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Re: **LCD Reconsideration Request - Oxygen and Oxygen Equipment (L33797)**

Dear DME MAC Medical Directors:

Inotec AMD Inc. (Inotec) submits the enclosed reconsideration of the local coverage determination for oxygen and oxygen equipment (LCD L33797) to establish Medicare coverage criteria for continuous topical oxygen therapy (CTOT) devices, such as the NATROX® Oxygen Wound Therapy System (the NATROX® System), for the treatment of diabetic foot ulcers. This letter outlines the clinical evidence in support of Medicare Part B coverage for CTOT devices under the durable medical equipment benefit. We have also enclosed the following materials:

- Proposed coverage criteria for the NATROX® System (Appendix A);
- Full-text copies of published clinical evidence (Appendix B); and
- FDA 510(k) Clearance Summary (Appendix C).

Please do not hesitate to contact me at Craig.Kennedy@natroxwoundcare.com with any questions regarding this request. We appreciate your consideration of this request.

Sincerely,

Craig Kennedy
CEO
Inotec AMD Inc.

I. INTRODUCTION

Inotec is a wound care company developed out of Cambridge University that manufactures and markets the NATROX® System, a device used to apply continuous topical oxygen to aid in the treatment of chronic wounds such as skin ulcers (e.g., diabetic and pressure injuries/ulcers), amputations, skin grafts, burns, and frostbite. The safety and efficacy of continuous topical oxygen therapy (CTOT) using devices like the NATROX® System have been supported by multiple randomized control trials (RCTs), which consistently show improved wound healing with CTOT, at a faster healing rate than standard of care, particularly for the treatment of chronic diabetic foot ulcers (DFUs).

Roughly 35% of diabetics develop a foot ulcer during their lifetime, including over 4 million Medicare beneficiaries.[1] Many of these wounds are complex, hard-to-heal wounds that take extended periods of time to heal, despite specialist care in multidisciplinary settings. Standard of care (SOC) treatments (sharp debridement, offloading, infection control, and moisture management) often do not achieve sufficient healing, and certain second-line treatments can be contraindicated for patients or offer limited evidence of efficacy. Without proper treatment, DFUs can result in serious infections and amputations, necessitating costly acute inpatient care.[2] In light of these complexities, it is critical that clinicians have access to the full range of therapies that provide safe, effective, and convenient treatment for Medicare beneficiaries suffering from DFUs.

The Centers for Medicare & Medicaid Services (CMS) acknowledged the increased evidence on chronic wound healing for topical oxygen therapy in 2017 when the Agency rescinded a long-standing national non-coverage decision, instead allowing the MACs to determine coverage for the topical application of oxygen.[3] The DME MACs considered the evidence for TOT (both intermittent and continuous) in an April 2020 revision to the joint LCD for oxygen and oxygen equipment (L33797) and concluded that "[t]opical oxygen delivery systems (E0446) will be denied as not reasonable and necessary."[4] Since the LCD revision was finalized, however, multiple studies have been published that further support the reasonably and necessary use of CTOT for the treatment of chronic wounds, particularly for patients with chronic non-healing diabetic foot ulcers (DFUs). This evidence includes a 145-patient RCT by Serena et al., and a 200-patient retrospective study by Kaufman et al., both of which are discussed further below.

Furthermore, we understand that the prior LCD reconsideration did not fully address questions raised by the DME MACs regarding the discrete population that benefits from topical oxygen therapy, and did not provide specificity as to the modality of topical oxygen therapy most

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[1] Zhang Y, Lazzarini PA, McPhail SM, et al. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care. 2020;43(5):964. doi:10.2337/dc19-1614.

[2] For instance, a 5-year study of approximately 1 million foot ulcer admissions found that diabetics accounted for 91.8% of ulcer-related hospital admissions, 96.1% of minor amputations, and 82.9% of major amputations. *See* Hicks CW, Selvarajah S, Mathioudakis N, et al. Burden of Infected Diabetic Foot Ulcers on Hospital Admissions and Costs. Ann Vasc Surg. 2016;33:149-158. doi:10.1016/j.avsg.2015.11.025.

[3] CMS, CAG-00060R: Decision Memo for Hyperbaric Oxygen (HBO) Therapy (Section C, Topical Oxygen) (Apr. 3, 2017).

[4] Joint DME MAC Publication, Local Coverage Determination (LCD): Oxygen and Oxygen Equipment (L33797) (revision effective Aug. 2, 2020).

likely to result in wound healing. The additional published evidence discussed here confirms the clinical benefits of CTOT in the discrete population of patients with chronic non-healing DFUs, and that the topical oxygen modality with sufficient evidence for Medicare coverage at this time is limited to continuous topical oxygen therapy.

Inotec hereby submits this LCD reconsideration request of LCD L33797 in order to reflect the totality of the clinical evidence in support of CTOT's efficacy in treating chronic diabetic foot ulcers, inclusive of these recently published studies. We respectfully request that the determination of non-coverage for topical oxygen delivery systems be removed from LCD L33797 and replaced with the evidence-based coverage criteria in Appendix A, which describe the circumstances under which CTOT is "reasonable and necessary" for the treatment of non-healing DFUs.

II. OVERVIEW OF TOPICAL OXYGEN AND THE NATROX® SYSTEM

A. Physiology of Topical Oxygen Application

Oxygen plays a critical role in the healing of chronic wounds, given oxygen's role in energy production, cell metabolism, growth processes, and collagen formation.[5] Unsurprisingly, a common feature in chronic wounds is persistent wound hypoxia, and improving oxygenation to the tissues can be an important aspect of any treatment pathway. Two methods to deliver oxygen to wounds include hyperbaric oxygen (HBO) and topical oxygen therapy (TOT). CMS considers HBO therapy (HBOT) to be a modality (currently covered by Medicare) in which the entire body is exposed to oxygen under increased atmospheric pressure, requiring the patient to sit in a pressurized oxygen chamber for several hours each week. In contrast, topical oxygen therapy is a method whereby a local supply of oxygen is applied directly to a wound via intermittent or continuous delivery techniques. Continuous TOT involves the continuous application of oxygen to the wound, delivered by a tube supplying pure oxygen at a normobaric pressure and low flow rate directly to the wound bed. Intermittent TOT involves the application of pressures slightly above atmospheric through an airtight chamber or soft sided 'bag' that is sealed around a wound present on the trunk or limb of the body. Unlike HBOT, neither intermittent nor continuous provision of TOT is dependent on the systemic circulation reaching the wound.

This LCD reconsideration request pertains to specific modality of CTOT, which has been the subject of the more research than the alternative modalities in the field of topical oxygen, as outlined below.

B. The NATROX® System

The NATROX® System (Figure 1) is a portable, wearable technology that is indicated to provide continuous topical oxygen to aid in the healing of chronic wounds across the care continuum. It consists of three main elements: the NATROX® Battery, the NATROX® Oxygen Generator, and the NATROX® Oxygen Delivery System. The NATROX® Oxygen Generator is powered by the rechargeable/interchangeable Batteries and generates oxygen through water electrolysis to deliver pure oxygen flow rate of 15 ml per hour. The NATROX® Oxygen Delivery

[5] *See* Oropallo AR, Serena TE, Armstrong DG, Niederauer MQ. Molecular Biomarkers of Oxygen therapy in Patients with Diabetic Foot Ulcers. Biomolecules 2021;11, 925. https://doi.org/10.3390/biom11070925.

System is a sterile, web-like wound interface connected to the Oxygen Generator that is used to optimize the flow and diffusion of oxygen across the wound bed. It has been designed to work with any standard secondary dressing, thus giving incredibly flexibility in application. The NATROX® System received a CE mark to allow for sale in Europe in June 2012 and received FDA clearance in July 2012.[6]

Figure 1. NATROX® System Components

III. MEDICARE BENEFIT CATEGORY – DURABLE MEDICAL EQUIPMENT

The NATROX® System meets the definition of durable medical equipment under applicable CMS regulations[7]:

- **Durability:** The NATROX® Oxygen Generator and rechargeable battery have an expected product life of at least three years and can withstand repeated use. The Oxygen Delivery System is supply necessary for the effective use of the NATROX System, and is to be used for a maximum of 7 days before replacement.

- **Primarily and customarily used to serve a medical purpose:** The NATROX® System is an FDA-cleared, prescription-only device. The NATROX® System has been the subject of numerous clinical trials and has been demonstrated in the published clinical evidence described below to be safe and effective in treating chronic wounds of various types,

[6] FDA, 510(k) Clearance Summary, No. K112634 (July 3, 2014).

[7] *See* 42 CFR 414.202.

including DFUs, an indication that can result in substantial negative health effects up to and including infection and amputation.

- **Generally not useful to an individual in the absence of an illness or injury:** The NATROX® System is available only by prescription and may only be prescribed to aid in the treatment of chronic wounds.

- **Appropriate for use in the home:** The NATROX® System is designed to be worn by the patient over a continuous period and is prescribed for use in the home setting.

We believe the NATROX® System is described by HCPCS code E0446 (topical oxygen delivery system, not otherwise specified, includes all supplies and accessories) as an item of DME.

IV. OVERVIEW OF CLINICAL EVIDENCE SUPPORTING COVERAGE

Inotec believes that a close review of the published evidence demonstrating effective CTOT use in treating DFUs, particularly in comparison to other covered treatments available to Medicare beneficiaries, strongly supports coverage of CTOT devices for this wound type. Before 2021, the safety and efficacy of CTOT was supported by results of multiple RCTs, involving a combined sample of nearly 300 patients. Recently, the results of both a large multicenter RCT of CTOT and a 200-patient retrospective study were published.

We understand that the medical directors are exceedingly familiar with Medicare's "reasonable and necessary" standard for coverage, but we do believe two aspects of that standard should be highlighted for the review of CTOT: (1) that the service or item be safe and effective; and (2) that the service or item be "at least as beneficial as an existing and available medically appropriate alternative." This section summarizes the clinical evidence for CTOT and demonstrates the adequacy of support for determining that CTOT is reasonable and necessary for the treatment of DFUs.

A. Pre-2021 Clinical Evidence

Prior to 2021, the evidence of CTOT's effectiveness in treating DFUs has included three RCTs, all with well-controlled study designs. The total sample size across these trials was nearly 300 patients, and follow-up periods ranged from 8-12 weeks of active treatment. Each of these trials examined the effect of TOT on complete wound healing, such that primary efficacy endpoints were largely consistent across all three studies. Most importantly, two trials exhibited statistically significant positive treatment effects in the treatment groups, and analysis presented in the third study identified a positive treatment effect specifically among the Medicare-aged population most relevant for this reconsideration request:

- **Niederauer et al. (2018)**[8] conducted a double-blind, placebo controlled RCT involving 146 patients assessed over a 12-week treatment phase. The primary endpoint was

[8] Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. J Wound Care. 2018;27(Sup9):S30–S45. doi:10.12968/jowc.2018.27.Sup9.S30.

full wound closure, defined as complete re-epithelialization with no drainage as assessed by treating clinician and blinded observer. For the intent-to-treat cohort, the rate of wound closure with TOT was 46%, nearly 25 percentage points greater than the rate of wound closure in the placebo group ($p = 0.016$).

- **Driver et al. (2017)**[9] conducted a blinded multicenter RCT involving 128 patients classified as intent-to-treat, followed over 12 weeks of treatment. The authors defined their primary endpoint as complete wound closure by week 12, and they conducted a subgroup analysis stratified by patient age ≥ 65 years. The authors' exclusion criteria restricted the study to patients without comorbidities, which may have resulted in the reduced wound-size typical among subjects. Although the authors found no statistically significant difference in complete wound healing between study arms, their subanalysis among Medicare-age subjects found a statistically significant increase in complete wound healing in the TOT group, as compared to the control group (82% vs. 50%, $p = 0.049$).

- **Yu et al. (2016)**[10] conducted a prospective RCT involving 20 patients assessed over 8 weeks of treatment. The authors used percentage of wounds healed as their primary endpoint, defined as the percentage of wounds measuring 0 cm^2 in surface area. Rate of healing was assessed as a secondary endpoint. The trial demonstrated that 90% in the TOT arm, versus 30% in the control arm, experienced complete healing, and TOT significantly decreased mean wound size from baseline ($p < 0.001$). There was no statistically significant decrease in mean wound area size in the control arm. TOT's differential improvement in wound healing was most notable in Grade 2 and Grade 3 ulcers.

CTOT has also been the subject of multiple non-randomized studies, including five (5) observational studies encompassing a sample size of 136 patients, with a significant portion suffering from DFUs. All of these studies concluded that CTOT improves ulcer outcomes to varying degrees and based on a range of endpoints. Most notably, a 2018 case series published by Kaufman et al. evaluated 100 patients (13 with DFUs) treated with the NATROX System.[11] The authors assessed endpoints of complete wound closure and weekly wound reduction rates; adherence to therapy was also evaluated. The authors report that the device was well- tolerated in patients (88% with complete adherence). Foot ulcers treated with TOT (which combined arterial and diabetic ulcers) experienced significant overall wound reduction of 74% from baseline. Examining patients receiving > 25 days of TOT, the researchers reported higher complete closure rates for foot ulcers as compared to leg ulcers (57% vs. 47%,
respectively).

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[9] Driver VR, Reyzelman A, Kawalec J, French M. A Prospective, Randomized, Blinded, Controlled Trial Comparing Transdermal Continuous Oxygen Delivery to Moist Wound Therapy for the Treatment of Diabetic Foot Ulcers. Ostomy Wound Manage. 2017;63(4):12–28.

[10] Yu J, Lu S, McLaren AM, Perry JA, Cross KM. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. Wound Repair Regen. 2016;24(6):1066–1072. doi:10.1111/wrr.12490.

[11] Kaufman et al. (2018), J Wound Care. 2018;27(7):426–433. *See also* Hayes et al. (2017), J Wound Care. 2017;26(11):652–660 (10 patients evaluated over an 8-week period); Kemp et al. (2011), J Diabet Foot Compl. 2011;3(2):6–12 (11 patients evaluated for complete wound healing of DFUs with TOT, showing 86% of ulcers treated with TOT healed completely).

B. New Publications

We understand from DME MAC feedback that prior coverage requests were not sufficiently focused on evaluating the efficacy of a particular modality (e.g., continuous versus intermittent TOT) nor a particular wound type (DFUs, venous leg ulcers, etc.), nor was the evidence presented in a manner that demonstrated the population most likely to benefit from this therapy. As discussed below, these gaps are addressed by two new studies, including a large, prospective, multicenter, RCT from Serena et al., evaluating the use of CTOT in 145 patients with hard-to-heal DFUs, and a 200-patient retrospective study from Kaufman et al., evaluating the conditions under which TOT is most effective in healing chronic wounds.

1. Serena et al. (2021) – Randomized Control Trial

Serena et al. (2021)[12] conducted a multi-center RCT in 19 outpatient centers across the United States to assess the efficacy of the NATROX® System in the treatment of 145 patients with hard-to-heal DFUs. The study was designed to address evidentiary questions raised by CMS and the DME MACs in prior coverage evaluations, including (among other things) smaller sample sizes in prior studies, shorter treatment periods, uncertainty about the standard of care being used in the reviewed studies, lack of a defined run-in period, and lack of systematic wound measurement.

A full text copy of the publication is enclosed at Appendix B. Several important aspects of the study's design are highlighted below:

- Run-In Period to Establish Wound Chronicity: Based on concerns that previous studies had failed to account for baseline differences in wound characteristics, the researchers designed the study to include a 4-week run-in period to exclude patients whose wounds were capable of healing with standard of care treatment. During the initial two weeks of the run-in period, all patients were documented as having received standard of care (SOC) treatment, as determined by their treating practitioner. If wound size reduced by 20% or more during this period, the patient was excluded; patients that experienced a reduction in wound size of less than 20% were eligible to proceed in the study protocol. All eligible patients then underwent a second 2-week run-in period, during which SOC was continued under a specific regimen set by the researchers. Again, only patients that experienced a <20% reduction in in wound size during this second 2-week period were eligible to proceed to randomization.

- Well-Defined SOC, Endpoints, and Wound Measurements: All study subjects received investigator-imposed SOC therapy for the final 2 weeks of the run-in period, and the control group received this SOC through the study's 12-week duration (for a total of 14 weeks). SOC therapy was defined to include sharp debridement, reduction of bacterial burden, standardized dressings to maintain proper moisture balance, and total contact casting. The investigators provided all dressings and contact casting used by study sites to

[12] Serena TE, Bullock NM, Cole W, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. J Wound Care. 2021;30(Sup5):S7-S14. doi:10.12968/jowc.2021.30.Sup5.S7.

ensure consistency during the researcher-determined SOC periods. The primary endpoint (complete would closure) was defined as complete reepithelialization without drainage. During the 12-week treatment period, all subjects were assessed at visits occurring once per week. Wound measurements were obtained using a planimetry imaging system (Tissue Analytics, Inc.), which allowed for consistent, objective wound measurements to be obtained.

- Large Sample Size, Discrete Wound Type, Majority Medicare-Age Representation: A total of 145 patients were enrolled in the study and included in the ITT analysis, after assessments of 224 patients for eligibility, making this trial among the largest ever conducted of TOT. Patients were considered eligible for inclusion if they had ISDA stage 1-2 DFUs.[13] Whereas previous trials and observational studies examined CTOT efficacy in wounds of diverse etiology, this RCT focused exclusively on patients with DFUs. In addition to the consistent clinical criteria for wound inclusion, the investigators designed their protocol to ensure enrollment of a substantial number of Medicare-age patients. Ultimately, more than half of subjects (54.5%) were over age 65.

The trial results, presented for both intent-to-treat (ITT) and per-protocol (PP) analyses, demonstrated that patients receiving CTOT experienced statistically significant improvement in complete wound healing. Specifically, the ITT analysis showed that 44% of patients receiving CTOT experienced complete healing, whereas only 28% healed in the SOC group—a statistically significant, 16 percentage-point difference between the groups (p=0.044). Looking to the secondary endpoint of wound size reduction, patients receiving CTOT were, on average, more likely to experience greater reductions in ulcer area. The difference in reduction between each cohort was statistically significant in the PP analysis, with patients treated with CTOT experiencing on average a 70 cm^2 reduction in wound size, as compared to a 40 cm^2 reduction in the control group.

This RCT represents a substantial advancement in the base of evidence available for CTOT's efficacy, and its study design addresses perceived gaps in prior studies identified by CMS and the DME MACs. By focusing on a well-defined target population and evaluating a particular modality, we believe this evidence provides a basis for reconsidering L33797 and establishing Medicare coverage for CTOT based on the coverage criteria proposed herein.

2. Kaufman (2021) – Large Retrospective Study

In addition to the new RCT discussed above, Kaufman (2021)[14] recently completed a multicenter, retrospective study of 200 patients treated with CTOT using the NATROX® System. This publication also presents evidence not previously considered by the DME MACs. While the patient sample included wounds of mixed etiology, 15% of patients had DFUs, all of which had been treated with standard of care wound care yet failed to heal. In addition, 61% of study

[13] This was generally consistent with Wagner stage 1-2. Wound staging data were missing for two patients, and one patient was recorded as having a Wagner stage 3 DFU.

[14] Kaufman, H. Topical oxygen therapy used to improve wound healing in a large retrospective study of wounds of mixed aetiology. *Wounds International.* 2021;12(2)63–68.

participants were over age 65. For purposes of analysis, wounds were grouped into four categories based on the status of wound healing (ranging from ≥ 90% closed to < 10% closed) to assess the wound characteristics among responders and non-responders. The study reported that venous ulcers and DFUs were most likely to respond to CTOT, and that wound response was determined, in part, by length of time treated with CTOT. [15]

V. PROPOSED COVERAGE CRITERIA

Taking into account this published clinical evidence, we request that the DME MACs reconsider LCD L33797 to include coverage criteria for CTOT devices like the NATROX® System when used to treat patients diagnosed with chronic non-healing DFUs. We specifically request that the proposed coverage criteria presented below and reproduced in Appendix A be included in L33797 to effectuate coverage. These criteria are consistent with existing Medicare coverage policies requiring 30 days of SOC prior to use of advanced modalities, while reflecting elements that define the relevant patient population examined in published studies to benefit from CTOT delivered by devices like the NATROX® System.

The proposed definition for standard of care (SOC) wound therapy is tailored to the treatment guidelines for patients with DFUs to ensure that use of CTOT is accompanied by appropriate management of potential complications in this patient population. For example, debridement to remove devitalized tissue and the maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings are common standard of care treatments for all types of wounds. Vascular assessment, nutritional evaluation, and glucose control are commonly assessed in diabetic patients and likewise should be addressed in conjunction with the application of CTOT to prevent potential delays in wound healing caused by complications and to improve the likelihood of success in the application of CTOT. Similar coverage criteria have been adopted by CMS and contractors with respect to other treatments for diabetic foot ulcers.[16]

Studies and consensus guidelines support the application of a four-week / 30-day period to assess the likelihood of success with standard of care therapy prior to application of an advanced therapy. Literature supports a determination that a reduction of less than 50% in diabetic ulcers at 4 weeks is an overall predictor of outcome for healing.[17] A study published in 2003 by Sheehan et al. showed the ability of the 4-week healing rate to predict complete healing by 12 weeks by demonstrating that 58% of patients who exceeded a benchmark of 53% wound area reduction in 4 weeks achieved healing by 12 weeks, while only 9% of patients who did not achieve the 53%

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[15] *Id*.

[16] *See e.g.*, Pub. 100-03, Medicare National Coverage Determination (NCD) Manual, Section 20.29 - Hyperbaric Oxygen Therapy; First Coast Service Options, Local Coverage Determination (LCD): Application of Skin Substitute Grafts for Treatment of DFU and VLU of Lower Extremities (L36377).

[17] *See* Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003;26:1879–1882; Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg 2002;137:822–827.

benchmark healed by 12 weeks ($p < 0.001$).[18] Accordingly, the "4-week 50% wound area reduction" has been adopted and confirmed as an indicator for predicting healing at 12 weeks, including by certain Medicare contractors.[19]

> *Topical oxygen therapy (TOT) is reasonable and necessary for the treatment of non-healing diabetic foot ulcers when the following criteria (A-D) are satisfied:*
>
> *A. The device applies low-flow oxygen (<1 liters/minute) to the wound surface continuously and is used in a manner consistent with its FDA approved or cleared indication;*
>
> *B. The beneficiary has a documented diagnosis of Type 1 or Type 2 diabetes mellitus;*
>
> *C. The beneficiary has a diabetic foot ulcer classified as Wagner grade I or II; and*
>
> *D. The patient has failed to respond meaningfully to standard of care wound therapy for the treatment of diabetic foot ulcers.*
>
> *a. "Standard of care wound therapy for the treatment of diabetic foot ulcers" should include a comprehensive medical evaluation, vascular assessment, metabolic/nutritional evaluation, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present.*
>
> *b. Failure to respond meaningfully to standard of care wound therapy occurs when the patient's wound-size reduction does not exceed 50% over 4 weeks of treatment. In many cases, failure to respond meaningfully may be accompanied by evidence of minor but not meaningful improvement, including changes in drainage (color, amount, consistency), inflammation, swelling, pain and/or tenderness, wound dimensions (reduction of less than 50%), granulation tissue, necrotic tissue, tunneling or undermining.*

[18] *See also* Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. *Adv Wound Care (New Rochelle)*. 2015;4(9):560-582.

[19] *See, e.g.,* Wisconsin Physician Services, Local Coverage Determination (LCD): Wound Care (L37116).