Drug Coverage Policy

Effective Date.....11/1/2025
Coverage Policy Number.....IP0495
Policy Title..... Regranex

Regranex

- Regranex® (becaplermin gel – Smith & Nephew)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

Regranex, a human platelet-derived growth factor (PDGF), is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have

an adequate blood supply.[1] Regranex is indicated as an adjunct to, and not a substitute for, good ulcer care practices.

Limitations of Use: The efficacy of Regranex has not been established for the treatment of pressure ulcers and venous stasis ulcers.[1] The effects of Regranex on exposed joints, tendons, ligaments, and bone have not been established in humans. Regranex is not intended to be used in wounds that close by primary intention.

Disease Overview

Diabetic Foot Ulcers

Diabetes mellitus is an endocrine disorder due to overall deficiency of insulin (Type 1) or defective insulin function (Type 2).[2] Abnormal glucose metabolism leads to chronic hyperglycemia and associated macro and microvascular diseases. Many adults live with macrovascular and microvascular diseases; macrovascular disease affects cardiovascular and cerebrovascular systems, whereas microvascular diseases includes nephropathy, retinopathy, and neuropathies. Diabetic peripheral neuropathy is one of the main causes of diabetic foot ulcers. Patients with diabetes mellitus have a total lifetime risk of diabetic foot ulcer as high as 25%.

There are several different systems that exist for wound classification, including the Wagner classification, University of Texas wound classification, the Site, Ischemia, Neuropathy, Bacterial Infection, Depth (SINBAD) classification, and the Infectious Diseases Society of America/International Working Group on the Diabetic Foot (IDSA/IWGDF), among others.[6]

The pivotal studies for Regranex utilized the International Association of Enterostomal Therapy (IAET).[1] In this classification system, there are five stages.[10] They are defined in the following way:

- Stage 1: non-blanchable erythema of intact skin; the heralding lesion of skin ulceration.
- Stage 2: partial thickness skin loss involving epidermis and/or dermis. Ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater.
- Stage 3: full thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.
- Stage 4: full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone, or supporting structures.

Efficacy

Diabetic Foot Ulcers

The efficacy of Regranex on the incidence of and time to complete healing in lower extremity diabetic neuropathic ulcers was assessed in four randomized, controlled studies.[1] Participants received either Regranex 0.003% or 0.01% or placebo; treatments were applied once a day and covered with a saline-moistened dressing. All participants had Stage III or Stage IV lower extremity diabetic neuropathic ulcers (i.e., wounds that extended into subcutaneous tissue or beyond), as defined by the International Association of Enterostomal Therapy (IAET). Diabetic ulcers were of at least 8 weeks duration and had an adequate blood supply. In the four trials, 95% of the ulcers measured in area up to 10 cm^2, and the median ulcer size at baseline ranged from 1.4 cm^2 to 3.5 cm^2. All treatment groups received ulcer care, which included initial sharp complete debridement, a non-weight bearing regimen, systemic treatment for wound-related infections if present, moist saline dressings changed twice a day, and additional debridement, as necessary. Participants were treated until complete healing, or for a period of up to 20 weeks. Treatment failure was defined as ulcers that did not show an approximately 30% reduction in initial ulcer area after 8 to 10 weeks of therapy.

In the first study, the incidence of complete ulcer closure for Regranex 0.003% was 48% compare with 25% for placebo gel ($P = 0.02$).[1] In the second study, the incidence of complete ulcer closure

for Regranex 0.01% was 50% compared with 36% for Regranex 0.003% and 35% for placebo; only the result for Regranex 0.01% was significantly different from placebo gel (P = 0.01). Incidences of complete ulcer closure were 44% for Regranex, 36% for placebo, and 22% for good ulcer care alone in Study 3. Finally, the incidence of complete ulcer closure for Regranex 0.01% and good ulcer care alone were 36% and 32%, respectively, in Study 4; these results were not statistically significant.

Guidelines
The American Diabetes Association Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes (2025) lists Regranex as an option for advanced wound therapies.[5] The Guidelines for the Management of Patients with Lower-Extremity Wounds due to Diabetes Mellitus and/or Neuropathic Disease (2021) list Regranex as an adjunctive therapy; adjunctive therapies are recommended for wounds that do not demonstrate improvement (i.e., 50% wound area reduction) after 4 weeks of standard therapy (moderate strength recommendation).[6]

The International Working Group on the Diabetic Foot, alongside the Infectious Disease Society of America, do not address PDGF therapies (i.e., Regranex).[7] The 2019 Guideline for Management of Wounds in Patients with Lower-Extremity Venous Disease also do not address Regranex.[8]

Safety
The prescribing information for Regranex previously contained a black boxed warning about increased rates of cancer mortality with use of Regranex; this has been removed as of November 2018.[1]

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for benefit coverage of Regranex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Regranex is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Diabetic Lower Extremity Ulcers.** Approve for 5 months if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 16 years of age; AND
   - **B)** Ulcers are classified as Stage III or IV; AND
     Note: This refers to the International Association of Enterostomal Therapy (IAET) classification system for wounds.
   - **C)** Regranex will be used in adjunct to standard ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Regranex for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Pressure Ulcers – Treatment.** In a randomized, double-blind study of Regranex (100 mcg/g once daily for 16 weeks) in subjects with Stage III or Stage IV pressure ulcers, the incidence of complete ulcer closure was 15% for Regranex compared with 12% in the vehicle control group.[1] The difference was not statistically significant. The prescribing information notes a lack of efficacy in pressure ulcers.

2. **Venous Stasis Ulcers – Treatment.** In two small, randomized, double-blind studies of Regranex (100 mcg/g once daily for 16 weeks) in subjects with venous stasis ulcers, the combined incidence of complete ulcer closure was 46% in the Regranex group compared with 39% in the vehicle control group.[1] The difference was not statistically significant. The prescribing information notes a lack of efficacy in venous stasis ulcers.

3. **Prevention of Ulcers/Wounds.** The efficacy of Regranex for prevention has not been evaluated.

References

1. Regranex® [prescribing information]. Fort Worth, TX: Smith & Nephew, Inc.; August 2019.
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3. Zaidi SRH, Sharma S. Pressure ulcer. [Updated 2024 Jan 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553107/.
4. Robles-Tenorio A, Ocampo-Candiani J. Venous leg ulcer. [Updated 2022 Sep 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567802/.
5. American Diabetes Association. Retinopathy, neuropathy, and foot care: standards of care in diabetes (2025). *Diabetes Care*. 2025;48(1): S252-265.
6. Bonham PA, Brunette G, Crestodina L, et al. 2021 guideline for management of patients with lower-extremity wounds due to diabetes mellitus and/or neuropathic disease. *J Wound Ostomy Continence Nurs.* 2022;49(3): 267-285.
7. Senneville E, Albalawai Z, van Asten SA, et al. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDS 2023). *Clinical Infectious Diseases*. 2023.
8. Kelechi TJ, Brunette G, Bonam PA, et al. 2019 guideline for management of wounds in patients with lower-extremity venous disease (LVED). *J Wound Ostomy Continence Nurs*. 2020;47(2): 97-110.
9. Qaseem A, Humphrey LL, Forciea MA, et al. Treatment of pressure ulcers: a clinical practice guideline from the American college of physicians. *Annals of Internal Medicine*. 2015; 162(5): 372-379.
10. Khandelwal S, Chaudhary P, Poddar DD, et al. Comparative study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations. *Clinics and Practice*. 2013;3(9): 20-24.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Policy Title**: **Updated from** "Becaplermin" **to** "Regranex" **Diabetic Lower Extremity foot Ulcers** **Updated from** "Diabetic foot ulcer" **to** "Diabetic Lower Extremity Ulcers." **Updated** authorization duration **from** "12 months" **to** "5 months." **Added** criterion "Patient is ≥ 16 years of age." **Added** criterion "Ulcers are classified as Stage III or IV" and also **added** "Note: This refers to the International Association of Enterostomal Therapy (IAET) classification system for wounds." **Removed** criterion "Use for the treatment of diabetic neuropathic ulcer of the lower extremity." **Conditions Not Covered:** **Added** "Pressure Ulcers – Treatment." **Added** "Venous Stasis Ulcers – Treatment." **Added** "Prevention of Ulcers/Wounds."	11/1/2025

The policy effective date is in force until updated or retired.