Medicare Hospital Outpatient Reimbursement for the LIXELLE® β2-microglobulin Apheresis Column

Presentation by Kaneka Medical America LLC to:

Office of Management and Budget / Office of Information and Regulatory Affairs

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Meeting Participants

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Meeting Agenda

1. LIXELLE® Apheresis: The Only FDA-Approved Treatment for Dialysis-Related Amyloidosis
2. LIXELLE® Is a Humanitarian Use Device (HUD)
3. LIXELLE® Apheresis Is Reasonable and Necessary to Treat Dialysis-Related Amyloidosis
4. Medicare Beneficiaries Cannot Access LIXELLE® Apheresis, Which Is Widely-Available in Japan
5. Three Options for OPPS Reimbursement for the LIXELLE® Apheresis Procedure
6. Conclusions and Next Steps

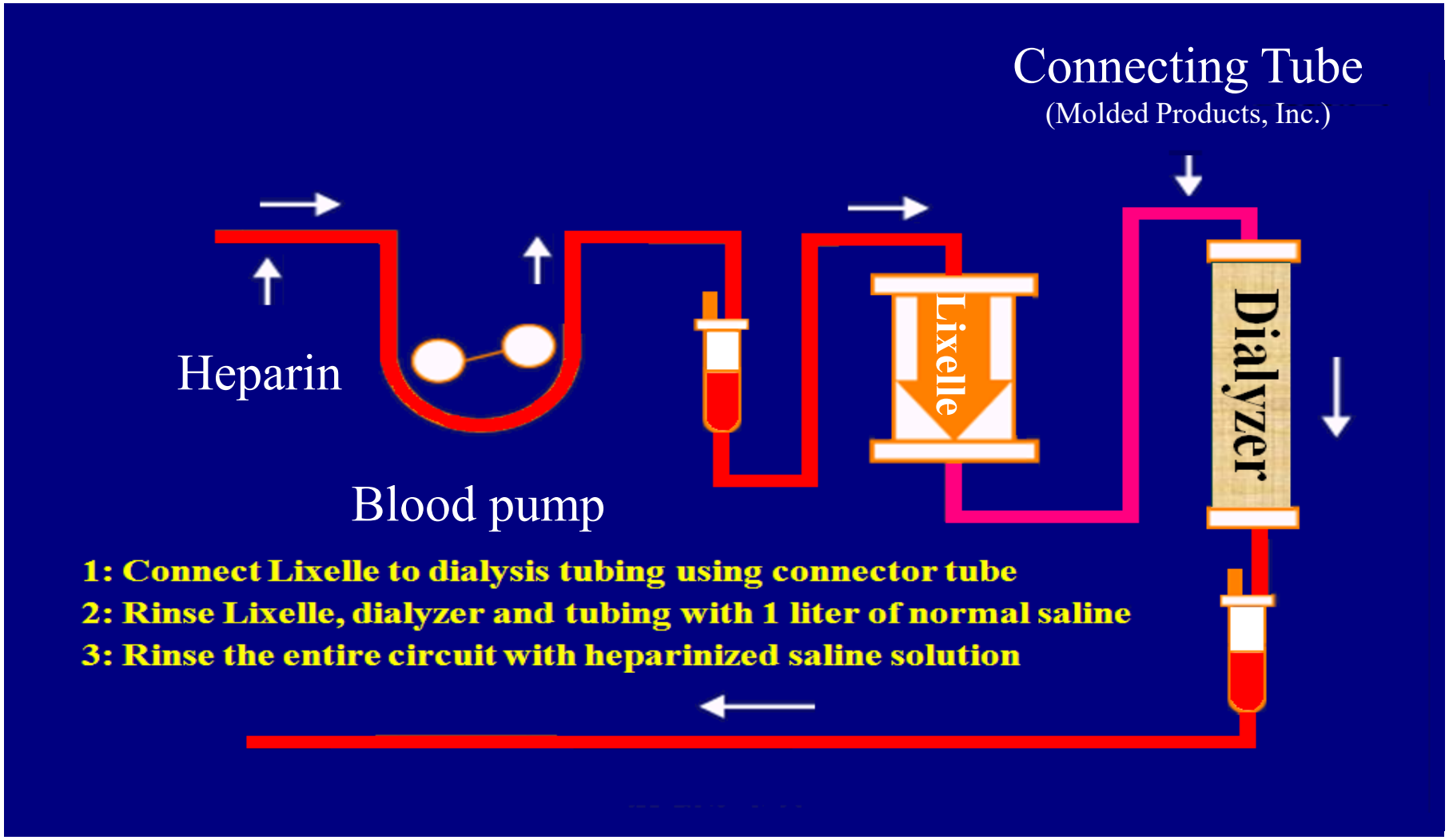
Dialysis-Related Amyloidosis (DRA)

- DRA is a disease that affects an estimated 3,000 patients with ESRD who have been receiving hemodialysis treatment for a long time (typically 5 years or more)
    - Almost all DRA patients are Medicare beneficiaries
- DRA results from the failure of the kidneys to filter and remove β2-microglobulin (β2m)
- The chronic and ongoing accumulation of β2m amyloid fibrils in hemodialysis patients causes deposits in synovial membranes and osteoarticular sites, leading to the following:
    - Subchondral bone cysts
    - Flexor tenosynovitis
    - Carpal tunnel syndrome
    - Deposition in, and dysfunction of, internal organs

The LIXELLE® β2m Apheresis Column

- LIXELLE® is a sterile extracorporeal apheresis column for adsorption of β2m from blood during dialysis
- LIXELLE® is used in conjunction with hemodialysis (at each dialysis session) and is placed in series with a hemodialyzer in a hemodialysis circuit
- By eliminating the need for separate apheresis treatments, use of LIXELLE® in conjunction with dialysis reduces treatment burdens and lowers treatment costs

LIXELLE® Apheresis Treatment Circuit



FDA Approval of LIXELLE®

In March 2015, LIXELLE® was approved by the FDA as a Class III Humanitarian Use Device (HUD) with an approved Humanitarian Device Exemption (HDE)

LIXELLE® is indicated "for the treatment of patients with clinically-diagnosed dialysis-related amyloidosis (DRA)"

- Used pursuant to a physician prescription in conjunction with hemodialysis
- Frequency of apheresis treatment is expected to be three times per week on a chronic basis
- Duration of an apheresis treatment session is linked to the length of time needed for dialysis to obtain an adequate Kt/V (approximately 1.5 to 2 hours longer duration than a dialysis session without LIXELLE®)

LIXELLE® Apheresis is Recognized in 2019 DRA Treatment Guidelines

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue

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AMYLOIDOSIS, SYSTEMIC

Incidence: Primary AL amyloidosis: 3-12/1,000,000/yr; DRA: Rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	DRA	$ß_2$-microglobulin column	Grade 2B	II
	Other causes	TPE	Grade 2C	IV
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
$ß_2$-microglobulin column	1(36)	2(84)	1(345)	NA
TPE	0	0	0	8(9)

AL amyloidosis = monoclonal immunoglobulin light chain; DRA = dialysis-related amyloidosis

LIXELLE® Is a Humanitarian Use Device

- LIXELLE® was approved by FDA pursuant to the following criteria:
  - (1) the device can be used to treat a disease or condition that affects fewer than 8,000 [previously, 4,000] individuals in the United States
  - (2) the device would not be available to a person with such a disease or condition unless the Secretary grants the exemption, and there is no comparable device (other than a device which has been granted such an exemption) available to treat or diagnose the disease or condition; and
  - (3) the device will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use
- The Secretary's determinations that the HUD is safe and that it is necessary for treatment of these micro-populations (i.e., there is no other comparable treatment for DRA available) serves as a strong and conclusive proxy for the Medicare "reasonable and necessary" determination

Congressional Intent—The HUD Program

- Congress created the HUD program in 1990 to "encourage the discovery of devices that are intended to benefit persons with rare diseases"
- Congress intended to improve access to these devices -- "The purpose of section 520(n) is . . . to encourage the discovery **and use** of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 [now 8,000] individuals in the United States per year . . ."
- CMS should facilitate reimbursement of HUDs consistent with Congressional intent

HUDs – Marketing and Charging Limitations

- The HUD statute contains specific limitations on the number of devices that a manufacturer may sell in the United States
  - The FDA must make a determination of the "annual distribution number" or "ADN" for each individual HDE device
  - For LIXELLE®, the FDA determined the ADN to be 624,000 (4,000 patients X 52 weeks X 3 devices per week)
  - The marketing limitation on HUDs serves to ensure that only beneficiaries for whom the device is reasonable and necessary will have access to the device
- HUDs cannot be sold for an amount that exceeds the costs of research and development, fabrication and distribution of the device, with certain limited exceptions (21 USC 360(j)m; 21 CFR 814,104(b)(5))
  - This "profit prohibition" prevents manufacturers from charging excessive rates for HUDs
  - The charging limitation provides guidance on the proper Medicare payment rate for HUDs—providers should be made whole for the cost of acquiring medically necessary devices for orphan populations

LIXELLE® Apheresis Is Reasonable and Necessary to Treat DRA

- FDA relied on four key Japanese controlled clinical trials as well as a post-market safety study conducted in Japan to provide supporting evidence of the safety and probable benefit of treatment of DRA by LIXELLE® Apheresis
- Unlike many HUDs, apheresis using LIXELLE® enjoyed a broad body of clinical literature demonstrating its efficacy in the treatment of DRA, both directly and compared to other treatments, when LIXELLE® was approved by the FDA as a HUD
- The NCD for Apheresis (Therapeutic Pheresis) (110.14) does not specifically address DRA as a covered indication—that is because it was last revised in 1992 and LIXELLE® Apheresis is the first and only FDA-approved treatment for DRA
    - In the CY2021 PFS Final Rule, CMS declined to finalize removal of the NCD but committed to "continue to engage with stakeholders on the issue and will consider whether to propose the NCD for removal in next year's PFS proposed rule." (85 Fed. Reg. 84800 (Dec. 28, 2020))
    - Under the current NCD, indications not specifically included are left to contractor discretion
- Kaneka understands that CMS is amenable to permitting coverage for apheresis procedures to treat DRA that are administered in the HOPD

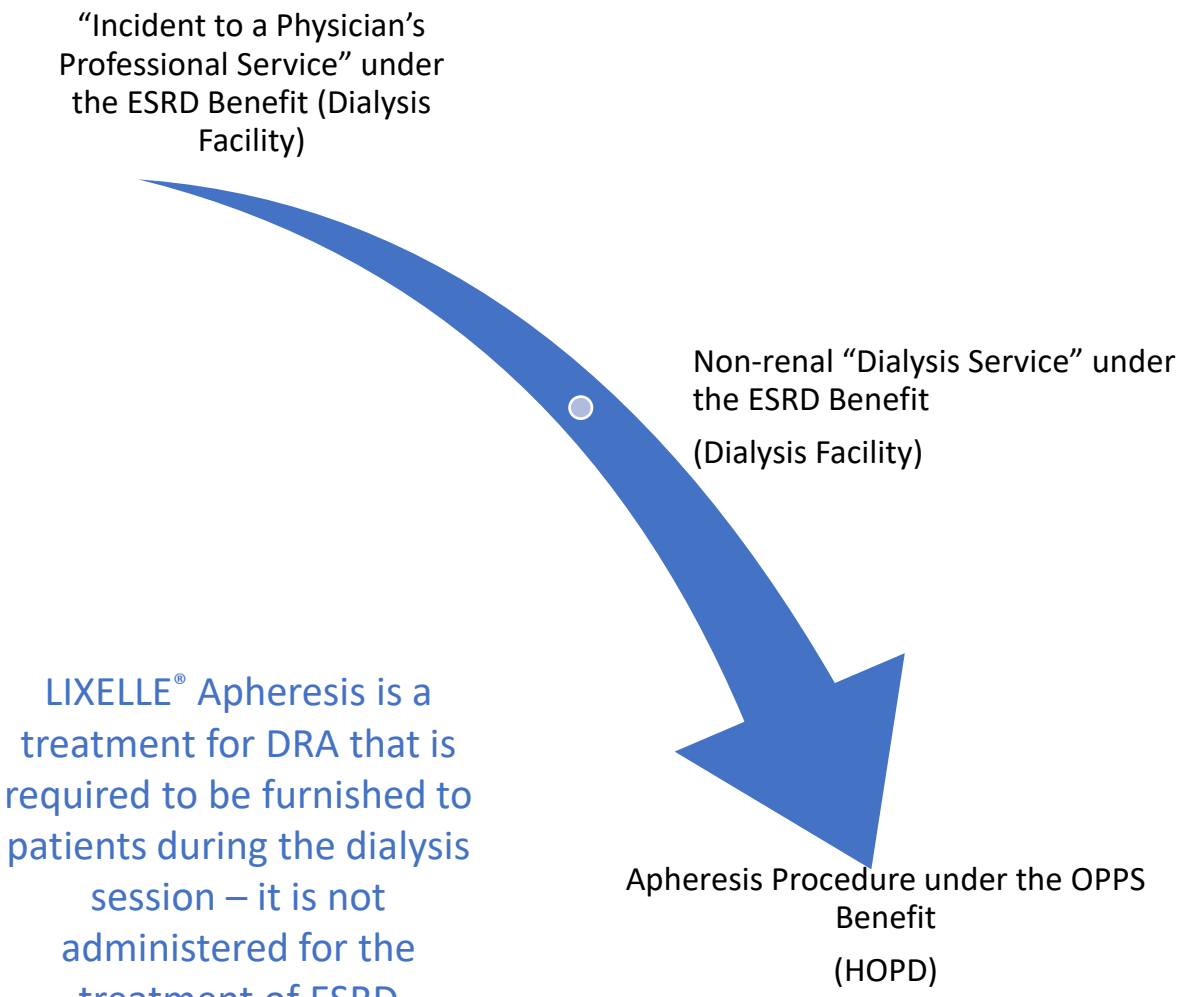
Medicare Beneficiaries Cannot Access LIXELLE® Apheresis

- Kaneka is required to conduct a Post-Approval Study (PAS) to evaluate LIXELLE® Apheresis in U.S. patients on chronic hemodialysis with clinically-diagnosed DRA
    - Prospective double-armed study at 3-6 clinical hemodialysis centers in the U.S.
    - Study arm of 30 DRA patients treated with LIXELLE® Apheresis and hemodialysis for 2 years
    - Natural history arm of 10 DRA patients treated with hemodialysis only for 2 years
    - Endpoints assess safety, changes in β2m reduction rate, and changes in symptoms/quality of life
- FDA approved the PAS protocol in August 2015
- The IRB has reviewed and approved the PAS protocol
- Although Kaneka has aggressively engaged U.S. clinical dialysis centers and investigators to participate in the PAS, there has been difficulty in patient enrollment because clinical trial sites do not want to start patients on LIXELLE® Apheresis if there is no reimbursement after the study ends

LIXELLE® Apheresis Is Widely Available in Japan

- LIXELLE® was approved in Japan in 1994 as an orphan medical device and has been marketed in Japan since 1996
- Over 5,000,000 columns have been sold in Japan since approval
- Approximately 3,000 DRA patients in Japan (of approximately 300,000 patients undergoing dialysis) are currently receiving treatment with LIXELLE® Apheresis
- The Japanese Ministry of Health, Labor and Welfare has approved health insurance coverage and payment for LIXELLE® Apheresis (treatment is reimbursed separately from the bundled dialysis payment by the national insurance system)

Potential Pathways for LIXELLE® Apheresis Reimbursement



LIXELLE® Apheresis is a treatment for DRA that is required to be furnished to patients during the dialysis session – it is not administered for the treatment of ESRD

2011 ESRD PPS Final Rule (75 Fed. Reg. at 49055 (Aug. 12, 2010):

"*Comment*: One commenter requested that we clarify that services that may be furnished to beneficiaries at the time of a dialysis session, but not furnished specifically for the treatment of ESRD, would be excluded from the proposed ESRD bundled payment system. The commenter cited apheresis treatment as an example. Because apheresis, like dialysis, filters a patient's blood, the commenter was concerned that this treatment regimen may be incorrectly viewed as a treatment for ESRD. The commenter further explained that although both dialysis and apheresis filter the patient's blood, the procedures accomplish different objectives. The commenter stated that in dialysis the purpose is to clear wastes from the blood, restore electrolyte balance, and eliminate excess bodily fluid, whereas the purpose of apheresis is to remove from the blood certain blood components such as abnormal proteins implicated in a disease.

The commenter recommended that Medicare policy take no steps that would financially incentivize fracturing dialysis and apheresis into separate patient visits, but encouraged service alignments.

. . .

LIXELLE® Apheresis May Be Reimbursed Under the OPPS Benefit

Response: As described in greater detail in section II.A. of this final rule, items and services included within the ESRD PPS are home dialysis and those items and services that meet the definition of "renal dialysis services" and are furnished to individuals for the treatment of ESRD. Moreover, such services are considered essential for the delivery of outpatient maintenance dialysis. Therefore, the fact that an unrelated, non-ESRD item or service is furnished at the time of a maintenance dialysis treatment would not mean that the particular item or service would be bundled into the ESRD PPS.

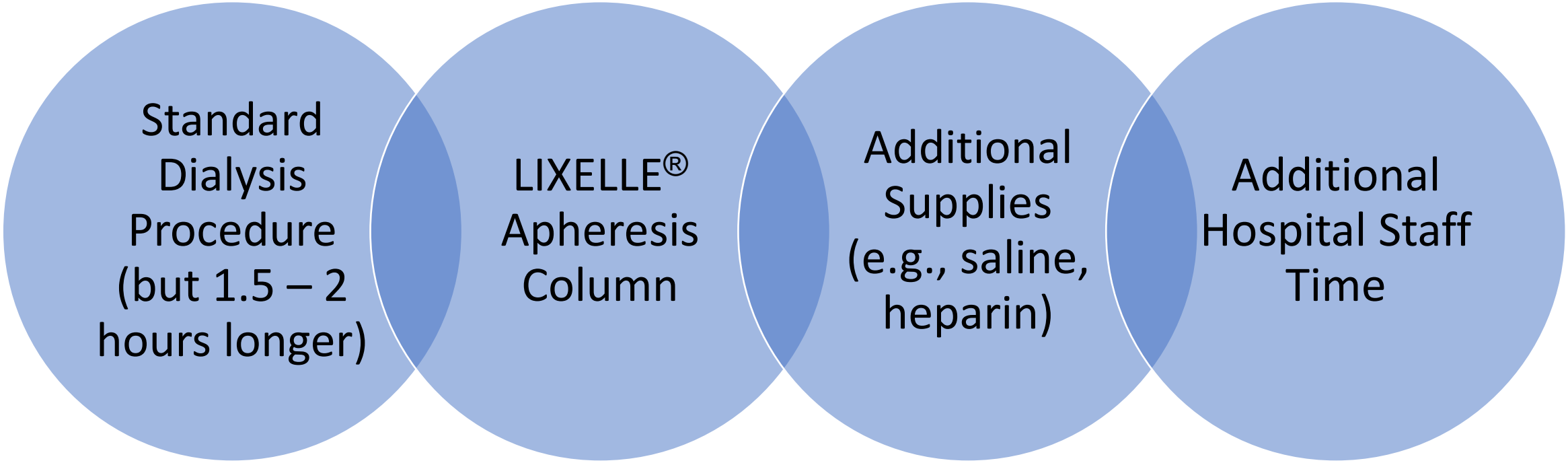
Because at this time, we do not consider apheresis to be a renal dialysis service that is furnished to individuals for the treatment of ESRD, or to be essential for the delivery of maintenance dialysis, we have not included apheresis services in the ESRD PPS. As a result, we would expect that the delivery of apheresis in the ESRD facility setting would occur infrequently. However, we note that to the extent that the coverage provisions for apheresis are met, as set forth in the National Coverage Determination (NCD) Manual, apheresis services may be payable outside the scope of ESRD facility payment, and in accordance with hospital or nonhospital setting payment policies (for example, hospital inpatient prospective payment system (IPPS), outpatient prospective payment system (OPPS), or the physicians' fee schedule).

Medicare coverage provisions for apheresis procedures for certain indications are set forth in the CMS Internet Only Manual (Pul. L. 100-03; Chapter 1, Part 2, section 110.14). . . Please note that indications not specifically addressed in section 110.14 of the NCD Manual are left to local contractor discretion."

-CY2011 ESRD PPS Final Rule (75 Fed. Reg. at 49055 (Aug. 12, 2010) (emphasis added)

OPPS Payment for LIXELLE® Apheresis Procedure

OPPS payment for the LIXELLE® Apheresis procedure would include the following components:



Payment to physicians for delivering and overseeing administration of the LIXELLE® Apheresis procedure falls within the Physician Fee Schedule and can be addressed through E&M codes

Medicare Permits OPPS Payment for Dialysis

Medicare does not allow payment for routine or related dialysis treatments, which are covered and paid under the ESRD PPS, when furnished to ESRD patients in the outpatient department of a hospital. ***However, in certain medical situations in which the ESRD outpatient cannot obtain her or his regularly scheduled dialysis treatment at a certified ESRD facility, the OPPS rule for 2003 allows payment for non-routine dialysis treatments (which are not covered under the ESRD benefit) furnished to ESRD outpatients in the outpatient department of a hospital.*** Payment for unscheduled dialysis furnished to ESRD outpatients and paid under the OPPS is limited to the following circumstances:

- ***Dialysis performed following or in connection with a dialysis-related procedure such as vascular access procedure or blood transfusions;***
- Dialysis performed following treatment for an unrelated medical emergency; e.g., if a patient goes to the emergency room for chest pains and misses a regularly scheduled dialysis treatment that cannot be rescheduled, CMS allows the hospital to provide and bill Medicare for the dialysis treatment; or
- Emergency dialysis for ESRD patients who would otherwise have to be admitted as inpatients in order for the hospital to receive payment.

In these situations, non-ESRD certified hospital outpatient facilities are to bill Medicare using the Healthcare Common Procedure Coding System (HCPCS) code G0257 (Unscheduled or emergency dialysis treatment for an ESRD patient in a hospital outpatient department that is not certified as an ESRD facility).

- Medicare Claims Processing Manual, Chapter 4, Section 200.2 (emphasis added).

CY2021 OPPS Final Rule

CMS recognized the Medicare reimbursement issues related to the LIXELLE® Apheresis Procedure and committed to considering them in future rulemaking:

> …Currently, there is no payment under the OPPS for the apheresis procedure used with the LIXELLE® device…
>
> …the commenter requested that CMS provide payment through the OPPS via one of three potential pathways…
>
> …the commenter also noted that they have been unable to complete the FDA-required post-approval study as a condition of the HDE, due to difficulty in securing patient enrollment because of lack of CMS payment for the LIXELLE® apheresis procedure.
>
> *Response:* We appreciate these comments and understand the various issues related to coverage and payment for the LIXELLE® Apheresis Procedure. We will consider these comments for future rulemaking.
>
> - CY2021 OPPS Final Rule, 85 Fed. Reg. 85982-83 (Dec. 29, 2020).

But CMS did not mention reimbursement for the LIXELLE® Apheresis Procedure in the CY2022 OPPS rulemaking.

OPPS Payment Pathway #1

Coding and payment for LIXELLE® Apheresis as a Therapeutic Apheresis procedure:

CPT 36516 (Therapeutic apheresis with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion)	APC 5243 (Level 3 Blood Product Exchange and Related Services) Status Indicator S CY2022 Payment Rate $4,130.46

The costs for a LIXELLE® Apheresis procedure should be significantly less than the APC 5243 payment rate, so we would recommend an add-on procedure code (C code) specific to LIXELLE® Apheresis or other modifier on the claim to generate a lower payment rate that better approximates the costs of the LIXELLE® Apheresis procedure (e.g., APC 5242 – Level 2 Blood Product Exchange and Related Services, with a CY2022 payment of $1,393.02)

OPPS Payment Pathway #2

Coding and payment for LIXELLE® Apheresis as a resource-intensive dialysis procedure:

HCPCS G0257 (Unscheduled or emergency dialysis treatment for an ESRD patient in a hospital outpatient department that is not certified as an ESRD facility)	APC 5401 (Dialysis) Status Indicator S CY2022 Payment Rate $668.91

The costs for a LIXELLE® Apheresis procedure should be more than a standard dialysis procedure as noted above, so we would recommend an add-on procedure code (C code) or other modifier on the claim to generate a higher payment rate

CPT 90947 (Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies) requiring repeated evaluations by a physician or other qualified health care professional, with or without substantial revision of dialysis prescription)	CY2022 Status Indicator B

A payment rate could be assigned to the above CPT code to generate an amount that appropriately covers the cost of the LIXELLE® Apheresis procedure

OPPS Payment Pathway #3

Coding and payment for LIXELLE® Apheresis as a unique procedure:

Create a unique HCPCS C code or HCPCS G code for LIXELLE® Apheresis	APC 5242 (Level 2 Blood Product Exchange and Related Services) Status Indicator S CY2021 Payment Rate $1,393.02

This pathway would be the most streamlined way to specifically track payment for the LIXELLE® Apheresis procedure, and could be accomplished at the next OPPS quarterly update (July 2022)

Conclusions and Next Steps

- Kaneka very much appreciates the extensive time and effort that CMS has devoted to finding a pathway for Medicare reimbursement for the LIXELLE® Apheresis procedure
- But Medicare beneficiaries with DRA are still unable to access the only FDA-approved treatment for DRA
- We urge CMS to find a pathway to Medicare reimbursement so that Medicare beneficiaries can access the LIXELLE® Apheresis procedure for treatment as well as through Kaneka's FDA-mandated Post-Approval Study

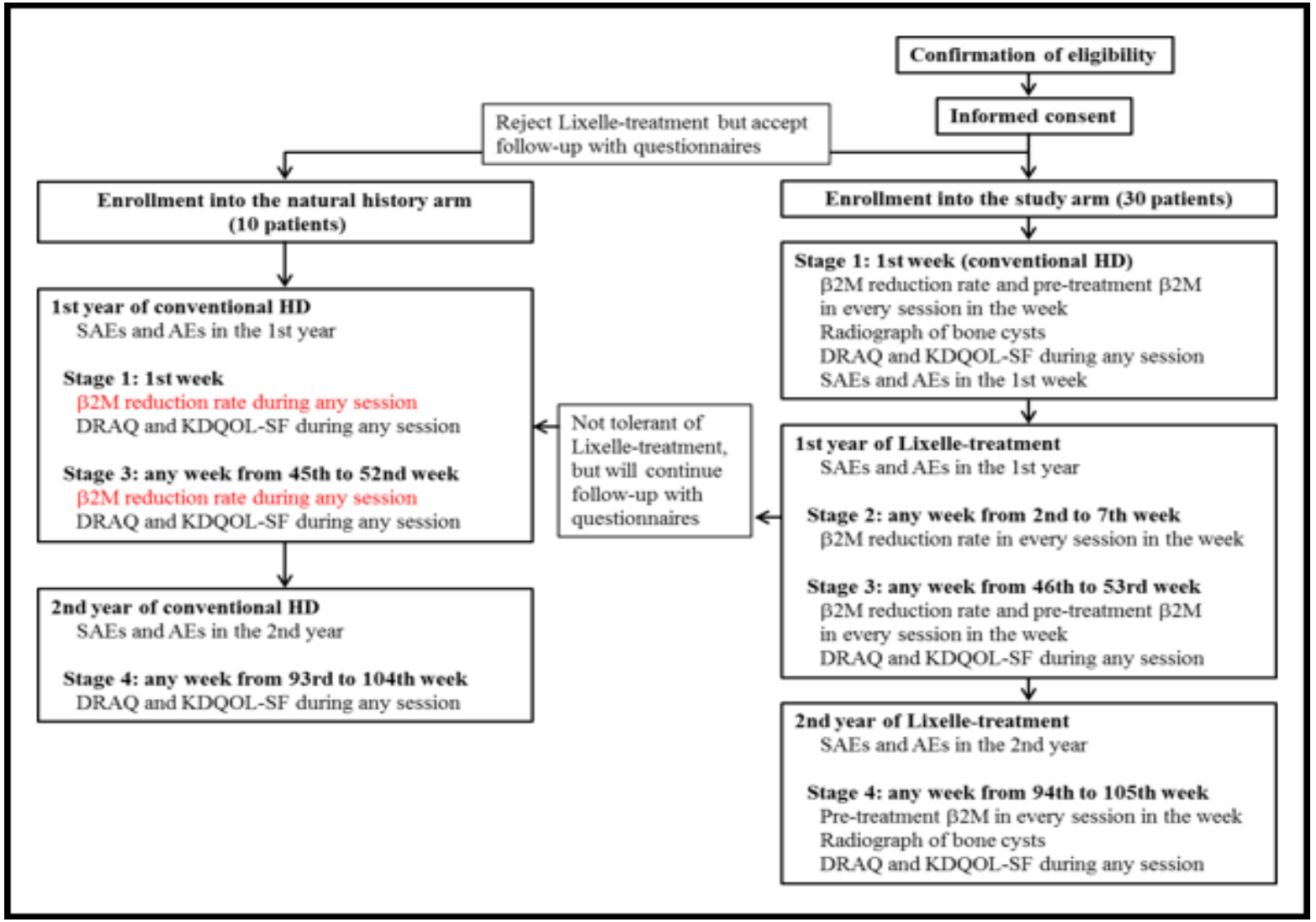
Appendix

Post-Approval Study Status

- Study Design
  - Prospective, multicenter study on LIXELLE® group （n=30） and natural history group n=10, 2 years
- Primary Endpoint：Evaluation of safety of LIXELLE® in US
- Secondary Endpoints:
  - β2M reduction rate (pre and post) comparison between LIXELLE® treatment and baseline
  - Evaluation of QOL by DRAQ* and KDQOL-SF
  - Change on β2M pre value
  - Change on bone cysts
- Flow Rate
  - Approved flow rate ≦ 250ml/min
  - Dialysis time should be adjusted to achieve adequate Kt/V
  - Planning a study to raise the flow rate to 400-500 (approval target: 2022)
- Current Status
  - 2 pts for LIXELLE® group and 1 pt for natural history group
  - Sites' concern: No reimbursement after the PAS
- Upon completion, will submit this as "U.S. safety data" to CMS for free standing clinics reimbursement.

* Dialysis-related amyloidosis questionnaire

Post-Approval Study Overview



Post-Approval Study: Study Arm

(Study arm)	Baseline	Stage 1				Stage 2				Stage 3				Stage 4		
		Mon Tue	Wed Thu	Fri Sat		Mon Tue	Wed Thu	Fri Sat		Mon Tue	Wed Thu	Fri Sat		Mon Tue	Wed Thu	Fri Sat
	conventional HD				Lixelle®-treatment period											
date	●	●	●	●		●	●	●		●	●	●		●	●	●
Baseline characteristics	●															
body weight, BMI	●										●				●	
Diagnosis relating to DRA	●															
Measurement																
KDQOL-SF score			●								●				●	
DRAQ score			●								●				●	
β2M at the start of session (Pre-treatment β2M)		●	●	●		●	●	●		●	●	●		●	●	●
β2M at the start of session (Post-treatment β2M)		●	●	●		●	●	●		●	●	●				
β2M reduction rate		●	●	●		●	●	●		●	●	●				
Bone cyst radiograph, numbering, and measurement (for patient with record of bone cyst at the enrollment)			●												●	
Change in size or number of bone cysts															●	
Treatment condition																
date of HD without Lixelle					●				●				●	●	●	●
cumulated number of HD Lixelle												●				●
cumulated % of (without Lixelle) / (total treatment)												●				●
use of S-25 or S-15		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kt/V urea	●		●				●				●				●	
blood flow rate (ml/min)	●	●	●	●		●	●	●		●	●	●		●	●	●
dialysis time (min)	●	●	●	●		●	●	●		●	●	●		●	●	●
dialyzer	●															
anticoagulant	●															
other medication	●															
any notable change of treatment condition										●						
any notable change of medication										●						
Blood data																
serum creatinine, serum total protein, serum albumin, CBC, hematocrit, RBC, WBC, and platelet			●				●				●				●	
Adverse event																
Every SAE is recorded and reported at the occurrence.		●							●							
Every AE other than SAE is recorded at the occurrence and reported after one and two years of treatment.												●				●

Post-Approval Study: Natural History Arm

(Natural history arm)	Baseline	Stage 1				Stage 3				Stage 4		
		Mon Tue	Wed Thu	Fri Sat		Mon Tue	Wed Thu	Fri Sat		Mon Tue	Wed Thu	Fri Sat
	conventional HD											
date	●	●	●	●		●	●	●		●	●	●
Baseline characteristics	●											
body weight, BMI	●						●				●	
Diagnosis relating to DRA	●											
Measurement												
KDQOL-SF score			●				●				●	
DRAQ score			●				●				●	
β2M at the start of session (Pre-treatment β2M)			●				●				●	
β2M at the start of session (Post-treatment β2M)			●				●					
β2M reduction rate			●				●					
Treatment condition												
Kt/V urea	●		●				●				●	
blood flow rate (ml/min)	●		●				●				●	
dialysis time (min)	●		●				●				●	
dialyzer	●		●				●				●	
anticoagulant	●											
other medication	●											
any notable change in medication							●					
Adverse event												
Every SAE is recorded and reported at the occurrence.							●					
Every AE other than SAE is recorded at the occurrence.							●					