DESCRIPTION
REGRANEX® Gel contains becaplermin, a recombinant human platelet-derived growth factor (PDGF-BB) for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the 24-kDa or 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 emulsified in a gel base (water, triethylamine, and sodium chloride), and supplied in vials and cartridges for superficial wounds under a shared manufacturing arrangement. REGRANEX Gel is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate, disodium edetate, sodium styrlyl sulfonate, water for injection, and methylparaben, propylparaben, and imidazolidinyl urea as preservatives and 1-methylisothiazolinone 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 Platelet Retrieval Therapy (IAPRT) guide to chronic wound staging; J. Entersalat Thir 154, 1988 and Decubitus 22:4, 1989) lower extremity diabetic ulcers received topical applications of becaplermin gel 0.01% at a close range of 0.30-2.95 g/kg (10-80 cm²) daily for 14 days. Six patients had non-healable, PDGF levels at baseline and throughout the study, two patients had PDGF levels at baseline that 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 (0.1 g/cm²) of wound area of becaplermin gel.

Clinical Studies
The effects of REGRANEX Gel on the incidence of and time to complete healing in diabetic and non-diabetic ulcers were assessed in four randomized controlled studies. Of 922 patients studied, 478 received either REGRANEX Gel 0.0075% or 0.01% or placebo gel. All study participants had lower extremity diabetic ulcers that extended into the subcutaneous tissue or beyond (Stage III or IV of the IAPRT guide to chronic wound staging; J. Entersalat Thir 154, 1988 and Decubitus 22:4, 1989). The patients received daily topical applications of REGRANEX Gel 0.0075% or 0.01% or placebo gel. The wounds were then healed and the heal time was determined. The results of the study are presented in Table 1.

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

<table>
<thead>
<tr>
<th>Week</th>
<th>REGRANEX 0.0075% (%)</th>
<th>Placebo Gel (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Week 4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Week 6</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Week 8</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Week 10</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Week 12</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Week 14</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>Week 16</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Week 18</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>Week 20</td>
<td>50</td>
<td>37</td>
</tr>
</tbody>
</table>

In a 12-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 debridement, pressure relief, and ulcer 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, IAPRT 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 neoplasms at the site of application.
WARNINGS
REGANEX (bacapenem) Gel is a narrow-spectrum, low-acetylpenicillin 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 bacapenem on exposed joints, tendons, ligaments, and bone have not been established in humans. In primate studies, rats injected at the metatarsals with 3 or 10 μg/site (approximately 60 or 200 μg/kg) of bacapenem every other day for 13 days developed osteolysis 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 fibrosis with accompanying mononuclear cell infiltration indicative of the ability of PDGF to stimulate connective tissue growth.
Information for Patients
Patients should be advised that:
- bands should be washed thoroughly before applying REGANEX Gel;
- the tip of the tube should not come into contact with the ulcer or any other surface; the tube should be replaced tightly after each use;
- a cotton swab, tongue depressor, or other applicator aid should be used to apply REGANEX Gel;
- REGANEX 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 4 mm in 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 REGANEX Gel per ulcer daily should be recalculated at weekly or biweekly intervals by the physician or pharmacist.

Step-by-step instructions for application of REGANEX Gel are as follows:
- Squeeze the calculated length of gel on to a clean, firm, non-stick absorbent surface, e.g., wax paper;
- With a clean cotton swab, tongue depressor, or similar application aid, spread the measured REGANEX Gel over the ulcer surface to obtain an even layer;
- A clean dressing, gel, or bandage should be applied to keep the ulcerated area covered;
- after approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened dressing (without REGANEX Gel);
- it is important to use REGANEX Gel together with a good ulcer care program, including a strict non-weight-bearing program;
- excess application of REGANEX Gel has not been shown to be beneficial;
- REGANEX Gel should be stored in the refrigerator. Do not freeze REGANEX Gel;
- REGANEX Gel should not be used after the expiration date on the bottom, crimson end of the tube.

Drug Interactions
It is not known if REGANEX Gel interacts with other topical medications applied to the ulcer site. The use of REGANEX Gel with other topical drugs has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Bacapenem was not genotoxic in a battery of in vitro assays, including the Ames bacterial mutation assay and mammalian cell transformation. In vitro, bacapenem did not affect sperm motility or fertility in mice. In vivo, bacapenem did not affect fertility in rats. Carcinogenicity and reproductive toxicity studies have not been conducted with REGANEX Gel.

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

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

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

ADVERSE REACTIONS
Patients receiving REGANEX 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 REGANEX 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 REGANEX Gel did not develop neutralizing antibodies against bacapenem.

DOSAGE AND ADMINISTRATION
The amount of REGANEX 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 length 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.

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

<table>
<thead>
<tr>
<th>Tube Size</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 g or 7.5 g tube</td>
<td>length X width X 0.6</td>
</tr>
<tr>
<td>2 g tube</td>
<td>length X width X 1.3</td>
</tr>
</tbody>
</table>

Using the calculation, each square inch of ulcer surface will receive approximately 0.6 inch length of gel squeezed from a 15 g or 7.5 g tube, or approximately 1.3 inch length of gel from a 2 g tube. For example, if the ulcer measures 1 inch by 2 inches, then a ½ inch length of gel should be used for 15 g or 7.5 g tube (0.6 × 1 × 2 = 1.2) and 2 inch length of gel should be used for 2 g tube (1.3 × 1 × 2 = 2.6).

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

<table>
<thead>
<tr>
<th>Tube Size</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 g or 7.5 g tube</td>
<td>length X width X 4</td>
</tr>
<tr>
<td>2 g tube</td>
<td>length X width X 2</td>
</tr>
</tbody>
</table>

Using the calculations for ulcer size in centimeters, each square centimeter of ulcer surface will receive approximately 0.25 centimeter length of gel squeezed from a 15 g or 7.5 g tube, or approximately 0.5 centimeter length of gel from a 2 g tube. For example, if the ulcer measures 1 cm by 2 cm, then a ½ centimeter length of gel should be used for 15 g or 7.5 g tube (0.25 × 1 × 2 = 0.5) and a 4 centimeter length of gel should be used for 2 g tube (0.5 × 1 × 2 = 1). The amount of REGANEX Gel to be applied should be recalculated by the physician or pharmacist at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of REGANEX Gel from 7.5 g and 15 g tubes is 0.65 g per inch length and 0.25 g per centimeter length.

To apply REGANEX Gel, the calculated length of gel should be squeezed on to a clean measuring surface, e.g., wax paper. The measured REGANEX Gel is transferred from the clean measuring surface using an application aid and spread evenly over the entire ulcer area to yield a thin continuous layer of approximately 4 mm in thickness. The excess application should then be covered by a saline moistened dressing and left in place for approximately 12 hours. The dressing should be removed and the ulcer rinsed with saline or water to remove residual gel and covered again with a second moist dressing (without REGANEX Gel) for the remainder of the day. REGANEX Gel should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 50% after 10 weeks of treatment, complete healing has not occurred. If there is no response, treatment with REGANEX Gel should be re-assessed. The step-by-step instructions for applying REGANEX Gel for home administration are described under "Information for Patients."

HOW SUPPLIED
REGANEX (bacapenem) Gel, supplied as a clear, colorless to straw-colored preserved gel containing 10 μg/g of bacapenem. It is available in multi-use tubes in the following sizes:
- 2 g: NDC 0045-0813-02
- 7.5 g: NDC 0045-0813-07
- 15 g: NDC 0045-0813-13

REGANEX Gel is for external use only.

Storage
Store refrigerated. Do not freeze. 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.

U.S. Patent A5,657,693

McNeil PHARMACEUTICALS

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