

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

Table of Contents

Commenters.....	1
Public Comments	1
References Provided by Commenters	17

Commenters

Identification	Stakeholder
A	Integra [Submitted February 1, 2016]
B	Lacey Loveland, DPM [Submitted March 23, 2016]
C	Lisa Nakadate, Executive Director, Oregon Podiatric Medical Association [Submitted March 24, 2016]
D	Chris Seuferling, DPM [Submitted March 26, 2016]
E	Smith & Nephew [Submitted March 31, 2016]
F	John T. Callahan, D.P.M., F.A.C.F.A.S., Santiam Foot Clinic, PC [Submitted April 1, 2016]
G	Alliqua Biomedical [Submitted April 3, 2016]
H	Osiris Therapeutics [Submitted April 3, 2016]

Public Comments

ID/#	Comment	Disposition
A1	<p>Integra LifeSciences requests that Skin Substitutes for Chronic Skin Ulcers be revised to include coverage of IDRT and Omnigraft™ for the treatment of diabetic foot ulcers. Specific coverage language could be taken from the indications for use tab within the attached payer packet.</p> <p>IDRT is an advanced, acellular, bilayer matrix specifically engineered for dermal regeneration. On the market since 1996, it is the only FDA-approved product indicated</p>	<p><i>Thank you for your comments and for your submission of the FOUNDER study which was published after the initial search. This was added to the evidence section. See new GRADE-informed framework.</i></p> <p><i>This FOUNDER study met inclusion criteria but was a single study at moderate risk of bias, so the level of confidence in conclusions is very low. Thus, the EbGS did not find sufficient</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>for the treatment of third degree burns and the reconstruction of scar contracture with a dermal regeneration claim.</p> <p>On January 7, 2016, FDA added an additional indication for use via PMA Supplement to IDRT based on the clinical results of a large multi-center, randomized, controlled clinical trial (the Foot Ulcer New Dermal Replacement Study (FOUNDER) Study). This study evaluated the safety and efficacy of IDRT for the treatment of non-healing chronic diabetic foot ulcers.</p> <p>The FOUNDER study is unmatched in the wound care area in terms of the strength of its study design, and the study results are both direct and conclusive. Key aspects of the FOUNDER study’s design include the following:</p> <ul style="list-style-type: none"> • <i>Large, Multi-Center RCT.</i> The FOUNDER study, published in the <i>Wound Healing and Tissue Regeneration</i> Journal, which served as the clinical basis for FDA approval, is the largest multi-center, randomized controlled clinical trial of its kind designed to evaluate the safety and effectiveness of a cellular and/or tissue-based product for the treatment of diabetic foot ulcers. It included 32 sites from across the United States, and it involved 307 subjects with Type II diabetes and at least one diabetic foot ulcer. • <i>14-Day Run-In Period.</i> In contrast to some previous trials of diabetic foot ulcer treatments that had no run-in period or a run-in period of 7 days, eligible patients were first required to complete a 14-day run-in period during which time they were treated with the standard of care regimen. This ensured that the study evaluated the most difficult to heal diabetic foot ulcers. • <i>Computerized Planimetry.</i> Third party computerized planimetry was used as an independent assessment method to confirm wound closure and wound size. • <i>Generalizability.</i> Despite strict inclusion and exclusion criteria, any bias against generalizability was minimized by enrolling and randomizing subjects from 32 academic and private practice sites across the US to ensure that study 	<p><i>evidence to recommend coverage.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>participants represent patients with chronic diabetic foot ulcers from a heterogeneous population. Further, a full range of age groups were represented in the study, including the Medicare-age population (e.g., 31 of 153 patients in the control group were age 65 or older [20.3%], and 20 of the 154 patients in the treatment arm [18.2%] were age 65 or older).</p> <p>Key outcomes of the FOUNDER study include the following:</p> <ul style="list-style-type: none"> • <i>Higher Relative Wound Closure.</i> Diabetic foot ulcers treated with IDRT/Omnigraft™ achieved a 125% relative improvement in closure compared to standard of care at 12 weeks • <i>Faster Time to Healing.</i> Patients treated with IDRT/Omnigraft™ healed 5 weeks faster than patients in the control group who received standard of care. • <i>Rapid Wound Closure Rate.</i> Patients who received IDRT/Omnigraft™ experienced a 50% faster wound size reduction compared to the control group. • <i>Single Application.</i> Of the wounds that healed, 96% of those treated with IDRT, Omnigraft™ healed with three or less applications with 72% healing in one application. In contrast, studies of cell-based products and minimally processed human tissue allografts required an average of 4-6 applications. • <i>Improved Quality of Life.</i> Patients treated with IDRT/Omnigraft™ experienced a significant improvement in Physical Functioning and a decrease in Bodily Pain over standard of care (as defined by SF-36). <p>We hope that you find these materials sufficient to act favorably on our request to add IDRT and Omnigraft™ as covered for the treatment of diabetic foot ulcers in Skin Substitutes for Chronic Skin Ulcers.</p>	
B1	<p>I am a board certified podiatrist practicing in Eugene, Oregon. I have used many skin substitutes on the market over the past years and also do wound care studies for the FDA as an investigator for the Center for Clinical Research based in San Francisco,</p>	<p><i>Thank you for your comments and for providing your clinical experience and the perspective on the greater ease of use for Epifix in clinical practice. Cost differences depend heavily on</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>California. By far the most utilized skin substitute in my office is Epifix, for both financial and medical reasons.</p> <p>Epifix is approved by Medicare, and comes in multiple sizes, so there is no waste compared to apligraf and other amniotic products. This is an important factor in financial based decision making, and I feel that it is an economically sound modality to utilize in all stalled wounds. In fact, the use of skin substitutes ultimately saves money by healing this at risk patient population sooner, which eliminates the cost of continued wound care modalities, infections, debridements and amputations. There is an actual financial cost as well as a human cost in the form of continued disability due to chronic open wounds.</p> <p>I feel that Medicare exemplifies the very most basic standard of care that should be available to all patients. It is my sincere hope that your program follows Medicare’s example and allows me to use this limb saving modality on all my patients.</p> <p>Epifix is by far the most easy to use and in my opinion, effective, skin substitute on the market. The shelf life of the product is five years, and it does not require refrigeration or other special storage circumstances. There is sound research supporting its efficacy in a variety of wounds, and I have attached references demonstrating this.</p> <p>Please feel free to contact me at any time if you have any questions or need additional information. Thanking you in advance for considering this important limb saving product for my patients who do not have it currently available to them.</p>	<p><i>wound characteristics and plan contracting, so EbGS’s coverage recommendations include all products with adequate evidence of effectiveness for each type of wounds, acknowledging that each plan will develop its own purchasing strategies. We did not identify any direct evidence from economic analyses to suggest that the use of skin substitutes is cost-saving.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
C1	<p>I am writing on behalf of the Oregon Podiatric Medical Association (OPMA) regarding the draft guidance for skin substitutes for chronic skin ulcers. Although OPMA does not advocate one skin substitute product over another, we do believe skin substitutes, in general, play a critical role in healing chronic wounds. Therefore, OPMA recommends HERC exercise caution before labeling a product as "not recommended."</p>	<p><i>Some products examined in this coverage guidance are recommended for coverage based on comparative evidence showing their effectiveness for given indications. The subcommittee's recommendations not to cover products with insufficient evidence of effectiveness could change as additional evidence becomes available. The subcommittee does not find a rationale for covering products not shown to be effective when there are effective alternatives.</i></p>
D1	<p>I would ask to please reconsider Epifix as Recommended. I have had excellent results in outpatient setting. I can obtain evidence data for you if necessary.</p> <p>[Submitted bibliography, including articles by Zelen and colleagues (2015), Serena and colleagues (2014), and Zelen and colleagues (2013), among others.]</p>	<p><i>Thank you for your comments. The commenter submitted two randomized controlled studies that would have met screening inclusion criteria had they been indexed in Medline at the time of the initial search (Zelen et al., 2015; Serena et al., 2014). A third randomized controlled study was included in the original evidence review (Zelen et al., 2013). The potential concerns regarding the validity of each of these trials are discussed below. The remaining trials submitted (Zelen 2013; Sheikh, 2013) are non-comparative trials and would not meet inclusion criteria. The final submitted document reviews various local coverage determinations (LCDs) as well as an explanation of the process by which Medicare contractors reach such decisions; relevant LCDs had already been noted and discussed in the original draft coverage guidance.</i></p> <p><i>Concerns regarding Zelen et al., 2015:</i></p> <ul style="list-style-type: none"> • <i>There were baseline differences in the three groups with respect to:</i> <ul style="list-style-type: none"> ○ <i>Mean wound size (2.6 cm² in the Apligraf group, 2.7 cm² in the EpiFix group, 3.3 cm² in</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<p><i>the standard care group)</i></p> <ul style="list-style-type: none"> ○ <i>Mean wound duration (129 days in the Apligraf group, 109 days in the EpiFix group, 113 days in the standard care group)</i> ○ <i>Percentage of patients with HbA1c>9 (30% in the Apligraf group, 10% in the EpiFix group, 25% in the standard care group)</i> <ul style="list-style-type: none"> ● <i>The primary outcome of complete wound closure at 4 and 6 weeks was assessed by an unblinded primary investigator.</i> ● <i>There are potential differences in the treatments and follow-up between groups. In the Apligraf and EpiFix groups, the products were applied weekly by study investigators. In the standard care group, daily dressing changes were done by the patients. Debridement was carried out in each group “as necessary.”</i> ● <i>Conclusions about comparative effectiveness for sustained wound healing beyond six weeks cannot be made because more than half (11/20) patients in the standard group exited the trial at 6 weeks.</i> <p><i>Concerns regarding Serena et al., 2014:</i></p> <ul style="list-style-type: none"> ● <i>The primary limitation of this study is its use of a surrogate measure (proportion of wounds achieving 40% reduction in size at 4 weeks) as the primary outcome. The trial does not report on complete wound healing, or any of the other critical or important outcomes pre-specified by HERC.</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<ul style="list-style-type: none"> • <i>Additional concerns are the use of an unblinded study investigator as the outcomes assessor and the absence of information on salient baseline characteristics including smoking and diabetes.</i> <p><i>Zelen et al., 2013 was included in the original evidence review. Concerns regarding this trial include:</i></p> <ul style="list-style-type: none"> • <i>This is a very small, single-center study with 13 patients in the treatment group and 12 patients in the control group.</i> • <i>There is no description of allocation concealment.</i> • <i>There were baseline differences in wound size between the two groups (2.6 cm² in the EpiFix group and 3.4 cm² in the standard care group. There were also differences between the groups with respect to mean body mass index (30 kg/m² in the EpiFix group and 35.4 kg/m² in the standard care group. Additionally, baseline information on smoking and glycemic control were not provided.</i> • <i>Dressing changes for the EpiFix group were performed by clinicians every two weeks, while the daily dressing changes in the standard care group were performed by patients or their caregivers.</i> • <i>The outcome assessor was unblinded.</i> • <i>Conclusions about comparative effectiveness for sustained wound healing beyond six weeks cannot be made because all but two of the 12 patients in the standard care group exited the trial at 6 weeks to</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<p style="text-align: center;"><i>pursue other treatments.</i></p> <p><i>Overall, these studies are at moderate to high risk of bias.</i></p>
E1	<p>In the latest draft guidance, the Commission recommends (with a weak recommendation) coverage of OASIS Wound Matrix for venous leg ulcers (“VLU”) and diabetic foot ulcers (“DFU”). We appreciate the Commission’s thoughtful review of the clinical evidence and comments from stakeholders to date. We support the recent changes in the draft coverage guidance, recommending for coverage of OASIS not only for VLU but also DFU, and we thank the Commission for its position.</p> <p>OASIS comprises OASIS® Wound Matrix and OASIS® Ultra Tri-Layer Matrix.</p> <p>Under the draft guidance, the Commission recommends coverage specifically for OASIS Wound Matrix for VLU and DFU. The OASIS product is currently sold as OASIS Wound Matrix (single layer) and OASIS Ultra Tri-layer Matrix (three layer) with OASIS Burn Matrix no longer commercially available. From a regulatory perspective, OASIS is a single product. Both OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix fall under the same 510(k), varying only in thickness (single (0.1 mm) versus tri-layer (0.3 mm)). OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix are both available in different size sheets allowing physicians to select the specific form most appropriate for their patients’ needs.</p> <p>The Commission has approved OASIS Wound Matrix for coverage based on the current clinical evidence. In our prior comment letter, we presented clinical evidence from multiple studies including a 2015 randomized controlled trial. We were pleased that as the Commission reviewed this evidence and other clinical evidence, the Commission decided to expand its coverage of OASIS Wound Matrix to include DFU. We would like to draw your attention to the fact that the 2015 randomized controlled trial evidence that we provided used the <u>OASIS Ultra Trilayer Matrix</u> versus standard care. In this trial, the results of which were published in 2015 in <i>Advances in Wound Care</i> 82 qualified</p>	<p><i>Thank you for your comments providing clarification regarding the range of available OASIS products. Both OASIS Wound Matrix and OASIS Ultra Tri-layer Matrix have been studied for DFU in RCTs. The included RCTs for VLU used OASIS Wound Matrix. We have revised our recommendations to recommend OASIS Wound Matrix and OASIS Ultra Tri-layer Matrix for DFUs and OASIS Wound Matrix for VLUs. We also deleted Q4103 as you requested.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>patients were randomly assigned to 12 weeks’ treatment with OASIS or standard care. The trial found that a greater proportion of the DFUs were closed by the end of the treatment period (week 12) for the OASIS group than for the standard care group (54% vs. 32%; p = 0.021). More ulcers were closed at each weekly study visit in the OASIS group than the standard care group beginning at week 3 (first visit showing ulcers closed). The overall treatment effect on proportion of ulcers closed over the 12 weeks and the interaction of treatment by week were found to be statistically significant in favor of the OASIS group. This study supports the effectiveness of the 3-layer product (Ultra Tri-layer) consistent with the evidence supporting single layer (Wound Matrix) product.</p> <p>Given that OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix represent different thicknesses of the same product, we request that the Commission recommend coverage for both, identified by HCPCS codes Q4102 and Q4124 respectively. In addition, we suggest that the Commission delete reference to OASIS Burn Matrix, identified by HCPCS Q4103, as it is no longer commercially available.</p>	
F1	<p>I write this letter in support of Oregon Health Plans, DMAP, ATRIO, etc. covering and approving the use of EPIFIX on ulcers. I have used this product over the past year and have saved many feet and toes from amputation, months of antibiotic use for the patient, hospitalizations etc. When insurances have chosen not to cover EPIFIX for some of my patients, the patient has endured months to almost years of debridements, hospitalizations, months of antibiotics and amputation of forefoot, foot or toe. I hope that you see the benefit to approving this product and appreciate your time in hearing from providers to have a better understanding of this product.</p>	<p><i>Thank you for your comments and for providing your clinical experience. However, no randomized controlled trials of EpiFix have demonstrated reductions in amputations or need for hospitalization. Alternative products are recommended for coverage for both indications.</i></p>
G1	<p>Alliqua BioMedical respectfully requests Biovance be included in this coverage guidance for Skin Substitutes For Chronic Skin Ulcers as we believe the evidence demonstrates net health outcome benefits compared to standard of care (SOC).</p>	<p><i>Thank you for your comments.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment				Disposition								
G2	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 15%;">Populations</th> <th style="width: 20%;">Interventions</th> <th style="width: 25%;">Outcomes</th> <th style="width: 40%;">References</th> </tr> </thead> <tbody> <tr> <td>Diabetic Foot Ulcers</td> <td>During 12 week trial each patient received up to 3 applications</td> <td>14 diabetic foot ulcer patients with 9 (55%) subjects showing complete wound closure within the 12 weeks of the study period.</td> <td>Publication: Letendre, S., et al., Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. Adv Skin Wound Care, 2009. 22(4): p. 161-6.</td> </tr> </tbody> </table>				Populations	Interventions	Outcomes	References	Diabetic Foot Ulcers	During 12 week trial each patient received up to 3 applications	14 diabetic foot ulcer patients with 9 (55%) subjects showing complete wound closure within the 12 weeks of the study period.	Publication: Letendre, S., et al., Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. Adv Skin Wound Care, 2009. 22(4): p. 161-6.	<p><i>None of the submitted references meet inclusion criteria. Letendre et al., 2009 is a non-comparative case series of 14 patients.</i></p>
Populations	Interventions	Outcomes	References										
Diabetic Foot Ulcers	During 12 week trial each patient received up to 3 applications	14 diabetic foot ulcer patients with 9 (55%) subjects showing complete wound closure within the 12 weeks of the study period.	Publication: Letendre, S., et al., Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. Adv Skin Wound Care, 2009. 22(4): p. 161-6.										
G3	Venous Leg Ulcers	Biovance placed initially and then at physician discretion (average 2.4 applications)	<p>Ulcers of venous stasis etiology comprised the largest subset within the chronic wound group with 85 wounds in 78 intent-to-treat (ITT) subjects. This analysis demonstrated clinical benefits in a real world, heterogeneous venous stasis ulcer population showing:</p> <ul style="list-style-type: none"> • 53% of the subjects in the Good Wound Care (GWC) Group completely closed in an average observation period of about 6 weeks. The impact of good wound care, as defined in this study, resulted in a 26% increase in the incidence of closure for the GWC Group, 	<p>“Key Factors Influencing Outcomes of Dehydrated, Decellularized Human Amniotic Membrane Allograft (DDHAM) Treated Venous Ulcers in a Real World Experience Study,” presented at Fall SAWC 2015, Las Vegas, NV.</p>	<p><i>None of the submitted references meet inclusion criteria.</i></p>								

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment				Disposition
			<p>compared to the ITT population.</p> <ul style="list-style-type: none"> • At an average of 8 weeks, the GWC Group’s venous stasis ulcers reduced in size by nearly 68%. • None of the venous stasis ulcers in the GWC Group that completely closed had reported infection prior to or during treatment while about one-third of those that did not close reported at least one episode of clinically suspected wound infection. 		
G4	Chronic Wounds (venous leg ulcers, diabetic foot ulcers)	Bioavance placed initially and then at physician discretion (Average application 2.3)	<p>The wound closure rate for Bioavance® is notable given the eight-week observation time point, when many chronic wound studies evaluate closure rate at 12 and/or 20 week endpoints; and the broad inclusion criteria for the patient and wound population. The typical wound size in the Use Registry Study was also almost double the size of the Margolis article (1.6 cm² vs. 3.1cm² in the Use Registry Study).</p> <p><u>Failure of prior therapies</u> Thirty-two subjects with a</p>	<p>Smiell JM, Treadwell T, Hahn HD, Hermans MH. Real World Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. Wounds. 2015;27(6):158-169.</p>	<p><i>Smiell et al., 2015 is a non-comparative study in which “any subject with a chronic wound who, in the investigator’s opinion, would benefit from treatment with DDHAM” was enrolled in a registry to track treatment outcomes .Thus, this is essentially a non-consecutive case series and does not meet inclusion criteria.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>variety of chronic ulcer types (venous, n = 14 [13 wounds]; diabetic foot, n = 10; pressure, n = 1; arterial [ischemic], n = 7 [4 wounds]) had failed previous courses of therapy with 1 or more advanced biologic therapies (ie, Apligraf, Organogenesis, Canton, MA; Dermagraft, Organogenesis, Canton, MA; Oasis, Smith and Nephew, Hull, UK; or Regranex, Smith and Nephew, Hull, UK). After a course of therapy that included the DDHAM allograft, nearly half (48.4%) of these ulcers closed despite previous biologic therapy failures. Those that did not close during a mean observation time of 10.3 weeks reduced in size from baseline by 50% (Table 8).</p>	
G5	<p>Improvements over currently available treatments include (1) a more rapid resolution of chronic non-healing wounds, as measured by time to closure and wound area reduction; (2) ability to treat a patient population unresponsive to currently available treatments; (3) reduced rate of device-related complications; and (4) decreased rate of subsequent therapeutic interventions.</p> <p>A prospective, multi-center registry was conducted, inclusive of all patients with any</p>	<p><i>As noted above there is no direct comparative evidence from randomized controlled trials demonstrating the effectiveness of Biovance.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>type of partial or full-thickness wound that would benefit from having a human amniotic membrane allograft as part of good wound care treatment (the “Use Registry Study”). The only requirement was that wounds were free of infection. The broad inclusion criteria resulted in a number of patients that were otherwise likely to be excluded from an RCT, either due to co-morbidities, age, wound size, or another factor</p> <p>A total of 19 sites across the U.S. enrolled 230 patients with a total of 246 wounds. Ultimately, the “intent to treat” (ITT) group (defined as any individual that was observed for greater than 3 days and had a documented wound start measurement and end measurement) consisted of 59 acute (traumatic and burn wounds) and 155 chronic wound patients (including diabetic, venous, arterial, pressure, and collagen vascular disease ulcers). The Good Wound Care (GWC) Group represents a large subset of the IIT population. Good wound care was described as compliance with the use of off-loading (DFU) or compression dressings/wraps (venous ulcers), maintenance of applied allograft, and without the concomitant use of enzymatic debriders.</p> <p>In the Use Registry Study, the chronic wound population demonstrated a closure rate of 50% at approximately 8 weeks. In contrast, Mostow demonstrated that 34% (20/58) of the control (standard care) arm in a venous leg ulcer study closed at 12 weeks with compression dressings and debridement as a SOC, and in the Apligraf® pivotal venous ulcer study, the control arm (n=100) achieved an incidence of complete closure in approximately 24% of the ulcers at 12 weeks.</p> <p>The wound closure rate for Biovance® is notable given the eight-week observation time point, when many chronic wound studies evaluate closure rate at 12 and/or 20 week endpoints; and the broad inclusion criteria for the patient and wound population. The typical wound size in the Use Registry Study was also almost double the size of the Margolis article (1.6 cm² vs. 3.1cm² in the Use Registry Study). This improvement in wound closure rates was most likely related to the use of Biovance® in combination with the SOC. The registry provides a persuasive demonstration of effectiveness for</p>	

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	Biovance® in a broad “real world” population of all wound types. In addition, there were no serious or unexpected adverse effects related to the use of Biovance® reported and subject and investigator opinions were generally positive.	
G6	<p>Citations to suggested commercial and Medicare coverage and guidance materials:</p> <ul style="list-style-type: none"> • Blue Cross Blue Shield Association - February 2016 Evidence Review – Bio-Engineered Skin and Soft Tissue Substitutes (submitted with this document) • Medicare Administrative Contractors References Attached- <ul style="list-style-type: none"> ○ Novitas Local Coverage Determination (LCD) - Application of Bioengineered Skin Substitutes to Lower Extremity Chronic Non-Healing Wounds (L35041) ○ First Coast LCD Application of Skin Substitute Grafts for Treatment of DFU and VLU of Lower Extremities (L36377) ○ WPS LCD (Retired 03/01/2016) - Application of Bioengineered Skin Substitutes (L34593) ○ Palmetto Future (effective date 05 17 2016) LCD – Application of Skin Substitutes (L36466) 	<p><i>The BCBS review bases their conclusion on the Smiell et al., 2015 trial which does not meet criteria for inclusion in the HERC review.</i></p> <p><i>Thank you for submission of various coverage policies. We would note that coverage of Biovance is variable and that many insurers regard the product as investigational or experimental.</i></p>
H1	<p>Osiris Therapeutics kindly requests a reconsideration review for the recommended coverage of Grafix® in this indication based on the following clarifications:</p> <ul style="list-style-type: none"> • Explanation of the biological characteristics of placental membranes, important and favorable properties for wound closure • Additional details of a randomized controlled trial (RCT) comparing Grafix to standard of care for the treatment of chronic diabetic foot ulcers, reported by Lavery et al in 2014. <ul style="list-style-type: none"> ○ Detailed description of subject characteristics ○ Clarification of study results ○ Randomization methodology ○ Maintaining the blind ○ Clarification of adverse event relationships to study product 	<p><i>Thank you for your comments and for providing clarification on several aspects of the Lavery et al., 2014 study. However, several concerns about the internal validity of the Lavery study persist:</i></p> <ul style="list-style-type: none"> • <i>There is still insufficient information to determine the appropriateness of the randomization scheme. The use of a central third party in treatment assignment likely satisfies the need for concealment of allocation.</i> • <i>There are potentially important baseline differences between the two groups, specifically, larger average ulcer size in the standard treatment group (3.93 cm² vs 3.41 cm² in the Grafix group), and the presence of</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<ul style="list-style-type: none"> ○ Characteristics of the study support the fact that this is a high-quality RCT ○ Review and assessment of Lavery et al by the National Institute for Health and Care Excellence (NICE) in the UK <p>In view of the independent evidence assessments indicating that the Lavery study is high quality and the meta-analysis indicating a larger strength of effect than other studies on advanced dermal substitutes, Osiris therapeutics requests that you reconsider your decision based on the enclosed information, and cover Grafix at Oregon Medicaid.</p>	<p><i>twice as many dorsal foot ulcers in the Grafix group (8 vs 4 in the standard care group).</i></p> <ul style="list-style-type: none"> • <i>The trial permitted the use of custom off-loading devices at the discretion of the investigator raising the possibility that this additional treatment was not equally applied in the treatment and control groups.</i> • <i>The overall rate of attrition in the trial exceeds 15% with 19 of 97 participants withdrawing prior to study completion. There were more dropouts in the control group (23%) compared with the Grafix group (16%).</i> • <i>There is a discrepancy in the reported outcome of complete wound healing which was originally stated as occurring in 31 of 50 patients in the Grafix group, but in later reporting on wound recurrence after the 12 week treatment phase the authors state that ulcers remained closed in 23 of 28 patients in the Grafix group.</i> • <i>Reporting the odds ratio for complete healing overstates the relative benefits of the treatment; it would be more appropriate to report a risk ratio (which in this case would be 2.91, 95% CI 1.61 to 5.26, as reported in the NICE appendix I submitted by the commenter).</i> • <i>Although the study states that “wound closure was independently confirmed via a central wound core laboratory” the initial determination of the primary outcome (complete wound closure) was made by an</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<p><i>unblinded site investigator.</i></p> <p><i>Thus, the Lavery study is at least at moderate risk of bias.</i></p> <p><i>We find the assessment of High GRADE quality in the NICE appendix to be perplexing in light of the potential risk of bias in this single trial. Furthermore, the final NICE recommendations for diabetic foot ulcers state that skin substitutes be considered an adjunct to standard care but do not recommend specific products.</i></p> <p><i>The Reguski et al., 2013 study (a retrospective non-consecutive case series) and the studies by Duan-Arnold et al., 2015 (all in vitro studies of the biologic properties of human amniotic membrane) do not meet inclusion criteria.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

References Provided by Commenters

ID/#	References
A1	Driver, V. R., Lavery, L. A., Reyzelman, A. M., Dutra, T. G., Dove, C. R., Kotsis, S. V., ... Chung, K. C. (2015). A clinical trial of Integra Template for diabetic foot ulcer treatment. <i>Wound Repair Regen</i> , 23(6), 891-900. DOI: 10.1111/wrr.12357.
D1	Zelen, C. M., Gould, L., Serena, T. E., Carter, M. J., Keller, J., & Li, W. W. (2015). A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. <i>Int Wound J</i> , 12(6), 724-732. DOI: 10.1111/iwj.12395.
D1	Serena, T. E., Carter, M. J., Le, L. T., Sabo, M. J., & DiMarco, D. T. (2014). A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. <i>Wound Repair Regen</i> , 22(6), 688-693. DOI: 10.1111/wrr.12227.
D1	Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. <i>Int Wound J</i> , 10(5), 502-507. DOI: 10.1111/iwj.12097.
G2	Letendre, S., LaPorta, G., O'Donnell, E., Dempsey, J., & Leonard, K. (2009). Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. <i>Adv Skin Wound Care</i> , 22(4), 161-166. DOI: 10.1097/01.asw.0000305463.32800.32.
G3	Hahn, H. D., & Smiell, J. M. (2015). Key factors influencing outcomes of dehydrated, decellularized human amniotic membrane allograft (DDHAM) treated venous ulcers in a real world experience study. Presented at Symposium on Advanced Wound Care Fall meeting. Retrieved from http://alliqua.com/biovance-venous-ulcers-poster/
G4	Smiell, J. M., Treadwell, T., Hahn, H. D., & Hermans, M. H. (2015). Real-world experience with a decellularized dehydrated human amniotic membrane allograft. <i>Wounds</i> , 27(6), 158-169. Retrieved from http://www.woundsresearch.com/article/real-world-experience-decellularized-dehydrated-human-amniotic-membrane-allograft
H1	Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: Results of a multi-centre, controlled, randomised, blinded, clinical trial. <i>Int Wound J</i> , 11(5), 554-560. DOI: 10.1111/iwj.12329.
H1	Duan-Arnold, Y., Uveges, T. E., Gyurdieva, A., Johnson, A., & Danilkovitch, A. (2015). Angiogenic potential of cryopreserved amniotic membrane is enhanced through retention of all tissue components in their native state. <i>Adv Wound Care (New Rochelle)</i> , 4(9), 513-522. DOI: 10.1089/wound.2015.0638.
H1	Duan-Arnold, Y., Gyurdieva, A., Johnson, A., Jacobstein, D. A., & Danilkovitch, A. (2015). Soluble factors released by endogenous viable cells enhance the antioxidant and chemoattractive activities of cryopreserved amniotic membrane. <i>Advances in Wound Care</i> , 4(6), 329–338. DOI: 10.1089/wound.2015.0637