ORTHO-McNEIL™
Division of
Ortho-McNeil-Janssen
Pharmaceuticals, Inc.

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Ortho-McNeil™, Division of Ortho-McNeil Janssen Pharmaceuticals, Inc., and ETHICON, INC., would like to inform you of important changes to the prescribing information for REGRANEX® (becaplermin) Gel 0.01%, a topical formulation of recombinant human platelet-derived growth factor indicated as an adjunct to the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply.

The WARNINGS section has been updated to include a BOXED WARNING (see below) and a description of the epidemiologic data that is the basis for it. These data come from a retrospective study that compared cancer incidence and cancer mortality among 1,622 patients exposed to REGRANEX Gel to 2,809 matched comparators. The results were consistent with no overall increase in cancer incidence among the patients exposed to REGRANEX Gel. However, there was a 5-fold increased risk of cancer mortality in the group exposed to 3 or more tubes of REGRANEX Gel.

The BOXED WARNING reads as follows:

WARNING
An increased risk 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**)

The epidemiologic material added to the warnings section as the basis for the boxed warning above reads as follows:

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 rate reported below may be under-reported 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 three 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.

Healthcare professionals should report all serious adverse events to 1-888-734-7263 (1-888-REGRANEX) or to FDA's MedWatch Adverse Event Reporting program online (at www.fda.gov/MedWatch/report.htm), by facsimile (1-800-FDA-0178), by telephone (1-800-FDA-1088), or by returning the postage-paid FDA form 3500 (which may be downloaded from www.fda.gov/MedWatch/getforms.htm) by mail (to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787).

REGRANEX Gel, manufactured by OMJ Pharmaceuticals, Inc. for its distributor Ortho-McNeil, is commercialized in the United States by Johnson & Johnson Wound Management, division of ETHICON, INC.

Please read the enclosed revised package insert for complete prescribing information for REGRANEX or visit www.REGRANEX.com. For additional information about REGRANEX Gel, please call the Customer Communications Center at 1-888-734-7263 (1-888-REGRANEX).

Signed,

James C. Hart, MD
Vice President
Global Medical Affairs
ETHICON, INC.

Norman Rosenthal, MD
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Ortho-McNeil Janssen Scientific Affairs, LLC

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