Warning Added to Diabetic Ulcer Treatment Label

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Information about the increased risk of cancer-related deaths in patients who have used three or more tubes of becaplermin is now included in a boxed warning on the label of the diabetic foot and leg ulcer treatment.

On June 6, the Food and Drug Administration announced that the warning had been added to the label of becaplermin (Regranex), a recombinant human platelet–derived growth factor that was approved in 1997. It is marketed as Regranex Gel 0.01% for treating nonhealing diabetic leg and foot ulcers.

The boxed warning says that the increased risk of mortality was observed in a postmarketing retrospective cohort study in patients who had been treated with three or more tubes, and advises that Regranex gel should only be used "when the benefits can be expected to outweigh the risks." The warning also says that it should be used "with caution" in patients with a known malignancy.

A retrospective study of 1,622 patients found cancer mortality was five times higher for those who had been exposed to three or more tubes of Regranex.

The retrospective study compared cancer incidence and cancer mortality among 1,622 patients who had been treated with Regranex to 2,809 similar patients who had not been treated with Regranex. The study found that the incidence of cancer was not increased among those in the Regranex group, but the risk of cancer mortality was five times higher among those patients who had been exposed to three or more tubes of Regranex.

"No single type of cancer was identified, but rather deaths from all types of cancer combined were observed," according to the FDA's statement announcing the change in the label.

In March, the FDA announced that it was conducting a safety review of Regranex after receiving information about the epidemiologic study, and that labeling changes were possible. The changes in the label also are explained in a "Dear Healthcare Professional" letter issued by the manufacturer, Ortho-McNeil.

Because it is a growth factor and promotes cellular proliferation and angiogenesis, the manufacturer of Regranex has monitored patients treated with the product for an increased risk of cancer or other adverse effects in postapproval safety studies.

A long-term safety study which was completed in 2001 found that cancer-related deaths were higher among patients who had used Regranex than among those patients who had not used it, according to the FDA statement. This was followed by the retrospective study, which compared cancer rates and overall cancer mortality among patients with similar diagnoses and drug use in a medical claims database.

The rate of deaths from all cancers among the patients who had been treated with three or more tubes of Regranex was 3.9 per 1,000 person-years, compared with 0.9 per 1,000 person-years among the comparators, an adjusted rate ratio of 5.2, according to the Ortho-McNeil letter. (The rate ratio was adjusted for several possible confounders.)

The letter points out that the results "were consistent with no overall increase in cancer incidence" among the patients who had been exposed to the Regranex diabetic ulcer treatment: The rate of all cancers was 10.2 per 1,000 person-years among those patients who were treated with Regranex, compared with 9.1 per 1,000 person-years among the comparators for a 1.2 adjusted rate ratio. The "types of cancers were varied and were remote from the site of treatment," the company said in its letter.

A Web link to the FDA's update and a link to the manufacturer's letter can be accessed at www.fda.gov/cder/drug/infopage/becaplermin/default.htm. ■

Any serious or unexpected adverse events believed to be associated with Regranex can be reported to the manufacturer at 888-734-7263 or online with the Food and Drug Administration MedWatch program at www.fda.gov/medwatch/report.htm.