



## PRIOR AUTHORIZATION POLICY

**POLICY:** Regranex® (becaplermin gel, 0.01% –Smith & Nephew)

**TAC REVIEW DATE:** 07/15/2015

**LAY CRITERIA EFFECTIVE DATE:** Previously in Effect

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### OVERVIEW

Regranex is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous (SC) tissue or beyond and have an adequate blood supply when used as an adjunct to, and not a substitute for, good ulcer care practices, including initial sharp debridement, pressure relief and infection control.<sup>1</sup> Regranex is a recombinant human platelet-derived growth factor (PDGF) for topical administration and has similar biological activity as endogenous PDGF, which promotes the chemotactic recruitment and proliferation of cells involved in wound repair and enhances the formation of granulation tissue.<sup>1</sup> The efficacy of Regranex has not been established for the treatment of pressure ulcers and venous stasis ulcers and has not been evaluated for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into SC tissue (Stage I or II International Association Enterostomal Therapy [IAET] staging classification), or ischemic diabetic ulcers. The effects of Regranex on exposed joints, tendons, ligaments, and bone have not been established in humans.

### Efficacy

#### *Diabetic Ulcers*

Published studies and combined meta-analyses have documented the efficacy of Regranex (0.01% and becaplermin gel 0.003%) in diabetic neuropathic ulcers.<sup>2-6</sup> The largest fully published trial<sup>3</sup> was a multicenter, double-blind, placebo-controlled study where 382 adults with type 1 or 2 diabetes and lower-extremity chronic ulcers (classified as Stage III or IV, as defined in the IAET guide to chronic wound staging) of at least 8 weeks duration were randomized to receive becaplermin gel 0.003%, Regranex, or placebo (vehicle gel) in addition to good wound care, which included debridement. Therapy continued until complete wound closure occurred or for a maximum of 20 weeks. Treatment with Regranex led to an increased incidence of complete healing by 43% compared with placebo (P = 0.007). Complete wound healing occurred in 50% of patients given Regranex (n = 61/123) compared with 35% of patients given placebo (n = 44/127). The time to achieve complete healing was decreased by 32% for patients given Regranex compared with placebo gel (86 days vs. 127 days, respectively; estimated 35<sup>th</sup> percentile, P = 0.013). Efficacy results with the becaplermin gel 0.003% were similar to those noted in the placebo group. In a 3-month follow-up evaluation, the incidence of ulcer recurrence was approximately 30% in all groups showing that the durability of ulcer closure was similar among the groups.

A published study compared the healing rates of Regranex (control agent) with OASIS® Wound Matrix after 12 weeks of treatment.<sup>7</sup> OASIS Wound Matrix is comprised of porcine-derived acellular small intestine submucosa, which is compatible with human tissue and is approved as a medical device and is indicated for the management of wounds including: partial- and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears), drainage wounds, and surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence).<sup>8-9</sup> At the end of Week 12, the healing rate was 49% (n = 18/37) for OASIS vs. 28% (n = 10/36) for Regranex (P = 0.055). The mean time to healing was also not

statistically different between the two groups (67 days for OASIS and 73 days for Regranex;  $P = 0.245$ ). OASIS did have statistically significantly higher healing rates for plantar ulcers (52% [ $n = 14/27$ ] vs. 14% [ $n = 3/21$ ] for Regranex;  $P = 0.014$ ) and in patients with type 2 diabetes (63% [ $n = 12/19$ ] vs. 29% [ $n = 8/28$ ] for Regranex;  $P = 0.034$ ), while there was no statistical difference in patients with type 1 diabetes (33% [ $n = 6/18$ ] vs. 25% [ $n = 2/8$ ] for Regranex;  $P = 1.0$ ). At the 6-month follow-up, the recurrence rate for OASIS was 25% ( $n = 2/8$ ) and for Regranex was 33% ( $n = 2/6$ ). There was no overall difference in the rate of complications/adverse events (AEs) for OASIS ( $n = 17$ ) and Regranex ( $n = 10$ ), however, there was a higher number of wound infections in the study ulcer ( $n = 9$ ) for OASIS than for Regranex ( $n = 3$ ).

Regranex is the first platelet-derived topical growth factor to demonstrate therapeutic efficacy, albeit modest, in healing neuropathic ulcers. No similar agent exists and because there is a paucity of well-designed, placebo-controlled studies in the area of wound healing, comparison between different modalities are difficult.<sup>3</sup> Most cases of diabetic neuropathic ulcers heal with conventional ulcer care and data have suggested that a linear correlation may exist between the degree of aggressive debridement and the level of healing.<sup>10-11</sup> However, for diabetic patients that have poorly healing neuropathic ulcers, despite adequate perfusion and a reasonable trial of wound care, this product may provide benefits.<sup>11</sup>

### *Pressure Ulcers*

Studies have also shown Regranex to have potential efficacy in the treatment of full thickness chronic pressure ulcers (Stage III or IV as defined by the National Pressure Ulcer Advisory Panel [NPUAP]).<sup>14-16</sup> In one trial, adults with non-healing full thickness pressure ulcers were given a standard regimen of good wound care and were randomized to one of four treatment arms for 16 weeks, which included Regranex ( $n = 31$ ) and placebo gel ( $n = 31$ ).<sup>16</sup> The incidence of complete healing was significantly greater for those given Regranex (23%), no patients receiving placebo had complete healing ( $P = 0.005$ ). At least 90% healing was noted in 58% of patients given Regranex compared to 29% assigned to placebo gel ( $P = 0.021$ ).

### *Other Ulcer/Wound Types*

Regranex has also been used in other chronic non-healing ulcers. In one retrospective chart review, 11 out of 17 venous stasis ulcerations healed with use of Regranex in an average of 67.6 days.<sup>21</sup> In another retrospective chart review of Regranex use in patients with chronic lower extremity ulcers (venous ulcer, lipodermatosclerosis ulcer, neurotrophic [diabetic and non-diabetic] ulcers, and multifactorial [mixed arterial and venous] ulcers), 14 of the 21 target ulcers healed completely with a mean time to complete healing of 111.1 days.<sup>22</sup>

Reports in the literature also note Regranex being used for surgical wounds or for surgical wound dehiscence.<sup>21,23-24</sup> In a small double-blind, preliminary trial, patients ( $n = 21$ ) with wound separation after cesarean delivery or benign abdominal gynecological procedures were randomized to receive Regranex or placebo (SurgiLube®) starting the day after the wound opened.<sup>23</sup> Wounds that were treated with Regranex closed more rapidly ( $35 \pm 15$  days) compared to those given placebo ( $54 \pm 26$  days;  $P = 0.05$ ). Additional studies are needed to determine the effectiveness of Regranex for wound granulation and closure. Case reports and/or case series note that Regranex has also been used successfully for the treatment of ulcerated hemangiomas (including ulcerated perineal hemangiomas in infants),<sup>25-26</sup> chronic orbital ulcers,<sup>27</sup> scleroderma skin ulcers,<sup>28</sup> ulcerative lichen planus,<sup>29</sup> necrobiosis lipoidicum diabeticorum,<sup>30</sup> chronic irradiated wounds/ulcers (including wounds/ulcers with no granulation tissue at baseline),<sup>31-33</sup> wound dehiscence (following total laryngectomy) with pharyngocutaneous fistula,<sup>24</sup> and ulceration due to a stingray injury.<sup>34</sup>

### **Guidelines**

### *Lower-Extremity Neuropathic Disease*

Guidelines from the Wound Ostomy and Continence Nurses (WOCN) Society published in 2004 for the management of wounds in patients with lower-extremity neuropathic disease recommend that use of Regranex can be considered for foot ulcers after necrotic tissue has been debrided, infection is cleared, and adequate perfusion has been established.<sup>12</sup>

### *Diabetic Ulcers*

The Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and treatment of diabetic foot infections recommend that all diabetic patients with a foot wound should receive appropriate wound care, which usually consists of debridement, redistribution of pressure off the wound to the entire weight-bearing surface of the foot, selection of dressings that allow for moist wound healing, and control excess exudation.<sup>35</sup> No adjunctive therapy has been proved to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents, growth factors, granulocyte colony stimulating factors, hyperbaric oxygen therapy, or negative pressure wound therapy. The guidelines note that although an initial study with the PDGFs demonstrated benefit, subsequent investigations have not shown these treatments to improve healing, or they have been conducted in a fashion where the data cannot be interpreted in the context of routine care.

The 2005 g=Guidelines for diabetic foot care, developed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society, note that ulcers without a deep crater and with no bone exposed can be treated with sharp debridement of infected or necrotic tissue and surrounding thick callus.<sup>13</sup> Dry or moist saline dressings can be used in combination with therapeutic shoes or footwear in small ulcers. In addition, for larger ulcers the guidelines note that healing may be expedited with one of the newer hydrocolloid-type dressings, or platelet-derived wound healing factors.

### *Pressure Ulcers*

Guidelines from the WOCN Society updated in 2010 for the prevention and management of pressure ulcers recommend that Regranex can be considered an adjunctive therapy to enhance the healing (treatment) of pressure ulcers (no stage specified).<sup>17</sup> Other guidelines and references have also supported the consideration of adjuvant use of Regranex or platelet-derived growth factor for managing pressure ulcers which are not healing with conventional therapy.<sup>18-20</sup>

## **Safety**

In 2008, after a follow-up from the Food and Drug Administration (FDA) about the ongoing safety review of Regranex,<sup>36-37</sup> the Regranex package labeling was revised to include a boxed warning noting that in a post-marketing retrospective cohort study, there was an increased rate of mortality secondary to malignancy observed in patients treated with three or more tubes of Regranex.<sup>1</sup> Also, additional detail was added to the warnings section in regards to a follow-up study performed to monitor for any evidence of adverse events (AEs) such as increased numbers of cancers and a retrospective study of a medical claims database.<sup>1,36-37</sup> This additional detail notes that malignancies distant from the site of application have occurred in Regranex users in both a clinical study and in post-marketing use. An increased rate of death from systemic malignancies was seen in patients who have received three or more tubes of Regranex gel.<sup>1</sup> In the follow-up study, 491 of the 651 patients from two randomized, controlled studies were followed up for a median of 20 months to identify malignancies diagnosed after the end of the controlled studies. The rate of cancer diagnosis in this follow-up period was 3% (n = 8/291) for Regranex users and 1% (n = 2/200) for vehicle/standard of care users, providing a relative risk of 2.7 (95% Confidence Interval [CI]: 0.6, 12.8). The types of cancers were varied and all were remote from the treatment site. In the retrospective medical claims database study, the incidence and mortality rates of

cancer were assessed in 1,622 Regranex users and 2,809 matched comparators. Both groups had a similar incidence rate of all cancers (10.2 per 1,000 person-years for Regranex and 9.1 per 1,000 person-years for the comparators (adjusted rate ratio 1.2 [95% CI: 0.7, 1.9]). However, there was more of a difference between the groups in regards to mortality from all cancers. The incidence rate of mortality from all cancers was 1.6 per 1,000 person-years for Regranex users and 0.9 per 1,000 person-years for comparators (adjusted rate ratio 1.8 [95% CI: 0.7, 4.9]), but the most prominent difference was the mortality incidence from all cancers among patients who received three or more tubes of Regranex gel which was 3.9 per 1,000 person-years vs. 0.9 per 1,000 person-years for comparators (adjusted rate ratio 5.2 [95% CI: 1.6, 17.6]). The retrospective medical claims database involved diabetic patients aged 19 years and older with no history of cancer and similar diagnoses, similar drug use, and similar use of health services who were applying Regranex to foot and leg ulcers or who did not receive treatment with Regranex.<sup>36-37</sup> Because inadequately treated ulcers can lead to complications such as infections, especially foot ulcer infections which are a leading cause of hospitalization among diabetics, the FDA recommends that Regranex be used only when the benefits are expected to outweigh the risks described in the labeling.<sup>37</sup>

The average amount of Regranex gel used per patient has not been fully evaluated, but most likely is highly variable and dependent upon the area of the ulcer or wound and the timeframe of healing. In an open-label study using Regranex in diabetics with lower extremity ulcers, the average amount of Regranex gel used was 27.2 g (slightly less than two-15 g tubes) for patients with baseline target ulcers < 2 cm<sup>2</sup>.<sup>4</sup> However, only 57% of patients in this study had a baseline ulcer of this size. Another study comparing Regranex use with the OASIS Wound Matrix in diabetic ulcer patients also had similar Regranex usage of slightly less than two-15 g tubes per patient.<sup>7</sup> And a retrospective chart review study of 51 patients with lower extremity ulcerations due to various causes had an average Regranex tube use of 1.8 tubes per patient (tube size was not described).<sup>21</sup> In addition, 78% (n = 40/51) of these patients used two or fewer Regranex tubes.

## **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Regranex. All approvals are provided for *5 months* unless otherwise noted below.

**Automation:** None.

## **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Regranex is recommended in those who meet the following criteria:

### **Food and Drug Administration (FDA)-Approved Indications**

- 1. Lower Extremity Diabetic Neuropathic Ulcer(s) that is/are Classified as Stage III or IV** (see addendum for NPUAP classification system).<sup>1</sup> Approve for 5 months if Regranex is used in adjunct to good ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

Regranex is indicated for the treatment of lower extremity diabetic neuropathic ulcer(s) that extend into the subcutaneous (SC) tissue or beyond and have good blood supply.<sup>1</sup> Regranex is indicated as an adjunct to, and not a substitute for, good ulcer/wound care practices including initial sharp debridement, pressure relief, and infection control.

### Other Uses with Supportive Evidence

- Clean and Granulating Ulcer/Wound Classified as Stage II** (e.g., Stage II diabetic neuropathic ulcers and pressure ulcers). Approve if the patients meets the following criteria **A and B**.
  - The patient has tried one other standard ulcer/wound care therapy (e.g., debridement, topical therapies [collagenase]) for at least 4 weeks; AND
  - Regranex will be used in adjunct to good ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

- Granulating Ulcer/Wound Classified as Stage III or IV**<sup>14-20,24-26,28,31-34</sup> (e.g., pressure ulcers, venous stasis ulcers, other diabetic ulcers) (see addendum NPUAP classification system<sup>38-39</sup>). Approve if Regranex is used in adjunct to good ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

Several studies<sup>14-16</sup> and case reports and/or case series<sup>24-26,28,31-34</sup> have found Regranex to be efficacious for treating/healing other non-diabetic neuropathic ulcers or wounds classified as Stage III or above. In addition, the WOCN Pressure Ulcer guidelines<sup>17</sup> list Regranex as an adjunctive therapy in the healing of pressure ulcers, and other references from the Wound Healing Society,<sup>18</sup> Canadian Association of Wound Care,<sup>19</sup> and a recent review<sup>20</sup> also support consideration of use of Regranex for treating non-healing chronic pressure ulcers. Regranex is indicated as an adjunct to, and not a substitute for, good ulcer/wound care practices including initial sharp debridement, pressure relief, and infection control.<sup>1</sup>

### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Regranex has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

Coverage of Regranex is not recommended in the following circumstances:

- First-Line Therapy for the Treatment of Stage II Ulcers/Wounds.** Standard ulcer/wound care should be used first-line.
- Prevention of Ulcers/Wounds.** The efficacy of Regranex for prevention has not been evaluated.
- Treatment of Wounds/Ulcers Classified as Stage I.** These wounds are not open and therefore are not appropriate for Regranex therapy.
- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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## HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
Integrated Policy	--	06/06/2012	--
Annual revision	--	06/05/2013	--
Annual revision	For clean and granulating ulcer/wound classified as Stage II, criteria were clarified to require one other standard ulcer/wound care therapy be tried prior to approval.	07/02/2014	07/18/2014
Annual revision	No criteria changes	07/15/2015	Previously in effect

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; \* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.

## ADDENDUM

### National Pressure Ulcer Advisory Panel (NPUAP) Pressure Ulcer Stages<sup>38-39</sup>

#### NPUAP Pressure Ulcer Stage Definitions<sup>38-39</sup>

**Suspected Deep Tissue Injury:** Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue.

**Stage I:** Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

**Stage II:** Partial-thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open-ruptured serum-filled blister.

**Stage III:** Full-thickness tissue loss. Subcutaneous fat may be visible but bone, tendon, or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

**Stage IV:** Full-thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

**Unstageable:** Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed.

\* Note that the WOCN was formerly called the International Association of Enterostomal Therapy (IAET).<sup>11,16</sup>