INDICATIONS AND USAGE

REGRANEX Gel contains becaplermin, a human platelet-derived growth factor that 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. REGRANEX Gel is indicated as an adjunct to, and not a substitute for, good ulcer care practices. (1.1)

Limitations of use:
- The efficacy of REGRANEX Gel has not been established for the treatment of pressure ulcers and venous stasis ulcers. (1.2)
- The effects of REGRANEX Gel on exposed joints, tendons, ligaments, and bone have not been established in humans. (1.2)
- REGRANEX Gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention. (1.2)

WARNING: INCREASED RATE OF MORTALITY SECONDARY TO MALIGNANCY

An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a postmarketing retrospective cohort study. REGRANEX Gel should only be used when the benefits can be expected to outweigh the risks. REGRANEX Gel should be used with caution in patients with known malignancy. (5.1)

LIMITATIONS OF USE

REGRANEX Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers. (5.2)
3 DOSAGE FORMS AND STRENGTHS

Gel: 0.01%; clear, colorless to straw-colored gel

3.1 Proper Use of Gel

Gel should be applied to entire ulcer surface using an application aid and then spread over the entire ulcer area to yield a thin continuous layer of gel. In a retrospective study of a medical claims database, cancer rates and overall cancer mortality were calculated. Ninety-three percent of the patients enrolled in these four trials had lower extremity diabetic ulcers that ranged in area from 1.4 cm² to 3.5 cm². All treatment groups received a program of good ulcer care consisting of daily ulcer inspection for the presence of infection if present, moist saline dressings changed twice a day, and additional debridement as needed. Ninety-five percent of the ulcers measured in area up to 10 cm², and the median ulcer size at baseline was 2.7 (95% confidence interval 0.6–12.8). The types of cancers varied and all were remote from the ulcer site. A relative risk of 2.7 (95% confidence interval 0.6–12.8) was seen in patients who received 3 or more tubes of REGRANEX Gel, compared between 1,622 patients who used REGRANEX Gel and 2,809 matched comparators. Estimates of the incidence rates reported below may be under-reported due to limited follow-up for each individual patient. The incidence rate for all cancers was 10.2 per 1,000 person years for patients treated with REGRANEX Gel and 9.1 per 1,000 person years for the comparators. Adjusted for several possible confounders, the rate ratio of all cancers was 1.01 (95% confidence interval 0.79–1.29). Types of cancers varied and were remote from the site of treatment. The incidence rate for mortality from all cancers was 1.6 per 1,000 person years for those who received REGRANEX Gel and 0.9 per 1,000 person years for the comparators. The adjusted rate ratio was 1.8 (95% confidence interval 0.74–4.9). The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGRANEX Gel was 2.0 per 1,000 person years and 0.9 per 1,000 person years in the comparators. The adjusted rate ratio for cancer mortality among those who received 3 or more tubes relative to those who received none was 5.2 (95% confidence interval 1.8–17.6). [See Boxed Warning]

7 DRUG INTERACTIONS

REGRANEX Gel does not interact with other topical medications applied to the ulcer site. The use of REGRANEX Gel with other topical drugs has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women treated with REGRANEX Gel. REGRANEX Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with REGRANEX Gel.

8.3 Nursing Mothers

It is not known whether becaplermin is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when REGRANEX Gel is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness of REGRANEX Gel in pediatric patients below the age of 16 years have not been established.

8.5 Geriatric Use

Among patients receiving any dose of REGRANEX Gel in clinical studies of diabetic lower extremity ulcers, 150 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between older (<65 years of age) and younger (≥65 years of age) patients. The incidence of patients aged 70 and older was insufficient (n=34) to determine whether they respond differently from younger patients.

10 OVERDOSAGE

There are no data on the effects of becaplermin overdose.

11 DESCRIPTION

REGRANEX Gel contains becaplermin, a recombinant human platelet-derived growth factor for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor (PDGF) into the yeast, Saccharomyces cerevisiae. Becaplermin has a molecular weight of approximately 25 KD and is a heterodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. REGRANEX Gel is a non-sterile, low boric acid, preserved, sodium 2-carboxymethylcellulose-based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: carbomethylcellulose sodium salt, tetra-acetic acid, L-histidine hydrochloride, m-cresol, methylparaben, propylparaben, sodium acetate trihydrate, sodium chloride, and water for injection. One gram of REGRANEX Gel contains 100 mcg of becaplermin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

REGRANEX Gel has biological activity similar to that of endogenous platelet-derived growth factor, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair and enhancing the formation of granulation tissue.

12.2 Pharmacodynamics

Clinical pharmacodynamic studies have not been conducted.

12.3 Pharmacokinetics

Ten patients with Stage II or IV (as defined in the International Association of Enterostructural Therapy (IAET) guide to chronic wound staging, “lower extremity diabetic ulcers received topical applications of becaplermin gel 0.01% at a dose range of 0.32–2.95 µg/cm² (7µg/cm²/day) for 14 days. Six patients had non-quantifiable PDGF levels at baseline and throughout the study, the two patients had PDGF levels at baseline which did not increase substantially, and two patients had PDGF levels that increased sporadically above their baseline values during the 14 day study period.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Becaplermin was not genotoxic in a battery of in vitro assays (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair). Becaplermin was also not mutagenic in an in vivo assay for the induction of micronuclei in mouse bone marrow cells. Carcinogenesis and reproductive toxicity studies have not been conducted with REGRANEX Gel.

13.2 Animal Toxicology and/or Pharmacology

In clinical studies, rats injected at the metastatic with 3 or 10 mcg/site (approximately 60 or 200 mcg/kg) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodeling consisting of periosteal hyperplasia and subperiosteal bone resorption and osteosclerosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration of the ability of PDGF to stimulate connective tissue growth. [See Indications and Usage (12.3)]

14 CLINICAL STUDIES

The effects of REGRANEX Gel on the incidence of and time to complete healing in lower extremity diabetic ulcers were assessed in four randomized controlled studies. Of 922 patients studied, 478 received either REGRANEX Gel 0.003% or 0.01%. All study participants had lower extremity diabetic ulcer who had an adequate blood supply (defined as TcpO2>30 mm Hg). In the four trials, ninety-five percent of the ulcers measured in area up to 10 cm², and the median ulcer size at baseline ranged from 1.4 cm² to 3.5 cm². All treatment groups received a program of good ulcer care consisting of daily ulcer inspection for the presence of infection if present, moist saline dressings changed twice a day, and additional debridement as needed. REGRANEX Gel 0.003% or 0.01% placebo gel was applied once a day and covered with a saline moistened dressing. After approximately 12 hours, the gel was gently rinsed off and a saline moistened dressing was then applied for the remainder of the day. Patients were treated until complete healing, or for a period of up to 20 weeks. Patients were considered a treatment failure if their ulcer did not show an approximately 30% reduction in initial ulcer area after eight to ten weeks of REGRANEX Gel therapy.

The primary endpoint, incidence of complete ulcer closure within 20 weeks, for all treatment arms is shown in Figure 1. In each study, REGRANEX Gel in conjunction with good ulcer care was compared to placebo gel plus good ulcer care or good ulcer care alone.

In Study 1, a multicenter, double-blind, placebo controlled trial of 118 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.003% (n=61) was 48% versus 25% for placebo gel (n=57; p=0.02, logistic regression analysis).

In a follow-up study, 491 (75%) of 651 subjects from two randomized, controlled trials of becaplermin gel 0.01% were followed for a median period of approximately 20 months to identify malignancies diagnosed after the end of the trials. Eighty of 291 subjects (3%) from the becaplermin group and two of 200 subjects (1%) from the vehicle/standard of care group were diagnosed with cancers during the follow-up period, a relative risk of 2.7 (95% confidence interval 0.6–12.8). The types of cancers varied and were remote from the site of treatment.

In a retrospective study of a medical claims database, cancer rates and overall cancer mortality were compared between 1,622 patients who used REGRANEX Gel and 2,809 matched comparators. Estimates of the incidence rates reported below may be under-reported due to limited follow-up for each individual patient. The incidence rate for all cancers was 10.2 per 1,000 person years for patients treated with REGRANEX Gel and 9.1 per 1,000 person years for the comparators. Adjusted for several possible confounders, the rate ratio of all cancers was 1.01 (95% confidence interval 0.79–1.29). Types of cancers varied and were remote from the site of treatment.

The incidence rate for mortality from all cancers was 1.6 per 1,000 person years for those who received REGRANEX Gel and 0.9 per 1,000 person years for the comparators. The adjusted rate ratio was 1.8 (95% confidence interval 0.74–4.9). The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGRANEX Gel was 2.0 per 1,000 person years and 0.9 per 1,000 person years in the comparators. The adjusted rate ratio for cancer mortality among those who received 3 or more tubes relative to those who received none was 5.2 (95% confidence interval 1.8–17.6). [See Boxed Warning]
In Study 2, a multicenter, double-blind, placebo controlled trial of 382 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.01% (n=123) was 50% versus 36% for REGRANEX Gel 0.003% (n=122) and 25% for placebo gel (n=122). Only REGRANEX Gel 0.01% was significantly different from placebo gel (p=0.01, logistic regression analysis).

The primary goal of Study 3, a multicenter controlled trial of 172 patients, was to assess the safety of vehicle gel (placebo; n=70) compared to good ulcer care alone (n=68). The study included a small (n=34) REGRANEX Gel 0.01% arm. Incidences of complete ulcer closure were 44% for REGRANEX Gel, 36% for placebo gel and 22% for good ulcer care alone. In Study 4, a multicenter, evaluator-blind, controlled trial of 250 patients, the incidences of complete ulcer closure in the REGRANEX Gel 0.01% arm (n=128) (38%) and good ulcer care alone (n=122) (32%) were not statistically different.

In a randomized, double-blind study of REGRANEX Gel (100 mcg/g once daily for 16 weeks) in patients with Stage III or IV pressure ulcers, the incidence of complete ulcer closure was 15% (28/189) in the becaplermin group and 12% (22/190) in the vehicle control group. This difference was not statistically significant.

In two small, randomized, double-blinded studies of REGRANEX Gel (100 mcg/g once daily for 16 weeks) in patients with venous stasis ulcers, the combined incidence of complete ulcer closure was 46% (30/65) in the becaplermin group and 39% (26/67) in the vehicle control group. This difference was not statistically significant.

In general, where REGRANEX Gel was associated with higher incidences of complete ulcer closure, differences in the incidence first became apparent after approximately 10 weeks and increased with continued treatment (Table 3). Table 3: Life Table Estimates of the Incidence (%) of Complete Healing over Time of Study 2

<table>
<thead>
<tr>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
<th>Week 14</th>
<th>Week 16</th>
<th>Week 18</th>
<th>Week 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 (%)</td>
<td>85 (%)</td>
<td>75 (%)</td>
<td>61 (%)</td>
<td>50 (%)</td>
<td>37 (%)</td>
<td>31 (%)</td>
<td>28 (%)</td>
<td>33 (%)</td>
<td>50 (%)</td>
</tr>
</tbody>
</table>

In a 3-month follow-up period where no standardized regimen of preventative care was utilized, the incidence of ulcer recurrence was approximately 35% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups.

Step-by-step instructions for application of REGRANEX Gel are as follows:

- Squeeze the calculated length of gel onto a clean, firm, nonabsorbable surface, e.g., wax paper.
- With a clean cotton swab, tongue depressor, or similar application aid, spread the measured REGRANEX Gel over the ulcer surface to obtain an even layer.
- Cover with a saline moistened gauze dressing.
- After approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened gauze dressing (without REGRANEX Gel).
- It is important to use REGRANEX Gel together with a good ulcer care program, including a strict non-weight-bearing program.
- Excess application of REGRANEX Gel has not been shown to be beneficial.
- REGRANEX Gel should be stored in the refrigerator. Do not freeze REGRANEX Gel.
- REGRANEX Gel should not be used after the expiration date on the bottom, crimped end of the tube.

Manufactured by: Smith & Nephew, Inc.
Fort Worth, TX 76107
U.S. Gov’t License # 2004
Marketed by: Smith & Nephew, Inc.
Fort Worth, TX 76107
REGRANEX is a registered trademark of Smith & Nephew, Inc.
Part No. 140384-0814
Reorder No. 0064-0810-15
Revised: August 2014

MEDICATION GUIDE
REGRANEX® (REC’–GRAN–IX) (becaplermin) Gel

Read this Medication Guide before you start using REGRANEX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about REGRANEX?

People who use 3 or more tubes of REGRANEX may have an increased risk of death from cancer.

- You should talk with your healthcare provider about the possible benefits and risks to you if you use more than 3 tubes of REGRANEX.

- If you already have cancer, you and your healthcare provider should carefully consider whether you will use REGRANEX.

If you decide to use REGRANEX, your healthcare provider will tell you how to use REGRANEX. See the section “How should I use REGRANEX?” below.

What is REGRANEX?

REGRANEX is a man-made protein medicine that is used with other ulcer care practices (such as good wound care) to treat diabetic sores (ulcers) of your legs or feet that are deeper than just your skin, in people who have good blood supply to the legs.

It is not known if REGRANEX is effective for the treatment of pressure ulcers or ulcers that are due to poor blood flow (circulation).

It is not known if REGRANEX is safe and effective in children under 16 years of age.

Who should not use REGRANEX?

Do not use REGRANEX if you have a skin tumor at the area where you apply REGRANEX.

What should I tell my healthcare provider before using REGRANEX?

Before you use REGRANEX tell your healthcare provider if you:

- have cancer
- have poor blood flow to your lower legs and feet
- have allergies to any of the ingredients in REGRANEX. See the end of this Medication Guide for a complete list of ingredients in REGRANEX.
• have any other medical conditions
• are pregnant or plan to become pregnant. It is not known if REGRANEX will harm your unborn baby.
• are breast-feeding or plan to breast-feed. It is not known if REGRANEX passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you apply other medicines to diabetic ulcers of your legs or feet. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use REGRANEX?
• Use REGRANEX together with good ulcer care, as prescribed by your healthcare provider. This includes following your healthcare provider’s instructions about not putting weight on the affected leg and foot (non-weight-bearing).
• Use REGRANEX exactly as your healthcare provider tells you to use it.
• REGRANEX is for use on skin ulcers only. Do not use REGRANEX in your mouth, eyes, or vagina.
• REGRANEX comes as a gel. Your healthcare provider should tell you how often to use REGRANEX and how much REGRANEX to use.
• Your healthcare provider should check the size of your ulcer every 1 to 2 weeks.
• Your healthcare provider may change the amount of REGRANEX to be applied to your ulcer as the size of your ulcer changes. So, the amount of REGRANEX to be squeezed from the tube may change as the size of your ulcer changes.
• Close your REGRANEX tube tightly after each use.
• Put the REGRANEX tube back in the refrigerator after each use.
• Use a cotton swab, tongue depressor, or other application aid when you apply your REGRANEX. Do not let the tip of your REGRANEX tube touch the ulcer or any other surface.
• Apply REGRANEX one time each day.

Apply REGRANEX as follows:
○ Wash your hands well before you apply REGRANEX.
○ Carefully measure the amount of REGRANEX that your healthcare provider tells you to use.
○ Squeeze the amount of REGRANEX needed for your ulcer on to a clean, firm, non-absorbable surface, such as wax paper.
○ Use a clean cotton swab, tongue depressor, or similar application aid, to spread the REGRANEX gel in a thin layer over the surface of the ulcer on your foot or leg.
○ Cover the area with a saline-moistened gauze dressing.
○ After about 12 hours, gently rinse the ulcer with saline or water to remove the rest of the REGRANEX. Cover the ulcer with a new saline-moistened gauze dressing. Do not apply any more REGRANEX.

What are the possible side effects of REGRANEX?
REGRANEX may cause serious side effects.
• Common side effects of REGRANEX include:
  ○ Red skin rash
  ○ Burning at the application site
Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of REGRANEX gel. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Smith & Nephew, Inc. at 1-800-441-8227.

How should I store REGRANEX?
• Store REGRANEX in the refrigerator at 36°F to 46°F (2°C to 8°C).
• Do not freeze REGRANEX.
• Do not use REGRANEX after the expiration date on the bottom (sealed end) of the tube.
• Throw away your REGRANEX that is out of date or no longer needed for your treatment.

Keep REGRANEX and all medicines out of the reach of children.

General information about REGRANEX
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGRANEX for a condition for which it was not prescribed. Do not give REGRANEX to other people, even if they have the same symptoms that you have. It may harm them.
This Medication Guide summarizes the most important information about REGRANEX. If you would like more information about REGRANEX, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about REGRANEX that is written for healthcare professionals.

What are the ingredients in REGRANEX?
Active ingredient: becaplermin
Inactive ingredients: carboxymethylcellulose sodium, glacial acetic acid, L-lysine hydrochloride, m-cresol, methylparaben, propylparaben, sodium acetate trihydrate, sodium chloride, and water for injection.
Manufactured by: Smith & Nephew, Inc.
Fort Worth, TX 76107
U.S. Gov’t License # 2004
Marketed by: Smith & Nephew, Inc.
Fort Worth, TX 76107
REGRANEX is a registered trademark of Smith & Nephew, Inc.
Part No. 140384-0814
Revised: August 2014
This Medication Guide has been approved by the U.S. Food and Drug Administration.