June 6, 2024

Re: Proposed Local Coverage Determination (LCD) on DL35041 and associated article

Dear Novitas Medical Directors,

Kerecis® (Kerecis) thanks you for the opportunity to provide comments in response to the proposed local coverage determination (LCD) for skin substitute grafts/cellular and tissue-based products for the treatment of diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) and accompanying coverage articles. We understand and appreciate the Medicare Administrative Contractors' (MACs) primary concerns are to ensure that Medicare covers, and beneficiaries receive, high-quality and effective DFU and VLU treatments, as determined by supporting clinical evidence. Kerecis strongly believes that its products have the clinical evidence to support coverage and request that you review our more recent evidence prior to finalizing the LCD. The only reason that the latest evidence was not included in the review is that the most recent publications were published after the LCD evidence collection was performed. As described below, Kerecis commends you for the thoughtful updates that are included in the proposed LCDs and urge inclusion of the Kerecis skin substitute products in the final LCD.

1. Introduction to Kerecis and Its Skin Substitute Products

Kerecis is a pioneering company in the field of wound care, dedicated to developing innovative solutions that harness the natural healing properties of fish skin. Kerecis' unique technology leverages the structural and biological similarities between fish skin and human skin to create advanced wound care products that promote rapid healing and tissue regeneration. The manufacturing process also is sustainable, with plentiful supply of the fish skin source that ensures a stable supply chain of Kerecis products.

Kerecis has demonstrated a strong commitment to patient safety and evidence-based medicine through its extensive clinical research and rigorous regulatory compliance, with a strong pipeline of additional research underway. As the first FDA-cleared product derived from intact fish skin, Kerecis has undergone safety testing that surpasses the requirements for most other products in this category, with the exception of PMA-approved devices. In addition to animal studies, Kerecis conducted thorough testing in human subjects to assess autoimmunity, seroconversion, and molecular mimicry before obtaining FDA 510k clearance.[1] This level of safety testing is a testament to the company's unwavering dedication to developing safe and effective wound care treatments. The comprehensive body of clinical evidence and the rigorous regulatory oversight to which Kerecis adheres demonstrate that Kerecis products are safe, effective, and manufactured to the highest standards.

Kerecis' fish skin grafts offer numerous benefits to Medicare beneficiaries, including superior clinical efficacy compared to standard of care and other products currently available, as demonstrated by the

[1] [Baldursson BT, Kjartansson H, Konrádsdóttir F, Gudnason P, Sigurjonsson GF, Lund SH. Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: a noninferiority study. Int J Low Extrem Wounds. 2015 Mar;14(1):37-43. doi: 10.1177/1534734615573661. Epub 2015 Mar 9. PMID: 25759413.]

robust body of randomized controlled trials and comparative evidence.[2, 3] Kerecis' products are used not only for outpatient wound care but also for inpatient surgeries to treat burns, trauma, and implantation, that require much larger surface areas. Kerecis has two specific products that fall under the scope of these LCDs: Q4158 (MariGen) and A2109 (MariGen Shield). Both products utilize our proprietary intact fish skin technology produced with our EnviroIntact™ processing and share the same mechanism of action and manufacturing process. The only difference between these two products is that MariGen Shield has a silicone protective cover on top of the fish skin graft. Both products produce the same clinical benefit and healing outcomes as described in the clinical evidence, which is predicated on the use of the fish skin graft. In other words, both products should be assessed as fish skin grafts pursuant to the same mechanism of action and supporting clinical evidence.

In addition to their evidence-supported effectiveness, Kerecis' fish skin products provide a valuable treatment option for beneficiaries with cultural or religious concerns related to the use of human- or mammalian-derived grafts. The shelf stability of Kerecis products also makes them particularly well-suited for use in rural and underserved communities, where access to advanced wound care solutions may be limited. More specifically, Kerecis' products have a three-year shelf life and do not require special storage or refrigeration. This is especially important for beneficiaries suffering from DFUs and VLUs in rural and underserved areas.

2. Clinical Evidence in Support of Kerecis Products

Kerecis brings to your attention a recent study by Lantis et al. published in 2023 (Lantis 2023). This study was published after the previous comment period and evidence collection for the LCD and therefore not included in the proposed LCD evidence review. This randomized controlled trial compares the intact fish skin graft to standard of care (SOC) with collagen alginate therapy (CAT) for the treatment of chronic diabetic foot ulcers (DFUs). The study enrolled 102 patients across 16 participating sites, with 51 patients randomized to each group. The primary outcome was the percentage of wounds healed at 12 weeks.

The study found that 56.9% of DFUs in the fish skin graft group healed at 12 weeks compared to 31.4% in the SOC group (p=0.0163). Additionally, the mean wound area reduction was 86.3% in the fish skin graft group vs 64.0% in the SOC group at 12 weeks (p=0.0282). Adverse events were similar between groups. These outcomes are comparable to, or even superior to, those reported in studies of other proposed covered products.

The Lantis 2023 study had several methodological strengths that are in line with the studies reviewed for proposed covered products. These include a randomized, controlled design, multicenter participation, clear inclusion/exclusion criteria, standardized treatment protocols, and independent blinded adjudication of wound healing. Both intention-to-treat (ITT) and per-protocol (PP) patient population analyses were

[2] Lantis II JC, Lullove EJ, Liden B, et al. Final efficacy and cost analysis of a fish skin graft vs standard of care in the management of chronic diabetic foot ulcers: a prospective, multicenter, randomized controlled clinical trial. Wounds. 2023;35(4):71-79. doi:10.25270/wnds/22094.

[3] Zehnder T, Blatti M. Faster Than Projected Healing in Chronic Venous and Diabetic Foot Ulcers When Treated with Intact Fish Skin Grafts Compared to Expected Healing Times for Standard of Care: An Outcome-Based Model from a Swiss Hospital. The International Journal of Lower Extremity Wounds. 2022;0(0). doi:10.1177/15347346221096205.

performed, which is consistent with the approach taken in many of the reviewed studies for proposed covered products.

We acknowledge that the study was industry-funded, which introduces the potential for funding bias. However, as noted in the LCD this is expected for trials for new drugs or devices and a common feature among the studies reviewed in the LCD. There are few established mechanisms for external funding of such research which is prohibitively complex and expensive for academics to self-fund. This is similar to the situation with new drug trials, where industry funding is the norm.

The study did have some limitations, such as a lack of participant and investigator blinding due to differences in product appearance and application, and patient dropouts with missing outcome data. However, these limitations are not unique to the Lantis 2023 study and are present in most of the studies included in the LCD review. The use of independent, blinded adjudication of wound healing outcomes helps mitigate the lack of product blinding and ITT analysis with last observation carried forward (LOCF) helps to mitigate the impact of missing data, which is a common approach in other MAC-reviewed studies.

Based on the LCD evidence criteria and the studies that were accepted, it appears that the MACs considered several factors when evaluating the quality and relevance of clinical evidence. Although not explicitly stated, the accepted studies suggest that to establish efficacy the following study characteristics are important:

1. Randomized, controlled trial design
2. Adequate sample size and statistical power
3. Clear inclusion/exclusion criteria and standardized treatment protocols
4. Multicenter participation
5. ITT and/or PP analyses
6. Blinded outcome assessment or independent adjudication
7. Clinically meaningful and statistically significant outcomes
8. Reasonable management of missing data and dropout rates
9. Appropriate statistical analyses and reporting

The Lantis 2023 study exhibits many of these characteristics, making it comparable to the accepted studies in terms of quality and relevance. Specifically, the Lantis 2023 study:

1. Utilized a randomized, controlled trial design
2. Enrolled a total of 102 patients, which is similar to or larger than many of the studies of proposed covered products
3. Employed clear inclusion/exclusion criteria and standardized treatment protocols
4. Involved 16 participating sites, demonstrating multicenter participation
5. Performed both ITT and PP analyses
6. Used independent, blinded adjudication of wound healing outcomes
7. Reported clinically meaningful and statistically significant improvements in wound healing rates and wound area reduction
8. Managed missing data through the use of ITT analysis with LOCF
9. Adequately powered, conducted appropriate statistical analyses and reporting

When compared to other studies reviewed for proposed Group 2 products, the Lantis 2023 study appears to be of comparable quality, with a robust design and outcomes. The study's strengths, such as its randomized, controlled design and multicenter participation, are shared by many of the studies that the MACs reviewed in support of the proposed Group 2 products.

Further, a non-industry funded, prospective, controlled study by Zehnder and Blatti in 2022 (Zehnder 2022) provides compelling evidence for the effectiveness and necessity of the Kerecis Omega3 fish skin graft in treating both DFUs and VLUs. This study found that wounds deemed unlikely to heal with standard care alone that were subsequently treated with the fish skin graft showed significantly faster healing times. Specifically, 12 out of 17 fish skin graft-treated wounds beat the predicted healing times based on standard care, with the majority healing over 50% faster than expected. Additionally, the fish skin graft was able to change the trajectory of wounds that had increased in size during the initial standard care phase, leading to complete healing in most cases.[4] These results demonstrate the reasonableness of the fish skin graft in promoting healing of difficult-to-treat DFUs and VLUs that fail to respond adequately to standard care.

In addition to the above-described assessment of Lantis 2023, Kerecis commissioned a third-party analysis by Avalere Health LLC of this RCT in relation to the requirements of the LCD and the clinical evidence cited for the 15 proposed covered products (Group 2). Avalere´s independent analysis ultimately concluded:

> Based on an independent Avalere analysis, the study design and outcomes (e.g., 12-week wound closure for DFU) presented by Lantis et al. is of comparable quality to the evidence base for products recommended for approval in this LCD, and therefore it warrants consideration by MACs in assessing the Kerecis fish skin graft technology for potential coverage.[5]

The full Avalere memorandum is included as an attachment for your consideration.

In light of this evidence, Kerecis respectfully requests that the Lantis 2023 and Zehnder 2022 studies be considered before releasing the final LCD and that the Kerecis MariGen and MariGen Shield fish skin graft products be evaluated for coverage based on the merits of these studies and their comparability to other proposed covered products. The inclusion of the studies would help to ensure that the LCD review process is comprehensive and up-to-date, and that coverage decisions are based on the most current and relevant scientific evidence available.

3. Beneficiary Access Concerns

The Kerecis products provide certain unique advantages in relation to other available and proposed Group 2 products, especially with respect to underserved patient populations. When the proposed LCD was released, Kerecis heard directly from healthcare professionals who rely on Kerecis products to treat underserved populations including Indian tribe members who cannot use human-derived skin substitute products, and rural beneficiaries who have limited access to other skin substitute products. As some healthcare professionals have described to us, the ability to travel to beneficiaries with the Kerecis products is a significant benefit, as the Kerecis products do not need to be specially stored or refrigerated. This expands beneficiary access to high-quality care, and there are broad concerns that the exclusion of Kerecis'

[4] Zehnder T, Blatti M. Faster Than Projected Healing in Chronic Venous and Diabetic Foot Ulcers When Treated with Intact Fish Skin Grafts Compared to Expected Healing Times for Standard of Care: An Outcome-Based Model from a Swiss Hospital. The International Journal of Lower Extremity Wounds. 2022;0(0). doi:10.1177/15347346221096205.
[5] Analysis produced by Avalere Health, LLC for Kerecis. Full memo available in the appendix.

products will be to the detriment of these patient populations who will not have ready access to equivalent alternatives should these LCDs be finalized as proposed.

Given the clinical evidence Kerecis is submitting as part of this comment letter and the provider and beneficiary preferences for Kerecis products, Kerecis strongly urges the MACs to include its products among the Group 2 products to sustain beneficiary access to care.

4. Comments Regarding the Proposed Coverage Criteria and Clinical Evidence

Kerecis commends the MACs for thoughtfully reviewing, considering, and incorporating stakeholder feedback in response to last year's proposed and final LCDs related to skin substitute products. Kerecis acknowledges the changes that have been incorporated into these proposed LCDs, including basing coverage on established evidence and providing a pathway for additional applications beyond the four applications during a 12-week period. As previously described, Kerecis urges the MACs to ensure more recent clinical evidence or evidence that was not considered as part of the proposed LCDs be considered in advance of issuing final LCDs. Kerecis also seeks transparency and predictability as they relate to the forthcoming final LCD and any future changes to this LCD.

Kerecis aligns with other comments submitted, including from The Advanced Medical Technology Association (AdvaMed), The Alliance of Wound Care Stakeholders, and offers additional comments regarding the coverage criteria and efficiently updating Group 1 and Group 2 codes as new clinical evidence becomes available.

a. Recommended Clarifications Regarding the Proposed Coverage Criteria

In general, Kerecis supports the proposed covered indications and coverage requirements for skin substitutes. However, Kerecis seeks and recommends the MACs clarify the definition of a skin substitute and elements of the "Limitations" during an episode of care.

The MACs should provide a clear and consistent definition of skin substitutes in the LCD, based on the most up-to-date scientific evidence. Currently, FDA uses one definition of a skin substitute, CMS uses another for assigning HCPCS codes, and the proposed LCD suggests a third definition. The MACs should work with CMS to adopt a unified definition and coding of skin substitute products, focusing on their biological properties and mechanism of action. Furthermore, we suggest removing synthetic products from the definition of skin substitutes, as they do not accurately represent the characteristics and functions of biological skin substitutes and would be better represented in other categories.

As it relates to the application of additional skin substitute grafts within an episode of skin replacement therapy, Kerecis urges greater specificity and details regarding when it would be appropriate to apply more than four applications within the episode and when it would be appropriate to apply skin substitutes beyond the 12-week episode. The proposed LCDs describe "exceptional cases" when more than 4 applications (or applications beyond the 12-week episode) may be considered with documentation that includes or demonstrates "progression of wound closure."

As the MACs know, such improvement can vary on a beneficiary-by-beneficiary basis. From a healthcare professional's standpoint, the vague requirement of progression of wound closure poses a legitimate barrier to continued treatment if a DFU or VLU is likely to improve but is not yet progressing to closure.

Within the same Limitations section of the proposed LCDs, the MACs describe unsuccessful treatment as “no measurable change” from baseline and “no sign of improvement or indication that improvement is likely.” These two limitations are inconsistent, and we recommend that the MACs provide greater clarity on when exceptions would be available and how healthcare professionals should appropriately measure and document when such exceptions exist.

The LCD states that "Patients receiving skin replacement surgery with a skin substitute graft/CTP should be under the care of a physician/non-physician practitioner (NPP) for the treatment of their systemic disease process (e.g., diabetes mellitus, chronic venous insufficiency, or peripheral vascular disease)."

In many remote and medically underserved communities, podiatric surgeons serve as an essential primary care resource for patients and should be included on the list as accepted caregivers for those underlying issues.

b. Ensuring the LCDs Timely Reflect New Clinical Evidence

Kerecis believes its products should be covered for the treatment of DFUs and VLUs upon review of Lantis 2023 and Zehnder 2022. To best support continued beneficiary access and, to the greatest extent possible, reducing unnecessary delays in care, Kerecis asks that the MACs ensure transparency and consistency in the evidentiary standard for covering skin substitute products. Kerecis recognizes that the MACs will release responses to comments when issuing the final LCD and encourages a thorough analysis and detailed discussion regarding the required level of clinical evidence, key metrics, and thresholds for coverage.

In addition, Kerecis recommends that the MACs establish a clear and transparent process for evaluating future studies and incorporating new evidence into the LCD. This process should allow for the timely expansion of covered indications in Group 1 and inclusion of products in Group 2 as the evidence base evolves. A structured, ongoing review process would help to ensure that the LCD remains up-to-date and reflective of the most current clinical practices and research findings. This is especially important for ensuring beneficiary access to effective skin substitute products as reasonable and necessary for covered indications. As stated by some MACs, the development of new clinical evidence would require a reconsideration of the LCDs, which could take several months, presenting unnecessary and highly burdensome review by each of the MACs each time new evidence is submitted, while inappropriately delaying beneficiary access to care.

These recommendations are especially important given Kerecis’ research pipeline and new evidence supporting the use of fish skin grafts in the treatment of deeper wounds, such as University of Texas (UT) grade 2 and 3 DFUs. Building upon the strong evidence foundation Kerecis already has, a new study will soon be published. This forthcoming study is one of the largest RCTs to date on deep, complex DFUs that extend to bone, joint, or tendon. This study, which includes 255 patients, found that the Kerecis products healed significantly more wounds at 16 weeks compared to SOC in complex DFUs extending to bone, tendon or joint. Kerecis believes this robust evidence would provide the MACs with the necessary data to expand the Group 1 covered indications. However, absent an efficient process to timely update the Group 1 codes, beneficiary access to care for these more complex diabetic foot wounds will be delayed.

5. Conclusion

We appreciate the opportunity to provide these comments in response to the proposed LCDs and to share our perspective as a manufacturer of advanced wound care products. We believe that the Lantis 2023 and Zehnder 2022 studies, along with the existing published data, provide strong evidence to support the reasonableness and necessity for inclusion of the Kerecis products (Q4158, A2019) as covered under Group 2 for the treatment of DFUs and VLUs. We also urge the MACs to provide more clarity and detail regarding the exceptions to the proposed Limitations. Finally, we urge the MACs to consider a more streamlined process to review clinical evidence and appropriately update the LCDs. We strongly believe that these changes are necessary to minimize delays in beneficiary access to care and skin substitute products that meet the MACs' evidentiary standards.

Please feel free to contact me at (703)- 980 - 4780 or gj@kerecis.com should you have any questions or if you would like to discuss these comments further.

Sincerely,

Gunnar Jóhannsson, MD

Senior Vice President & Medical Director

Kerecis LLC

Attachments:

1. Kerecis-Avalere RCT Assessment Memo_20240531_final.pdf
2. 2023 -Lantis et al – Final efficacy and cost analysis of a fish skin graft vs SOC in the management of chronic DFUs - a pro.pdf
3. 2022- Zehnder & Blatti – Faster Than Projected in Chronic Venous and DFUs When Treated with Intact Fish Skin Grafts.pdf
4. 2015 Baldursson et al – Healing Rate and Autoimmune Safety of Full- Thickness Wounds Treated With Fish Skin Acellular Derma.pdf
5. Kerecis Skin Substitute Manufacturing Letter v4.docx