

# Panel Backs Peginterferon for Stage III Melanoma

BY ELIZABETH MEHCATIE

GAITHERSBURG, MD. — Peginterferon alfa-2b has a favorable risk-benefit ratio as an adjuvant treatment for stage III melanoma, a Food and Drug Administration advisory panel said.

The FDA's Oncologic Drugs Advisory Committee voted 6-4 after reviewing the data on the adjuvant use of peginterferon alfa-2b after complete lymphadenec-

tomy, the indication up for approval. The panel did not vote specifically on whether to recommend approval of peginterferon for the indication.

Peginterferon alfa-2b (Peg-IFN), a long-acting formulation of interferon alfa-2b, is marketed by Schering-Plough Corp. as Pegintron and was approved as a treatment for chronic hepatitis C in 2001. Interferon alfa-2b (Intron A), also manufactured by Schering-Plough, was approved

as an adjuvant treatment for melanoma in 1995, on the basis of a study that found it had a significant impact on overall survival, the primary end point.

Those voting positively generally agreed that although the substantial toxicity and the modest effect on relapse-free survival were concerns, the toxicity did not appear to be worse than that associated with high-dose interferon, and that it would be a reasonable alternative

treatment option. Several said that the pegylated formulation would be more convenient, since it is administered subcutaneously once a week.

Peg IFN is administered subcutaneously once a week, with a higher dose during the 8-week induction period, and is recommended for 5 years.

The results of a multicenter, phase III study, of 1,256 patients (median age 50 years) with stage III melanoma were submitted for approval.

Subjects had either microscopic or palpable nodal involvement, and were randomized to either treatment with Peg-IFN or observation after undergoing regional lymph node dissection. Most of the patients were in Europe,

**Median relapse-free survival was 34.8 months for patients on the long-acting interferon and 25.2 months among those in the observation arm, a statistically significant 18% reduction.**

but none was in the United States.

The primary endpoint was relapse-free survival (defined as the earliest detection of locoregional relapse, distant metastasis, or death). The rate of these events was 52.3% among those on Peg-IFN, compared with 58.5% in the observation group. The median relapse-free survival was 34.8 months, compared with 25.5 months among those in the observation arm, an 18% reduction in the risk of relapse or death associated with treatment, which was statistically significant. However, there were no significant differences in overall survival or distant metastasis-free survival between the two arms.

Fatigue was the most common serious adverse event associated with treatment. Depression was more than twice as high among patients on Peg-IFN, and severe depression was also higher among treated patients (7% vs. 0.5%). Of those on Peg-IFN, 44% stopped treatment because of adverse events. Only 13% of patients completed 5 years of treatment.

There were three deaths considered possibly related to peginterferon, which were cardiovascular related.

The FDA usually follows the recommendations of its advisory panels. ■

## RENOVA® (tretinoin cream) 0.02%

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### FOR TOPICAL USE ON THE FACE. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

#### Brief Summary

RENOVA (tretinoin cream) 0.02% contains the active ingredient tretinoin in a cream base.

**IMPORTANT NOTE — This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.**

#### INDICATIONS AND USAGE:

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

RENOVA (tretinoin cream) 0.02% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sun/avoidance programs. **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, OR RESTORE MORE YOUTHFUL OR YOUNGER SKIN.** In double-blind, vehicle-controlled clinical studies, many patients in the vehicle group achieved desired palliative effects on fine wrinkling of facial skin with the use of comprehensive skin care and sun/avoidance programs including sunscreens, protective clothing, and non-prescription emollient creams.

- RENOVA 0.02% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sun/avoidance exposure such as coarse or deep wrinkling, tactile roughness, mottled hyperpigmentation, lentiginosities, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- RENOVA should be used under medical supervision as an adjunct to a comprehensive skin care and sun/avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing.

- Patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of RENOVA 0.02%. Thus the effectiveness and safety of RENOVA 0.02% in these populations are not known at this time.
- Neither the safety nor the effectiveness of RENOVA for the prevention or treatment of actinic keratoses or skin neoplasms has been established.

- Neither the safety nor the efficacy of using RENOVA 0.02% daily for greater than 52 weeks has been established, and daily use beyond 52 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See WARNINGS section.)

#### CONTRAINDICATIONS:

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

#### WARNINGS:

- RENOVA 0.02% is a dermal irritant, and the results of continued irritation of the skin for greater than 52 weeks in chronic use with RENOVA are not known. There is evidence of atypical changes in melanocytes and keratinocytes and of increased dermal elastosis in some patients treated with RENOVA 0.05% for longer than 48 weeks. The significance of these findings and their relevance for RENOVA 0.02% are unknown.

- RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of RENOVA because of heightened sunburn susceptibility. Patients should be warned to use sunscreens (minimum SPF of 15) and protective clothing when using RENOVA. Patients with sunburn should be advised not to use RENOVA until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using RENOVA and follow the precautions outlined in the Patient Package Insert.

RENOVA should be kept out of the eyes, mouth, angles of the nose, and mucous membranes. Topical use may cause severe local erythema, pruritus, burning, stinging, and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether and consider additional appropriate therapy.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with caution in patients with this condition.

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

#### PRECAUTIONS:

**General:** RENOVA should be used only as an adjunct to a comprehensive skin care and sun/avoidance program. (See INDICATIONS AND USAGE section.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of RENOVA should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using tretinoin-containing products.

**Information for Patients:** See Patient Package Insert

**Drug Interactions:** Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with RENOVA because they may increase irritation with RENOVA.

RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of this clinical formulation (0.02%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day. These doses are 10 and 20 times the maximum human systemic dose, when adjusted for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.5 times the maximum human systemic dose, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 gram of 0.02% RENOVA applied daily to a 50 kg person (0.004 mg tretinoin/kg body weight).

Studies in hairless albino mice suggest that con-

current exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

In dermal Segment I fertility studies in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (20 times the maximum human systemic dose adjusted for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (10 times the maximum human systemic dose adjusted for total body surface area) and above were observed. A dermal Segment III study with RENOVA has not been formed in any species. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (83 times the human topical dose adjusted for total body surface area).

#### Pregnancy:

**Teratogenic effects: Pregnancy Category C.**

ORAL tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which, metabolically, is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (417 times the maximum human systemic dose adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

**TOPICAL tretinoin** in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (42 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was dermally applied.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (17 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animal studies have shown that dermally applied tretinoin may be fetotoxic, but not overtly teratogenic, in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (42 times the maximum human systemic dose adjusted for total body surface area in both species).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of

these spontaneous reports in terms of risk to the fetus is not known.

#### Non-teratogenic effects:

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death, in rats when administered 2.5 mg/kg/day (104 times the maximum human systemic dose adjusted for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women. RENOVA should not be used during pregnancy.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, mitigation of fine facial wrinkles with RENOVA 0.02% may be postponed in nursing mothers until after completion of the nursing period.

**Pediatric Use:** Safety and effectiveness in patients less than 18 years of age have not been established.

**Geriatric Use:** In clinical studies with RENOVA 0.02%, patients aged 65 to 71 did not demonstrate a significant difference for improvement in fine wrinkling when compared to patients under the age of 65. Patients aged 65 and over may demonstrate slightly more irritation, although the differences were not statistically significant in the clinical studies for RENOVA 0.02%. Safety and effectiveness of RENOVA 0.02% in individuals older than 71 years of age have not been established.

#### ADVERSE REACTIONS:

(See WARNINGS and PRECAUTIONS sections.)

In double-blind, vehicle-controlled studies involving 339 patients who applied RENOVA 0.02% to their faces, adverse reactions associated with the use of RENOVA were limited primarily to the skin. Almost all patients reported one or more local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus. In 32% of all study patients, skin irritation was reported that was severe, led to temporary discontinuation of RENOVA 0.02%, or led to use of a mild topical corticosteroid. About 7% of patients using RENOVA 0.02%, compared to less than 1% of the control patients, had sufficiently severe local irritation to warrant short-term use of mild topical corticosteroids to alleviate local irritation. About 4% of patients had to discontinue use of RENOVA because of adverse reactions.

Approximately 2% of spontaneous post-marketing adverse event reporting for RENOVA 0.05% were for skin hypo- or hyperpigmentation. Other spontaneously reported adverse events for RENOVA 0.05% predominantly appear to be local reactions similar to those seen in clinical trials.

#### OVERDOSAGE:

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

#### Rx only.



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## VERBATIM

*‘One of the fellows here said, “Wow, this is fantastic; now I will get time to know my metastatic melanoma patients.” That’s how bad the field was.’*

Dr. Alexander Eggermont, discussing a new oral agent, p. 18