

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Soluble Systems <i>[Submitted December 7, 2015]</i>
B	Smith & Nephew Advance Wound Management <i>[Submitted December 15, 2015]</i>

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Public Comments

ID/#	Comment	Disposition
A1	<p>“We would like to request that Oregon Medicaid reconsider the current non-coverage recommendation of Theraskin based on the following conclusions obtained from previously submitted clinical data. Upon review of the included references, Theraskin is as effective and at least equivalent to products currently recommended for coverage by Oregon Medicaid (Apligraf and Dermagraft).”</p>	<p>Thank you for your comment. We will address each of these studies individually below.</p>
A2	<p>“The 2011 Landman’s study concluded that Theraskin healed (closed) 60% of previously non-progressing diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) at 12 weeks and 74% at 20 weeks.”</p>	<p>Because this is a non-comparative retrospective case series, it does not meet individual inclusion criteria for the evidence review.</p>
A3	<p>“DiDomenico’s 2011 study concluded that TheraSkin had a greater rate of wound healing than Apligraf, both at 12 weeks (66.7% vs. 41.3%) and 20 weeks (66.7% vs. 47.1%).”</p>	<p>This study is included in the systematic review by Snyder, Sullivan, & Schoelles (2014), and has thus already been included in the evidence review for the draft coverage guidance. DiDomenico and colleagues did not report a test of statistical significance of the difference observed in the trial; the authors of the AHRQ report found that the difference was not statistically significant (p=0.21).</p>

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A4	<p>“Sanders 2014 clinical study showed wounds treated with TheraSkin are <u>twice</u> as likely to close by week 12, with half the number of grafts, versus wounds treated with Dermagraft.”</p>	<p>This manuscript is not indexed in Medline and therefore was not included in the evidence review. Furthermore, this small (n=23) RCT is of poor quality because of uncertainty about allocation concealment; baseline differences in study population (particularly with respect to number of diabetes medications, peripheral arterial disease, tobacco use and wound duration before treatment); differences in the number of office visits in each treatment group and use of offloading techniques; and inadequate blinding of participants, personnel, and outcomes assessors. Additionally, two authors are paid consultants of Soluble Systems and the research was funded by Soluble Systems.</p>
A5	<p>“Snyder, Sullivan and Schoelles 2012 (AHRQ Review included on page 26 of Oregon’s Draft Policy) evaluated the effectiveness of Apligraf and TheraSkin for DFUs with average wound sizes. The study also concluded that there were no significant differences reported in complete wound closure between the two products Apligraf 41% vs. Theraskin 67%, p=0.21.”</p>	<p>The AHRQ systematic review concluded that there is insufficient evidence to draw conclusions about the comparative effectiveness of Theraskin and Apligraf. The single trial that informed this comparison (DiDomenico, 2011) was a small (n=28) and imprecise trial deemed to be at moderate risk of bias by the authors of the AHRQ review.</p>

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A6	<p>“We respectfully recommend Oregon Medicaid to take into consideration that Theraskin is broadly and long accepted by the medical community and insurance carriers as medically and reasonably necessary therapy for the treatment of a broad range of chronic wound indications.</p> <ul style="list-style-type: none"> ○ All A/B <u>Medicare Administrative Contractors (MACs)</u> across the U.S., including Oregon, cover Theraskin. ○ 41 <u>Medicaid</u> plans throughout the country, including many states surrounding Oregon, also provide Theraskin coverage. ○ Many large <u>Private Health Plans</u> cover Theraskin including Regence, Kaiser, Cigna, Blue Cross Independence, HCSC (BCBS IL/NM/OK/TX), Amerihealth, BCBS Highmark, United Health Care, Tricare, UPMC Health Plan, etc.” 	<p>Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that Theraskin is commonly, but not uniformly, covered.</p>

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A7	<p>“Oregon Medicaid proposes a recommendation of non-coverage for Theraskin due to ‘product cost being moderate compared to alternative treatment options.’</p> <p>Listed within the Oregon Medicaid draft policy under ‘Frequency of application and cost of skin substitute’ Apligraf and Dermagraft product costs were based upon clinical studies while Theraskin’s product cost was based upon Medicare LCD limits. Thus, causing Theraskin associated cost-savings to appear modest when compared to alternative treatments.</p> <p>We respectfully recommend that Oregon Medicaid reevaluate Theraskin’s product cost in a similar manner as Apligraf and Dermagraft or adults <u>all</u> product cost using Medicare’s’ LCFD maximum limits.”</p>	<p>The right-hand column of the frequency of application document presented to EbGS was based on the maximum number of applications from the study, while lower limits were used for other products. The rationale column does note that most patients in the study only required a single application.</p> <p>At its November 3, 2015 meeting, the subcommittee recognized that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level. Therefore we have removed a specific number of applications for each product from the right column of the applications table and added information on application frequency used in the studies for those products recommended for coverage.</p> <p>However, the subcommittee still finds insufficient evidence of effectiveness to recommend this product for coverage.</p>
B1	<p>“In the draft guidance, the Commission recommends (with a weak recommendation) coverage of OASIS Wound Matrix for venous leg ulcers (‘VLU’). We support the recommendation for coverage of OASIS for VLU, and we thank the Commission for its position.”</p>	<p>Thank you for your comment.</p>
B2	<p>“By contrast, the Commission recommends against coverage of OASIS Wound Matrix for the treatment of diabetic foot ulcers (‘DFU’) concluding that there is ‘inadequate evidence of benefit, other alternatives available, and its costliness.’ We respectfully disagree with this recommendation for the reasons summarized below.</p>	<p>The study by Cazzell and colleagues was not indexed in Medline at the time of the search; it has subsequently been indexed. The previous RCTs of Oasis for DFU were included in the AHRQ review. Landsman, et al (2008) found no statistically significant difference between OASIS and Dermagraft for DFU wound healing at 12 weeks. Niezgoda, et al (2005) compared OASIS to Regranex Gel and found a</p>

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	<p>There is new evidence, published after the 2012 Agency for Healthcare Research & Quality ('AHRQ') systematic review from supporting the use of OASIS in the treatment of diabetic foot ulcers. This evidence was not considered by the Commission.</p> <p>The findings from a prospective, randomized controlled trial of OASIS Ultra Trilayer Matrix versus standard care were published in 2015 in <i>Advances in Wound Care</i>. In this 16 week trial, 82 qualified patients were randomly assigned to 12 weeks' treatment with OASIS or standard care. The trial demonstrated 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 ($p = 0.047$) in favor of the OASIS group.</p> <p>In the draft coverage guidance, the Commission defined five outcomes considered in its evaluation:</p> <ul style="list-style-type: none"> ▪ Critical Outcomes <ul style="list-style-type: none"> – Deep soft tissue or bone infection – Complete wound healing ▪ Important Outcomes <ul style="list-style-type: none"> – Quality of life – Time to complete wound healing – Adverse effects <p>The randomized, controlled study above included three of these outcomes and supports the use of OASIS compared to the standard care with statistically significant results.”</p>	<p>difference in healing at 12 weeks that approached statistical significance (49% vs 28% respectively, $p=0.06$).</p> <p>Cazzell is an open-label RCT of 82 patients comparing OASIS to standard care for treatment of DFU. In the intervention group, OASIS was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator (standard care included sliver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS group (54%) compared with the standard care group (32%) ($p=0.021$). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and inadequate blinding, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS compared to standard care.</p>

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B3	<p>“OASIS has the same level of general acceptance by the medical community as Apligraf.</p> <p>While not a consideration for coverage, the Commission does review the policy landscape and payer coverage policies. Under Medicare, with respect to local coverage determinations, the policy must be based on published authoritative evidence derived from definitive RCTs or other definitive studies, and general acceptance by the medical community (standard of practice), as supported by sound medical evidence. Use of OASIS in the treatment of DFU is well established in the payer community:</p> <ul style="list-style-type: none"> ▪ All of the MACs cover OASIS for VLU and DFU ▪ OASIS has positive coverage based on medical necessity from 760 private payers” 	<p>Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that OASIS is commonly, but not uniformly, covered.</p>
B4	<p>“OASIS is the least costly product per application compared with Apligraf and Dermagraft.</p> <p>The Commission’s recommendation against coverage for OASIS for DFUs is based, in part, on the Commission’s conclusion that the product is costly. In fact, as is shown below, OASIS has a lower cost per application compared with Apligraf and Dermagraft—two other products recommended for coverage for diabetic foot ulcers.” <i>See chart in submitted comments.</i></p>	<p>OASIS does have a lower unit cost than Apligraf and Dermagraft. However, as noted in the cost comparison chart, studies which showed effectiveness of OASIS used 8 to 10 applications of this product per patient versus smaller quantities used in the studies showing effectiveness for Dermagraft and Apligraf.</p> <p>The subcommittee does recognize that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level.</p>
B5	<p>“The Commission stated in the draft guidance that OASIS ‘is not recommended for coverage for diabetic foot ulcers based on inadequate evidence of benefit, other alternatives available, and its costliness.’ We believe that this new evidence, together with the position taken by private and public payers as well as the relative low cost of OASIS compared to Apligraf and Dermagraft, support coverage for OASIS for the treatment of diabetic foot ulcers.”</p>	<p>Thank you for your comment.</p>

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A2	Landsman A. S., Cook J., Cook E., Landsman A. R., Garrett P., Yoon J., Kirkwood A., Desman E. (2011). A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. <i>Foot Ankle Spec.</i> 4(1):29-41. DOI: 0.1177/1938640010387417.
A3	DiDomenico, L., Landsman, A. R., Emch, K. J., Landsman, A. (2011). A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. <i>Wounds</i> , 23(7):184-9.
A4	Sanders, L., Landsman, A. S., Landsman, A., Keller, N., Cook, J., Cook, E., Hopson, M. (2014). A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. <i>Ostomy Wound Manage</i> , 60(9):26-38
B2	Cazzell, S. M., Lange, D. L., Dickerson, J. E. Jr., Slade, H. B. (2015). The Management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: A randomized controlled trial. <i>Adv Wound Care</i> , 4:1-8. DOI: 10.1089/wound.2015.0645.