NON-FORMULARY USE OF BECAPLERMIN (REGRANEX™) GEL IN VETERAN PATIENTS

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria are based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

Becaplermin (Regranex®) is a recombinant human platelet-derived growth factor (rhPDGF) with biologic activity similar to endogenous platelet-derived growth factor (PDGF). Biologic activity of PGDF includes encouraging chemotaxis and proliferation of cells responsible for wound repair and augments production of granulation tissue. Becaplermin gel is FDA approved for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond (stage III or IV as defined by the Wound Ostomy Continence Nurse Association (WOCN), formerly called the International Association of Enterostomal Therapy (IAET), and the National Pressure Ulcer Advisory Panel (NPUAP) for staging chronic wounds) and possess an adequate blood supply. There are two other wound classification systems that are commonly used to assess the severity of a diabetic wound. The University of Texas wound classification system assesses wounds for depth, presence of ischemia and infection. The Wagner system assesses wound for depth and for the presence of osteomyelitis or gangrene.

Becaplermin is to be used as an adjunct to, not a replacement for, good ulcer care including sharp debridement, non-weight bearing, standard of care moist dressing changes, and prevention and treatment of infection. Becaplermin gel is **not** approved for the treatment of pressure, venous stasis or other types of non-diabetic related ulcers.

I. Indication for use of becaplermin gel in veterans: ***All of the following criteria must be met for use of becaplermin gel.***

a. Patients should have a recent glycosylated hemoglobin (hemoglobin A1c or HbA1c) less than 8. If not, active treatment to improve glycemic control, including referral to Endocrinology if appropriate, should be attempted.
b. Patients should be nonsmoking and if not, plans for smoking cessation should be initiated.
c. Classification of diabetic wound severity: (All wounds must be free from infection)
   - WOCN and NPUAP (formerly IAET): Stage III or IV lower extremity diabetic ulcer (extending through the dermis into the subcutaneous tissue or beyond).
   - University of Texas: Diabetic ulcer classified as a grade 2 or 3, stage A (clean, nonischemic, noninfected wounds penetrating to the tendon or capsule or into bone or joint).
   - Wagner: Grade 1 or 2 (partial/full thickness ulcer or probing to tendon or capsule)
d. The wound must have an adequate blood supply measured by oscillometry (at least 2 units), transcutaneous oxygen pressure (TcpO2 >30 mm Hg), ankle-brachial index (ABI) >0.7, ankle systolic pressure >70 mm Hg, or toe pressure >30 mm Hg.
e. Identification and removal of the underlying etiology of the wound (e.g. poor fitting shoes, reinforce non-weight bearing, etc.) The provider will consult the appropriate department to evaluate the patient for the proper orthotic to maximize minimal to non-weight bearing of the affected area.
f. The wound must be free from infection.
g. If present, lower extremity edema should be treated.
h. The patient's nutritional status has been addressed for any protein and/or calorie malnutrition.
i. The patient must have failed standard therapy for at least 2 months (careful-frequent debridement, moist dressing changes and non-weight bearing).

j. The provider must assess the ulcer, either in person or via telemedicine, on a weekly to biweekly basis to assess ulcer response and to determine need for further debridement.
k. The provider must recalculate a new amount of becaplermin gel to be applied at every visit.

II. Education:

a. Patients and care providers must be educated regarding proper application of becaplermin gel, storage (must be refrigerated) and cost of the product. An assessment of their ability to properly apply becaplermin gel should be done.
b. Patients and care providers need to be educated on proper wound care including dressing changes not involving application of becaplermin gel (second dressing change of the day). They also need to be educated on the **importance** of non-weight bearing measures.

III. Length of Therapy:

a. Patient and providers must be committed to 10 weeks of becaplermin gel. The maximum duration of treatment is 20 weeks.

IV. When to Discontinue Therapy:

a. Becaplermin gel should be discontinued if there is <30% decrease in ulcer size after 10 weeks of treatment or the ulcer is not completely healed after 20 weeks.
b. If the patient or caregiver is unable to properly apply the becaplermin gel.
c. If the patient is non-compliant with non-weight bearing measures or moist dressing changes.
d. If the patient is non-compliant with weekly to biweekly follow up appointments (misses 2 consecutive appointments).

V. Restricted providers:

The decision to prescribe becaplermin gel should be made by providers who are experienced in chronic care of recalcitrant ulcers (Vascular/wound clinics, plastic surgery clinics, podiatry clinics, etc). In addition, providers should be able to see patients on a weekly to biweekly basis for debridement, reinforcement of non-weight bearing measures, assessment of ulcer response, and recalculation of the new amount of becaplermin gel to be applied.

VI. Dosage and Administration:

The amount of becaplermin gel applied will vary depending upon the size of the ulcer. To calculate an adequate dose of becaplermin gel, measure the greatest length multiplied by the greatest width of the ulcer in inches or centimeters.

To calculate the proper dose in inches (in): 0.65 g of becaplermin per inch

Tube Size	Formula
15 g tube	Length (in) **X** Width (in) **X** 0.6

To calculate the proper dose in centimeters (cm): 0.25 g of becaplermin per centimeter

Tube Size	Formula
15 g tube	Length (cm) **X** Width (cm) divide by 4

The calculated dose of becaplermin gel (in centimeters or inches) should be squeezed out onto a clean surface (wax paper) in a linear fashion. The measured dose can be

transferred from this clean surface using an applicator (tongue blade or cotton swab) and spread over the ulcer's surface. The dose of becaplermin gel should be applied only once a day and spread evenly over the surface of the ulcer to produce a thin continuous layer about 1/16 of an inch in thickness. The gel should then be covered with saline moistened gauze and a secondary dressing and left for approximately 12 hours. For the second dressing change of the day, the gel can be gently rinsed off using saline or water and a saline moistened dressing applied to the ulcer without reapplication of becaplermin gel. It should be left for the remaining 12 hours of the day.

Instruct patients that application of excessive becaplermin gel has not been shown to be of greater benefit in ulcer healing.

VII. Warnings/Adverse Effects:

Becaplermin gel is contraindicated in patients with known hypersensitivity to parabens and patients with a known neoplasm(s) at application sites.

Adverse effects seen in clinical trials were similar to those seen with placebo gel. Erythematous rash was the only adverse effect that occurred to a greater extent with becaplermin and placebo gel compared to good ulcer care alone (2% versus none, respectively).

VIII. Monitoring Parameters:

At each appointment, assessment of ulcer response and patient compliance with good ulcer care should be determined (non-weight bearing, no smoking, dressing changes, ability to properly apply becaplermin gel).

If the ulcer does not decrease by approximately 30% in size after 10 weeks of therapy, continued treatment with becaplermin should be reassessed. Treatment with becaplermin gel should continue until the ulcer is completely healed or a **maximum** of 20 weeks. If the ulcer has not completely healed after 20 weeks, continued treatment with becaplermin should be reassessed.

IX. Cost:

Becaplermin gel 15 g tube: $ 274.14
Cost of 20 weeks of therapy: $ 1,370.70 (5 tubes)

X. Outcomes: (Clinical Trial Evidence)

In 2000, the FDA released a document intended to provide guidance to industry for the development of products used in the management of chronic cutaneous ulcers (e.g. venous stasis, diabetic foot and pressure ulcers) or burns.[17] In this report, recommendations are made regarding labeling claims, outcome measures, and trial design. The authors considered several outcome measures to be of clinical importance with incidence of complete wound closure being the most desired outcome. Others included accelerated wound closure (time to complete closure) and improved quality of healing (cosmetic and durability).

Also in this report, authors caution that “wounds differ pathophysiologically, making it difficult, if not impossible, to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type.” Therefore, if a product is found to increase the incidence of complete wound closure in a diabetic foot ulcer, the results of that trial cannot be extrapolated to those with pressure wounds or other wound types.

Diabetic Foot Ulcers:

To date, two investigators (Steed, et al, and Weiman, et al) have shown becaplermin gel to be statistically more effective than placebo or good wound care alone in healing chronic, full-thickness, neuropathic diabetic ulcers. In the study by Steed, et al, complete wound healing occurred in 48% of those receiving becaplermin 30mcg/g compared to 25% of those receiving placebo gel (p=0.02). However, in the study by Weiman, et al, the ulcer healing benefit was statistically significant (p=0.01) in the group receiving becaplermin 100 mcg/g gel (50%), but not the 30 mcg/g gel (36%), which was equal to placebo gel (35%). In both of these studies, the time to complete ulcer healing was decreased in the becaplermin groups compared to placebo gel or good ulcer care groups by approximately 30-40 days. A third study by D'Hemecourt, et al, compared placebo gel (NaCMC-vehicle contained in becaplermin) to good ulcer care alone. They also included a becaplermin 100mcg/g arm that was not powered for statistical significance. Although no statistical analysis was provided, authors noted that the placebo gel appeared to have a beneficial effect on ulcer healing compared to good wound care alone (complete healing 36% versus 22%, respectively). The final study, available only in abstract form, compared becaplermin 100 mcg/g gel to good ulcer care alone. Complete ulcer closure occurred in 36% of patients in the becaplermin group compared to 32% of patients receiving good ulcer care alone, which was not statistically different.
Explanations for the conflicting data regarding the use of becaplermin gel may include non-compliance with good ulcer care on the part of the patient and/or provider; inadequate education on the proper use of becaplermin gel; and insufficient follow up care for ulcer assessment and debridement. Compliance with these factors is extremely important to the success of complete ulcer healing.

A more recent open-label study was conducted in 134 patients with diabetes mellitus and full thickness lower extremity ulcers.[21] All patients were given becaplermin 100 mcg/d and an Adaptic (non-adhering dressing) with their once daily saline dressing changes for 20 weeks or until complete ulcer healing. Outcome measures included percentage of patients with complete ulcer healing, time to complete healing and ulcer recurrence (at 6 months). To encourage patients not to bear weight on the ulcer site, a product called Aircast Foamwalker was used after debridement and continued throughout the study. In addition, off-loading devices were used at the discretion of the clinician (e.g. crutches, wheelchair or Darco Med-Surg shoes). After complete wound healing, patients were provided with fitted insoles and footwear (New Balance Athletic shoes or PW Minor Xtra-Depth shoes). Complete healing occurred in 57.5% of wounds with a recurrence rate of 21% at 6 months. Mean time to complete healing was 63 days. When interpreting the results of this study, one needs to consider that the study did not include a control group, was not blinded, used a specialized nonadherent dressing that may have had some benefit in wound healing. In addition, great care was taken to achieve a non-weight bearing status, and insoles and footwear were provided at the completion of the study. As a result, the same results may not be reproducible in usual care.

As a result of the limited and modest results of the published data regarding the use of becaplermin gel in diabetic patients with non-healing, full-thickness, neuropathic, lower extremity ulcers, it is recommended that becaplermin use be restricted to those patients meeting the above listed criteria.

Pressure Ulcers:

The use of becaplermin gel was assessed in the healing of pressure ulcers in 3 different phase I/II randomized, double-blind, placebo-controlled studies.[18-20] In the first study, 41 patients with stage 3 or 4 pressure ulcers were randomized to becaplermin 100 mcg/d, 300 mcg/d or placebo for 28 days. In this study, change in ulcer volumes (using alginate molds) was the primary endpoint. After 28 days, the median ulcer volumes decreased to 83%, 29%, and 40% of initial size in the placebo, becaplermin 100 mcg/d and 300 mcg/d groups, respectively. After adjusting for initial volume, ulcer volumes were less in the becaplermin groups versus placebo (p=0.056). The authors concluded that

becaplermin **may** be beneficial in accelerating the healing of pressure ulcers. In the second study, 20 patients with pressure ulcers were randomized to receive 1, 10 or 100 mcg/ml/d or placebo for 28 days. Primary outcome measures were percentage of initial depth of ulcer and percentage of initial volume. The lowest doses of becaplermin were not different from placebo but the 100mcg/ml/d dose was associated with a smaller ulcer size (percentage of initial depth: 14.1 vs. 34.9, $p \leq 0.05$) and volume (percentage of initial volume: 6.4 vs. 21.8, $p=0.12$) compared to placebo. In the final study, 124 patients with pressure ulcers were randomized to receive becaplermin gel 100 mcg/d, 300 mcg/d or placebo for 16 weeks or until complete healing. Study endpoints were incidence of complete wound closure, the incidence of $\geq$ 90% wound closure and the percentage of initial ulcer volume at endpoint. Both becaplermin groups were associated with a higher incidence of complete wound closure (23%, 19%, 0% for 100mcg/d, 300 mcg/d or placebo, respectively. $p<0.008$ vs. placebo), $\geq$ 90% closure (58%, 59%, 29%, respectively. $p \leq 0.021$ vs. placebo) and a lower percentage of initial wound volume ($p<0.025$ for all comparisons). There were no differences between the 100 and 300 mcg/d becaplermin groups.

In 1999, a phase III study, designed to evaluate the effectiveness of becaplermin in healing pressure ulcers, was stopped due to inconsistent findings for efficacy which did not support the findings in the third study discussed above.

Published data, evaluating the benefit of becaplermin in healing pressure ulcers, is limited. Furthermore, the primary outcomes assessed in two of the published studies were not clinical outcomes included in the FDAs guidance for industry in developing agents for healing chronic cutaneous wounds or burns. In addition, a phase III trial was stopped in 1999 due to inconsistencies in efficacy. As a result, becaplermin cannot be recommended for the healing of pressure ulcers.

Other Chronic Ulcers:

A retrospective analysis was performed to determine the healing benefits of becaplermin in a variety of ulcer types.[22] Fifty-one patients with 59 chronic ulcers were identified and reviewed. The types of ulcers in this investigation included 17 venous stasis ulcers, 17 neuropathic ulcers, 4 ischemic ulcers, 18 wound dehiscence, 1 traumatic wound, 1 ulcer due to necrotizing fasciitis and 1 due to skin necrosis as a result of drug use. Forty of the 59 ulcers (67.8%) healed completely. Average time to complete healing was 99.9 days (range 7-589 days). The authors did not analyze incidence of complete healing and time to healing by ulcer type.

Conclusion

Data from prospective, controlled clinical trials evaluating becaplermins benefit in healing various types of ulcers (other than diabetic ulcers) is lacking. As a result, becaplermin should not be used routinely for ulcers other than those ulcers that are non-healing, full-thickness, neuropathic, lower extremity diabetic ulcers meeting the criteria listed on page 1 and 2 of this document.

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XI. References:

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Becaplermin Gel Monitoring Sheet

- For appropriate becaplermin gel candidates, refer to the criteria for nonformulary use.
- A new amount of becaplermin gel to be applied should be recalculated at each visit.
- Becaplermin should be discontinued if the ulcer has not decreased in size by 30% after 10 weeks or has not completely healed after 20 weeks of treatment.

Calculation of dosage: (15 g tube size)

Inches: Length (in) **X** Width (in) **X** 0.6 (0.65 gram of becaplermin per inch length)

Centimeters: Length (cm) **X** Width (cm) divided by 4 (0.25 gram of becaplermin per centimeter length)

Patient Name_____SSN_____

Duration and location of ulcer:_____

HGB A1C_____Date taken:_____

Date/week	**Ulcer size** (length)	**Ulcer size** (width)	**Ulcer size** (depth)	**Becaplermin Dose** (cm or inches)	**Comments**