# Pediatrics – Only Articles

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Age Range</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dann, 2013</td>
<td>Cohort</td>
<td>2-9</td>
<td>5</td>
</tr>
<tr>
<td>Hattori, 2003</td>
<td>Clinical trial</td>
<td>7-14</td>
<td>11</td>
</tr>
<tr>
<td>Hudgins, 2008</td>
<td>Registry</td>
<td>3-15</td>
<td>29</td>
</tr>
<tr>
<td>Oto, 2009</td>
<td>Case report</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Palcoux, 2008</td>
<td>Registry</td>
<td>3-14</td>
<td>27</td>
</tr>
<tr>
<td>Stefanutti, 1995</td>
<td>Case series</td>
<td>7-11</td>
<td>2</td>
</tr>
<tr>
<td>Stefanutti, 1997</td>
<td>Case report</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Stefanutti, 2001</td>
<td>Case report</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Stefanutti, 2004</td>
<td>Cohort</td>
<td>3-15</td>
<td>11</td>
</tr>
<tr>
<td>Zwiener, 1995</td>
<td>Case series</td>
<td>7-10</td>
<td>2</td>
</tr>
</tbody>
</table>

- 10 articles
  - 5 case reports/series
  - 2 cohort studies
  - 2 registry studies
  - 1 non-randomized clinical trial
- Sample sizes 1-29
- Age range 2-15
- Patient diagnosis: FSGS or FH
Pediatric – Only Articles

- Adverse events reported:
  - 3 serious AEs (n=1,191 treatments; Hudgins et al., 2008)
    - 1 patient became hypotensive and unresponsive
    - 2 patients developed bacteremia from central catheter insertion
  - 3 anaphylactic reactions probably due to bradykinin (n=27 patients; Palcoux et al., 2008)
    - Cutaneous flushing, nausea, headache, blood pressure drop
    - Unknown whether patients were taking ACE inhibitors
  - Iron deficient anemia: mixed results
    - Dann et al., 2013: 5/5 patients
    - Hudgins et al., 2008: reported anemia, no rate reported
    - Stefanutti et al., 1995: 1/2 patients
    - Palcoux et al., 2008: 0/27 patients
Pediatric – Only Articles

- Other adverse events reported (<3% of treatments):
  - Mild hypotension
  - Catheter infection
  - Hypovolemia
  - Shivering
  - Vertigo
  - Nausea
  - Chest pain
  - Abdominal cramps
  - Urticaria
  - Vasovagal reaction

Hudgins et al., 2008; Stefanutti et al., 2004; Zwiener et al., 1995
Pediatric – Only Articles

• Other adverse events reported:
  • Access/machine problems
    • Slow blood flow
    • Needle infiltration or dislodgement
  • Pain at the needle site
  • Technical difficulties

Hudgins et al., 2008; Palcoux et al., 2008; Stefanutti et al., 1997; Stefanutti et al., 2004; Zwiener et al., 1995
Articles with Pediatric & Adult Patients

- 5 articles
  - 1 non-randomized clinical trial (2 articles)
  - 1 cohort study
  - 2 retrospective studies
- Sample sizes 16-120
- Age range 2-84
- Patient diagnosis: FH, NS due to FSGS and other diseases

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Age Range (mean)</th>
<th>Number of pediatrics/ Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bambauer, 1997, 1999</td>
<td>Non-randomized Clinical Trial</td>
<td>10-77 (46)</td>
<td>NR/120</td>
</tr>
<tr>
<td>Keller, 2009</td>
<td>Retrospective</td>
<td>2-21 (NR)</td>
<td>15/16</td>
</tr>
<tr>
<td>Muso, 2014</td>
<td>Cohort</td>
<td>18-84 (55)</td>
<td>NR/44</td>
</tr>
<tr>
<td>Sachais, 2005</td>
<td>Retrospective</td>
<td>18-67 (50)</td>
<td>NR/34</td>
</tr>
</tbody>
</table>
Articles with Pediatric & Adult Patients

• AE data not stratified by age
• Adverse events reported (<2%):
  • Hypotension
  • Bleeding
  • Serious reactions in patients taking ACE inhibitors (contraindicated)
  • Lightheadedness
  • Nausea/vomiting
  • Chest pain
  • Other: fatigue (73%), edema (85%)
Discussion

• Reviewed 15 articles with wide age range and heterogeneous patient sample (FH, FSGS)
• Most AEs were uncommon
  • Mild hypotension
  • Technical problems (compliance, venous access difficulties) possibly due to patient age and size
• Anemia: mixed results
• 3 anaphylactic reactions (ACE inhibitor use unknown)
• 3 serious AEs (hypotension, bacteremia)
Limitations of the Literature

• Relatively small sample sizes (<30 patients)
• Study designs
• Only 15 articles identified despite broad search criteria
• Heterogeneous patient samples
  • Mixed sample of pediatric/adult: results not stratified by age
  • Diagnosis
• 3 studies conducted in US; all others conducted in Europe or Japan
Conclusions

• Literature published since 1995 regarding pediatric use of Liposorber LA-15 system was found to be limited in number of studies and quality of evidence.

• Most common adverse events were mild hypotension and venous access problems (<4% of treatments).

• No new safety concerns.
Medical Device Reporting (MDR)

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Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Limitations of MDRs

- Under-reporting
- Data quality issues
- Inability to determine rate
- Biased information
- Cannot definitively determine causality/relationship to device
Methods

**MAUDE (Manufacturer And User Facility Device Experience) Database**

**MDR Search Criteria:**

- **Brand Name:** Liposorber® LA-15 System
- **Product Codes:** PBN, Apheresis for Focal Glomerulosclerosis in Pediatric Patients and MMY, Lipoprotein, Low Density, Removal
- **Date Report Received:** April 21, 1995 to October 31, 2014

**Search Result:**

- **20 MDRs**
- **1 MDR was a Pediatric report**
# Overall Event Type Distribution

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Total MDR Count</th>
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<tbody>
<tr>
<td>Death</td>
<td>2</td>
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<tr>
<td>Injury</td>
<td>17</td>
</tr>
<tr>
<td>Malfunction</td>
<td>1</td>
</tr>
</tbody>
</table>
Total Count of MDRs Received by Year

![Bar Chart]

- **Year**: 1997 to 2014
- **Total MDR Received**
- **Number of MDRs**
- **Categories**:
  - Pediatric Injury
  - Death
  - Malfunction
  - Injury

- **Note**: The chart shows the total count of MDRs received by year, with specific categories indicated by different colors.
Reported Death MDRs

- Two reported patient deaths
- The patients ages were 76 and 86
- Multiple co-morbidities cited in both MDRs
- No clearly stated device causality
Reported Pediatric MDR

• One injury MDR
• 11 year old male
• Over-infusion of heparin
### Top Ten Reported Patient Problems

<table>
<thead>
<tr>
<th>Patient Problem</th>
<th>Total Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>8</td>
</tr>
<tr>
<td>Shock</td>
<td>8</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac Arrest/ Cardiopulmonary Arrest</td>
<td>4</td>
</tr>
<tr>
<td>Shock, Hypovolemic</td>
<td>3</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>3</td>
</tr>
<tr>
<td>Pain, Abdominal</td>
<td>2</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
</tr>
</tbody>
</table>
### Reported Device Problems

<table>
<thead>
<tr>
<th>Device Problem</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction</td>
<td>2</td>
</tr>
<tr>
<td>Disconnection</td>
<td>1</td>
</tr>
<tr>
<td>Leak</td>
<td>1</td>
</tr>
<tr>
<td>Excess flow or over-infusion</td>
<td>1</td>
</tr>
<tr>
<td>Loose connection</td>
<td>1</td>
</tr>
<tr>
<td>Device operated differently than expected</td>
<td>1</td>
</tr>
</tbody>
</table>
Conclusion

• One pediatric MDR
• Possible interaction with ACE-Inhibitor, which is contraindicated in the device labeling
• Reported patient problems within device labeling
FDA Conclusions

• As of January 5, 2015, treatment for FSGS patients has not started.

• Our review of the published literature and received MDRs since the time of approval has not identified any new or unexpected risks for the pediatric population when compared to the premarket data.

• FDA concludes that the benefit/risk profile of the Liposorber® LA-15 System for the indication of treatment in pediatric FSGS patients continues to support the HDE for which the exemption was granted.
FDA Recommendations and Question to the PAC

- FDA recommends continued surveillance and will report the following to the PAC in 2016:
  - Annual distribution number
  - PAS follow-up results
  - Literature review
  - MDR review

Question: Does the Committee agree with FDA’s conclusions and recommendations?