REGRANEX- becaplermin gel
Smith & Nephew, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REGRANEX◊ gel safely and effectively. See full prescribing information for REGRANEX gel.

REGRANEX (becaplermin) gel, for topical use

Initial U.S. Approval: 1997

RECENT MAJOR CHANGES

Boxed Warning, increased rate of cancer mortality	Removed 11/2018
Warnings and Precautions, cancer mortality	Removed 11/2018

INDICATIONS AND USAGE

REGRANEX is a human platelet-derived growth factor 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)

Limitations of Use:

- The efficacy of REGRANEX gel has not been established for the treatment of pressure ulcers and venous stasis ulcers. (1)
- The effects of REGRANEX gel on exposed joints, tendons, ligaments, and bone have not been established in humans. (1)
- REGRANEX gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention. (1)

DOSAGE AND ADMINISTRATION

- For topical use; not for oral, ophthalmic or intravaginal use. (2)
- To calculate the length of REGRANEX gel to apply, measure the greatest length of ulcer by greatest width of ulcer in either inches or centimeters. (2)

Formula to Calculate Length of Gel to Be Applied Daily

Tube Size	Formula
15g Tube	Inches: ulcer length x ulcer width x 0.6
15g Tube	Centimeters: ulcer length x ulcer width ÷ 4

DOSAGE FORMS AND STRENGTHS

Gel: 0.01% (3)

CONTRAINDICATIONS

Known neoplasm(s) at the site(s) of application (4)

WARNINGS AND PRECAUTIONS

Malignancies distant from the site of application have been reported in both a clinical study and in postmarketing use. The benefits and risks of REGRANEX gel treatment should be carefully evaluated before prescribing in patients with known malignancy. (5.1)

ADVERSE REACTIONS

Erythematous rashes occurred in 2% of patients treated with REGRANEX gel (6.1)

To report SUSPECTED ADVERSE REACTIONS contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch, or Smith & Nephew, Inc. at 1-800-441-8227.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REGRANEX gel 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, when used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control.

Limitations of Use:

The efficacy of REGRANEX gel has not been established for the treatment of pressure ulcers and venous stasis ulcers [*see Clinical Studies (14.2)*] and has not been evaluated for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue [Stage I or II, International Association of Enterostomal Therapy (IAET) staging classification] or ischemic diabetic ulcers.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans [*see Nonclinical Toxicology (13.2)*].

REGRANEX gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in

wounds that close by primary intention.

2 DOSAGE AND ADMINISTRATION

Regranex gel is for topical use; it is not for oral, ophthalmic or intravaginal use.

The amount of REGRANEX gel to be applied depends upon the size of the ulcer area. To calculate the length of gel to apply to the ulcer, measure the greatest length of the ulcer by the greatest width of the ulcer in either inches or centimeters. To calculate the length of gel in inches, use the formula shown below in Table 1, and to calculate the length of gel in centimeters, use the formula shown below in Table 2.

Table 1: Formula to Calculate Length of Gel in Inches to Be Applied Daily

	INCHES
Tube Size	**Formula**
15g tube	length × width × 0.6

Using the calculation, each square inch of ulcer surface will require approximately 2/3 inch length of gel squeezed from a 15g tube. For example, if the ulcer measures 1 inch by 2 inches, then a 1 1/4 inch length of gel should be used for 15g tubes (1 × 2 × 0.6 = 1 1/4).

Table 2: Formula to Calculate Length of Gel in Centimeters to Be Applied Daily

	CENTIMETERS
Tube Size	**Formula**
15g tube	length × width ÷ 4

Using the calculations for ulcer size in centimeters, each square centimeter of ulcer surface will require approximately a 0.25 centimeter length of gel squeezed from a 15g tube. For example, if the ulcer measures 4 cm by 2 cm, then a 2 centimeter length of gel should be used for a 15g tube [(4 × 2) ÷ 4 = 2].

The amount of REGRANEX gel to be applied should be recalculated by the physician or wound caregiver at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of REGRANEX gel from 15g tubes is 0.65g per inch length and 0.25g per centimeter length.

To apply REGRANEX gel, the calculated length of gel should be squeezed on to a clean measuring surface, e.g., wax paper. The measured REGRANEX gel is transferred from the clean measuring surface using an application aid and then spread over the entire ulcer area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The site(s) of application should then be covered by a saline moistened dressing and left in place for approximately 12 hours. The dressing should then be removed and the ulcer rinsed with saline or water to remove residual gel and covered again with a second moist dressing (without REGRANEX gel) for the remainder of the day. REGRANEX gel should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with REGRANEX gel should be reassessed. The step-by-step instructions for applying REGRANEX Gel for home administration are described under "Patient Counseling Information". [*see Patient Counseling Information (17)*]

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

REGRANEX gel is contraindicated in patients with known neoplasm(s) at the site(s) of application.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Cancer

Malignancies distant from the site of application have occurred in REGRANEX gel users in a clinical study and in postmarketing use [*see Adverse Reactions (6.1)* and *Clinical Studies (14.3)*]. REGRANEX gel contains becaplermin, a recombinant human platelet-derived growth factor, which promotes cellular proliferation and angiogenesis [*see Clinical Pharmacology (12.1)*].

The benefits and risks of REGRANEX gel treatment should be carefully evaluated before prescribing in patients with known malignancy.

5.2 Application Site Reactions

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered. Consider interruption or discontinuation and further evaluation (e.g. patch testing) as dictated by clinical circumstances.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

- In clinical trials, erythematous rashes occurred in 2% of subjects treated with REGRANEX gel (and good ulcer care) or placebo (and good ulcer care), and none in subjects receiving good ulcer care alone. Subjects treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.
- In a retrospective follow-up study of 491 of 651 subjects (75%) from two randomized, controlled trials of another formulation of becaplermin gel 0.01%, the subjects were followed for a median of approximately 20 months to evaluate safety and recurrence of healed diabetic lower extremity ulcers. Eight of 291 subjects (2.7%) from the becaplermin gel 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 [CI], 0.6-12.8). The types of cancers varied and all were remote from the treatment site [*see Warnings and Precautions (5.1)*].

6.2 Postmarketing Experience

Because post-approval adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug. The following adverse reactions have been identified during postapproval use of REGRANEX gel.

- Increased rate of death from systemic malignancies in patients dispensed 3 or more tubes of REGRANEX gel, observed in one of three retrospective postmarketing studies [*see Clinical Studies (14.3)*].
- Burning sensation at the site of application and erythema.

7 DRUG INTERACTIONS

It is not known if REGRANEX gel interacts 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

Risk Summary

There are no available data on REGRANEX gel use in pregnant women to inform a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with REGRANEX gel.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

There are no data on the presence of becaplermin in human milk, the effects on the breastfed infant, or the effects on milk production after topical application of REGRANEX gel to lactating women. The developmental and health benefits of breastfeeding should be considered along with the lactating woman's clinical need for REGRANEX gel and any potential adverse effects on the breastfed child from becaplermin.

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 patients < 65 years of age and patients ≥ 65 years of age. The number of patients aged 75 and older were insufficient (n=34) to determine whether they respond differently from younger patients.

10 OVERDOSAGE

There are no data on the effects of REGRANEX gel 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 homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. REGRANEX gel is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose-based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: carboxymethylcellulose sodium, glacial acetic acid, l-lysine hydrochloride, m-cresol, methylparaben, propylparaben, sodium acetate trihydrate, sodium chloride, and water for injection. Each 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 III or IV [as defined in the International Association of Enterostomal 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/kg (7µg/cm^2) daily for 14 days. Six patients had non-quantifiable PDGF levels at baseline and throughout the study, 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 nonclinical studies, rats injected at the metatarsals 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 exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

14 CLINICAL STUDIES

14.1 Efficacy in Diabetic Lower Extremity Ulcers

The effects of REGRANEX gel on the incidence of and time to complete healing in lower extremity diabetic neuropathic ulcers were assessed in four randomized controlled studies (Studies 1-4). Of 922 subjects studied, 478 received either REGRANEX gel 0.003% or 0.01%. All study participants had lower extremity diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond [Stages III and IV of the International Association of Enterostomal Therapy (IAET) guide to chronic wound staging]. Ninety-three percent of the subjects enrolled in these four trials had foot ulcers. The remaining 7% of the subjects had ankle or leg ulcers. The diabetic ulcers were of at least 8 weeks duration and had an adequate blood supply (defined as T_cpO_2 > 30 mm Hg). 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 a program of good ulcer care consisting of initial complete sharp debridement, a non-weight-bearing regimen, systemic treatment for wound-related infection if present, moist saline dressings changed twice a day, and additional debridement as necessary. REGRANEX gel 0.003% or 0.01% or 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. Subjects 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 therapy.

The results of 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.

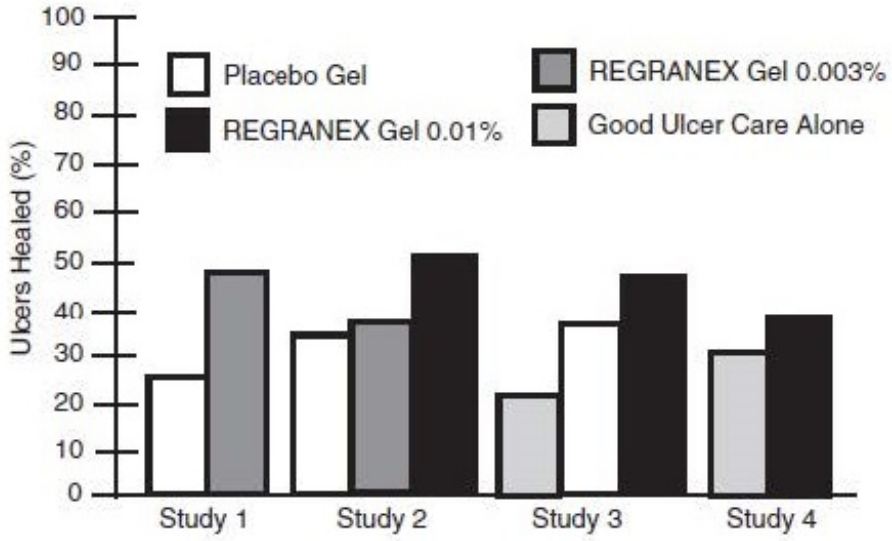
In Study 1, a multicenter, double-blind, placebo-controlled trial of 118 subjects, the incidence of complete ulcer closure for REGRANEX gel 0.003% (n=61) was 48% versus 25% for placebo gel (n=57; p=0.02, logistic regression analysis).

In Study 2, a multicenter, double-blind, placebo-controlled trial of 382 subjects, the incidence of complete ulcer closure for REGRANEX gel 0.01% (n=123) was 50% versus 36% for REGRANEX gel 0.003% (n=132) and 35% for placebo gel (n=127). 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 subjects, 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 subjects, the incidences of complete ulcer closure in the REGRANEX gel 0.01% arm (n=128) (36%) and good ulcer care alone (n=122) (32%) were not statistically different.

Figure 1. Incidence of Complete Diabetic Lower Extremity Ulcer Healing in Studies 1-4



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 Diabetic Lower Extremity Ulcer Healing over Time of Study 2

	REGRANEX Gel 0.01% (%)	Placebo (%)
Week 2	1	0
Week 4	6	2
Week 6	9	6

Week 8	16	14
Week 10	23	18
Week 12	34	25
Week 14	37	28
Week 16	43	33
Week 18	46	34
Week 20	50	37

In a 3-month follow-up period where no standardized regimen of preventative care was utilized, the incidence of ulcer recurrence was approximately 30% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups.

14.2 Lack of Efficacy in Pressure Ulcers and Venous Stasis Ulcers

In a randomized, double-blind study of REGRANEX gel (100 mcg/g once daily for 16 weeks) in subjects with Stage III or IV pressure ulcers, the incidence of complete ulcer closure was 15% (28/189) in the REGRANEX gel 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 subjects with venous stasis ulcers, the combined incidence of complete ulcer closure was 46% (30/65) in the REGRANEX gel group and 39% (26/67) in the vehicle control group. This difference was not statistically significant.

14.3 Observational Studies to Evaluate Cancer Development and Mortality

The observational studies described below do not involve random allocation of treatments. They are susceptible to bias and confounding.

A retrospective study using medical claims database to assess cancer incidence with up to 6 years of follow-up observed development of 28 cancers and 8 cancer deaths in the REGRANEX gel-exposed cohort (n = 1,622) and 43 cancers and 8 cancer deaths in the matched comparator cohort not exposed to REGRANEX gel (n = 2,809). The rate ratio for incident cancer comparing the REGRANEX gel-exposed cohort to the unexposed comparator cohort was 1.2 (95% CI, 0.7 -1.9). The rate ratio for cancer mortality comparing the REGRANEX gel-exposed cohort to the unexposed comparator cohort was 1.8 (95% CI, 0.7 -4.9). The rate ratio comparing patients exposed to three or more tubes of REGRANEX gel to those not exposed was 5.2 (95% CI, 1.6 -17.6) [*see Adverse Reactions (6.2)*].

A retrospective study using medical claims from the Veteran Affairs health care database with up to 11 years of follow-up among patients *without* prior cancer observed 197 cancer deaths in the REGRANEX gel-exposed cohort (n = 6,429) and 206 cancer deaths in the matched comparator cohort not exposed to REGRANEX gel (n = 6,429), resulting in a hazard ratio of 0.9 (95% CI, 0.8-1.2). The hazard ratio for cancer mortality comparing patients exposed to three or more tubes of REGRANEX gel to those not exposed was 1.0 (95% CI, 0.7 -1.5). The hazard ratio for incident cancer in a smaller cohort (1,507 REGRANEX gel-exposed and 1,507 unexposed patients) comparing patients exposed to REGRANEX gel to those not exposed was 1.1 (95% CI, 0.8-1.4).

A second retrospective study using medical claims from the Veteran Affairs health care database with up to 11 years of follow-up among patients *with* prior cancer observed 87 cancer deaths in the REGRANEX gel-exposed cohort (n = 477) and 340 cancer deaths in the matched comparator cohort not exposed to REGRANEX gel (n = 1,756), resulting in a hazard ratio of 0.9 (95% CI, 0.7-1.2). The hazard ratio for cancer mortality comparing patients exposed to three or more tubes of REGRANEX gel to those not exposed was 0.9 (95% CI, 0.6 -1.2).

16 HOW SUPPLIED/STORAGE AND HANDLING

REGRANEX gel (0.01%) is clear, colorless to straw-colored and is available in multi-use tubes in the following size:

15 g tube NDC 50484-810-15

Store refrigerated at 2° – 8° C (36° – 46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Counsel patients to review and discuss any questions or concerns with their healthcare provider before starting REGRANEX and at regular intervals while receiving REGRANEX.

Advise patients that:

- hands should be washed thoroughly before applying REGRANEX gel;
- the tip of the tube should not come into contact with the ulcer or any other surface; the tube should be recapped tightly after each use;
- a cotton swab, tongue depressor, or other application aid should be used to apply REGRANEX gel;
- REGRANEX gel should only be applied once a day in a carefully measured quantity [*see Dosage and Administration (2)*]. The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The measured length of the gel to be squeezed from the tube should be adjusted according to the size of the ulcer. The amount of REGRANEX gel to be applied daily should be recalculated at weekly or biweekly intervals by the physician or wound care giver.

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 76109

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Part No. 141054-1118

MEDICATION GUIDE

REGRANEX◊ (*RE–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?

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 protein medicine made in yeast 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 the active ingredient of 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:

- o Wash your hands well before you apply REGRANEX.
  o Carefully measure the amount of REGRANEX that your healthcare provider tells you to use.
  o Squeeze the amount of REGRANEX needed for your ulcer on to a clean, firm, non-absorbable surface, such as wax paper.
  o Use a clean cotton swab, tongue depressor, or similar application aid, to spread the REGRANEX gel in a thin even layer over the surface of the ulcer on your foot or leg.
  o Cover the area with a saline-moistened gauze dressing.
  o 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.

- **See the section, "What is the most important information I should know about REGRANEX?"**
- Common side effects of REGRANEX include:
  o Red skin rash
  o 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 health 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 76109

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Marketed by:

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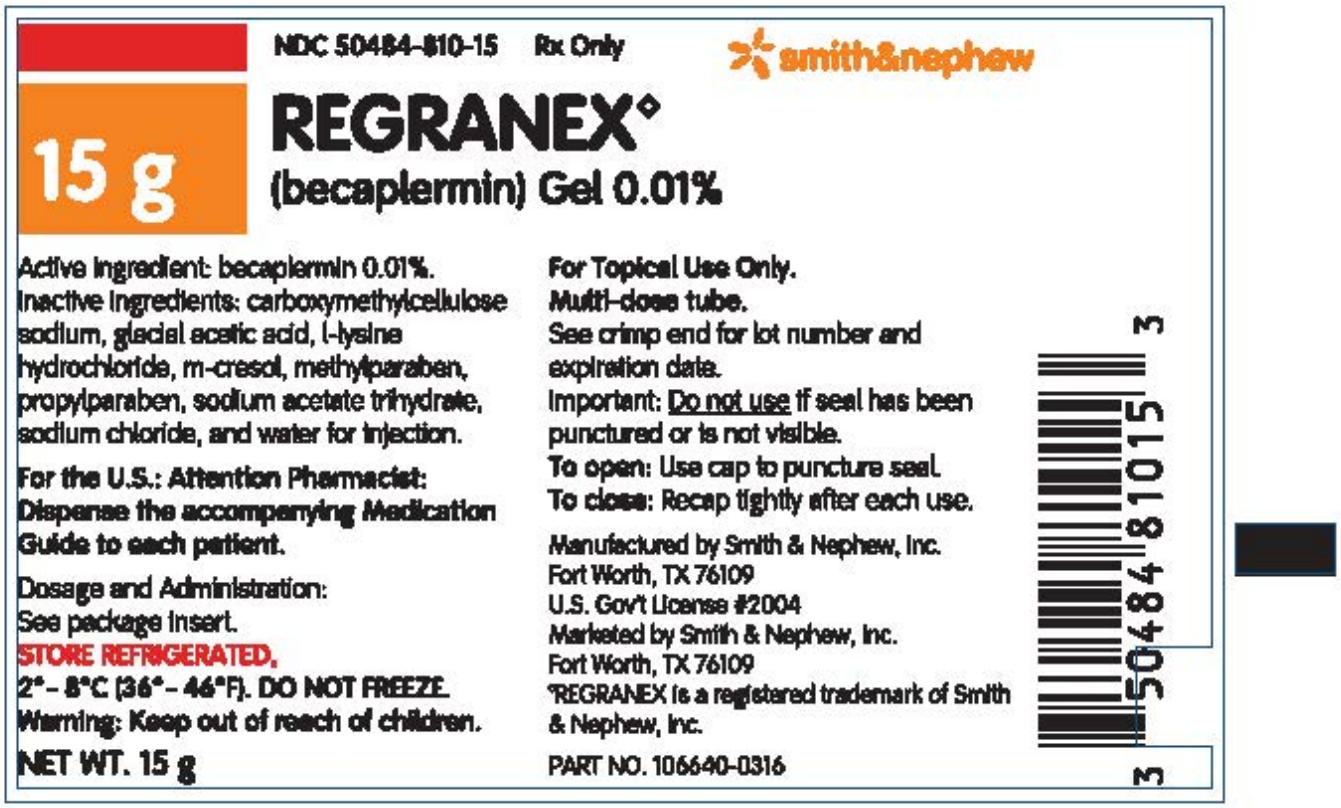
Part No. 141054-1118

Revised: November 2018

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Tube LABEL.PRINCIPAL DISPLAY PANEL



REGRANEX

becaplermin gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50484-810
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BECAPLERMIN (UNII: 1B56C968OA) (BECAPLERMIN - UNII:1B56C968OA)	BECAPLERMIN	100 ug in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
ACETIC ACID (UNII: Q40Q9N063P)	
LYSINE HYDROCHLORIDE (UNII: JNJ23Q2COM)	
METACRESOL (UNII: GGO4Y809LO)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
SODIUM ACETATE (UNII: 4550K0SC9B)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics			
Color	YELLOW (CLEAR, COLORLESS TO STRAW-COLORED)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50484-810-15	1 in 1 CARTON	08/01/2014	
1		15 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103691	11/01/2011	

Labeler - Smith & Nephew, Inc. (827731451)

Establishment

Name	Address	ID/FEI	Business Operations
Renaissance Lakewood LLC		077744035	MANUFACTURE(50484-810) , pack(50484-810) , analysis(50484-810)

Revised: 11/2018 Smith & Nephew, Inc.