REGRANEX® GEL 0.01%
(becaplermin)

DESCRIPTION

REGRANEX® Gel contains becaplermin, a recombinant human platelet-derived growth factor (rhPDGF-BB) 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. Becaplermin Concentrate is produced by Chiron Corp. and supplied to OMJ Pharmaceuticals under a shared manufacturing arrangement. 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: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of REGRANEX Gel contains 100 µg of becaplermin.

CLINICAL PHARMACOLOGY

REGRANEX 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.

Pharmacokinetics

Ten patients with Stage III or IV (as defined in the International Association of Enterostomal Therapy (IAET) guide to chronic wound staging, *J. Enterostomal Ther* 15:4, 1988 and *Decubitis* 2:24, 1989) 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.

Systemic bioavailability of becaplermin was less than 3% in rats with full thickness wounds receiving single or multiple (5 days) topical applications of 127 µg/kg (20.1 µg/cm^2 of wound area) of becaplermin gel.

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 neuropathic ulcers that extended into the subcutaneous tissue or beyond (Stages III and IV of the IAET guide to chronic wound staging). Ninety-three percent of the patients enrolled in these four trials had foot ulcers. The remaining 7% of the patients 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, ninety-five percent 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. 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.

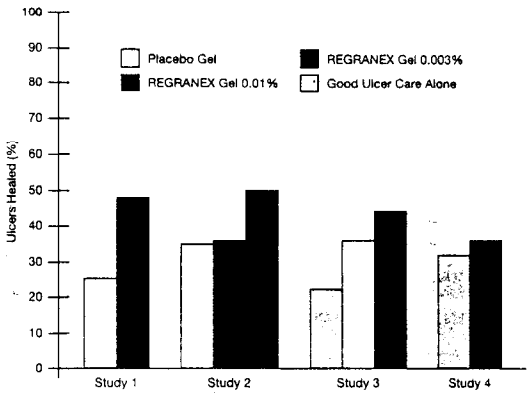
In Study 1, a multicenter, double-blind, placebo controlled trial of 118 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.003% (n=61) was 48% versus 25% for placebo gel (n=57; p=0.02, logistic regression analysis).

In 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=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 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) (36%) and good ulcer care alone (n=122) (32%) were not statistically different.

Figure 1: Incidence of Complete Healing



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 1).

Table 1: Life Table Estimates of the Incidence (%) of Complete Healing Over Time for Study 2

	REGRANEX Gel 0.01% (%)	Placebo Gel (%)
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.

The efficacy of REGRANEX Gel for the treatment of non-diabetic ulcers is under evaluation.

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, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

The efficacy of REGRANEX Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers has not been evaluated.

CONTRAINDICATIONS

REGRANEX Gel is contraindicated in patients with:
- known hypersensitivity to any component of this product (e.g., parabens);
- known neoplasm(s) at the site(s) of application.

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WARNINGS
REGRANEX (becaplermin) Gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

PRECAUTIONS
For external use only.

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. In pre-clinical studies, rats injected at the metatarsals with 3 or 10 µg/site (approximately 60 or 200 µg/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.

Information for Patients
Patients should be advised 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 section). The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately ⅛ 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 on to a clean, firm, non-absorbable 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.

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.

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.

Pregnancy: Category C
Animal reproduction studies have not been conducted with REGRANEX Gel. It is also not known whether REGRANEX Gel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. REGRANEX Gel should be given to pregnant women only if clearly needed.

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.

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

ADVERSE REACTIONS
Patients receiving REGRANEX Gel, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. However, erythematous rashes occurred in 2% of patients treated with REGRANEX Gel and placebo, and none in patients receiving good ulcer care alone. The incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Mortality rates were also similar across all treatment groups. Patients treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.

DOSAGE AND ADMINISTRATION
The amount of REGRANEX Gel to be applied will vary depending 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 2, and to calculate the length of gel in centimeters, use the formula shown below in Table 3.

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Table 2: Formula to Calculate Length of Gel in Inches to be Applied Daily

INCHES

Tube Size	Formula
15 or 7.5g tube	length X width X 0.6
2g tube	length X width X 1.3

Using the calculation, each square inch of ulcer surface will require approximately ⅜ inch length of gel squeezed from a 15g or 7.5g tube, or approximately 1½ inch length of the gel from a 2g tube. For example, if the ulcer measures 1 inch by 2 inches, then a 1¼ inch length of gel should be used for 15g or 7.5g tubes (1 X 2 X 0.6 = 1¼) and 2¾ inch gel length should be used for 2g tube (1 X 2 X 1.3 = 2¾).

Table 3: Formula to Calculate Length of Gel in Centimeters to be Applied Daily

CENTIMETERS

Tube Size	Formula
15 or 7.5g tube	length X width ÷ 4
2g tube	length X width ÷ 2

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 or 7.5g tube, or approximately a 0.5 centimeter length of gel from a 2g tube. For example, if the ulcer measures 4 cm by 2 cm, then a 2 centimeter length of gel should be used for 15g or 7.5g tube [(4 X 2) ÷ 4 = 2] and a 4 centimeter length of gel should be used for 2g tube [(4 X 2) ÷ 2 = 4].

The amount of REGRANEX Gel to be applied should be recalculated by the physician or wound care giver at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of REGRANEX Gel from 7.5g and 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 ⅛ 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 "Information for Patients".

HOW SUPPLIED
REGRANEX (becaplermin) Gel, supplied as a clear, colorless to straw-colored preserved gel containing 100µg of becaplermin per gram of gel, is available in multi-use tubes in the following sizes:

2g tubes	NDC 0045-0810-02
7.5g tubes	NDC 0045-0810-07
15g tubes	NDC 0045-0810-15

REGRANEX Gel is for external use only.

Storage
Store refrigerated, 2-8°C (36-46°F). DO NOT FREEZE. DO NOT USE THE GEL AFTER THE EXPIRATION DATE AT THE BOTTOM OF THE TUBE.

Caution: Federal (USA) law prohibits dispensing without prescription.

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McNEIL PHARMACEUTICAL

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