

REGRANEX® Gel 0.01% (becaplermin)

WARNING

An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a post-marketing 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. (See **CONTRAINDICATIONS** and **WARNINGS**)

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 Novartis NPC and supplied to OMJ Pharmaceuticals under a shared manufacturing arrangement. REGRANEX Gel is 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 µg of becaplermin.

CLINICAL PHARMACOLOGY

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.

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/cm²) daily for 14 days.

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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/cm² of wound area) of becaplermin gel.

Clinical Studies

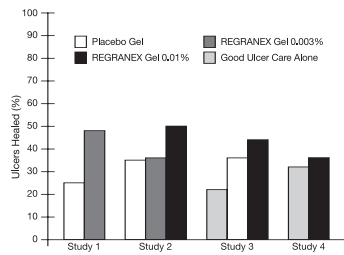
The effects of REGRANEX Gel on the incidence of and time to complete healing in lower extremity diabetic ulcers were assessed in four randomized controlled studies. Of 922 patients studied, 478 received either REGRANEX Gel 0.003% or 0.01%. All study participants had lower extremity diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond (Stages II 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_{PO₂} > 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 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).

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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	6
Week 6	9	2
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.

In a randomized, double-blind study of REGRANEX Gel (100 µg/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 µg/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.

INDICATIONS AND USAGE

REGRANEX (becaplermin) 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 (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 has not been established for the treatment of pressure ulcers and venous stasis ulcers (See Clinical Studies) 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, IAET staging classification) or ischemic diabetic ulcers.

CONTRAINDICATIONS

REGRANEX (becaplermin) 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.

WARNINGS

REGRANEX Gel contains becaplermin, a recombinant human platelet-derived growth factor, which promotes cellular proliferation and angiogenesis. (See Clinical Pharmacology). The benefits and risks of becaplermin treatment should be carefully evaluated before prescribing. Becaplermin should be used with caution in patients with a known malignancy. Malignancies distant from the site of application have occurred in becaplermin users in both a clinical study and in postmarketing use, and an increased rate of death from systemic malignancies was seen in patients who have received 3 or more tubes of REGRANEX Gel.

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 of approximately 20 months to identify malignancies diagnosed after the end of the trials. Eight 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 all were remote from the treatment site.

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 underreported due to limited follow-up for each individual.

- 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 was 1.2, (95% confidence interval 0.7-1.9). 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 0.7-4.9).
- The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGRANEX Gel was 3.9 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 1.6-17.6). (See Boxed Warning)

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

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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 preclinical 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 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 on to a clean, firm, non-absorbent 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 ulcerated area or if REGRANEX Gel interacts 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.

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.

Pediatric Use

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

ADVERSE REACTIONS

In Clinical Trials, patients receiving REGRANEX (becaplermin) 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 in-

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incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Patients treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.

Post-Marketing Events

Burning sensation at the site of application has been reported during post-approval use of REGRANEX Gel. Because post-apprval 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.

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.

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

	INCHES
Tube Size	Formula
15g 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 2/3 inch length of gel squeezed from a 15g tube, or approximately 1 1/3 inch length of the gel from a 2g 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 X 2 X 0.6 = 1/4) and 2 3/4 inch length should be used for a 2g tube (1 X 2 X 1.3 = 2 3/4).

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

	CENTIMETERS
Tube Size	Formula
15g 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 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 a 15g tube [(4 X 2) ÷ 4 = 2] and a 4 centimeter length of gel should be used for a 2g tube [(4 X 2) ÷ 2 = 4].

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 "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 tube in the following size:

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.

U.S. Patent #5,457,093

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MEDICATION GUIDE

REGRANEX® (RE'-GRAN-IX) Gel (Becaplermin)

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:

- to treat diabetic sores (ulcers) of your legs or feet that are deeper than just into your skin, in people who have good blood supply to the legs.
- 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 and feet to help increase the chance that your ulcer will heal completely.

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

Who should not use REGRANEX?

Do not use REGRANEX if you:

- have a skin tumor at or near the area where you apply REGRANEX
- have allergies to any of the ingredients in REGRANEX. See the end of this Medication Guide for a complete list of ingredients in REGRANEX.

Do not use this medicine if any of the above apply to you.

What should I tell my healthcare provider before using REGRANEX?

Before you use REGRANEX tell your healthcare provider if you:

- have cancer
- know that you have swelling or an infection in the tissue or the bone of your lower leg or foot
- have poor blood flow (circulation) to your lower legs and feet
- 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 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, including:

- See the section, “What is the most important information I should know about REGRANEX?”
- Infection of the ulcer, the skin around the ulcer or cellulitis (infection below the surface of the skin, which may cause redness, warmth at the site, swelling and pain)
- Bone infection (osteomyelitis). This may cause constant fever, pain, swelling or redness around the bone that is affected.

Tell your healthcare provider if you have any symptoms of the serious side effects listed above.

- Common side effects of REGRANEX include:
 - o Rash
 - o Redness at 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.

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 gel 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 pre-

scribed. 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.

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

Manufactured by:

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San German, Puerto Rico 00683

Manufactured for:

Ortho-McNeil, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869

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