

9-mm Margins Urged for Melanoma Excision

BY ALICIA AULT

AUSTIN, TEX. — The commonly accepted standard of using 5-mm margins for surgical excision of melanoma in situ may not be enough to clear the large majority of tumors, said Dr. Joy Kunishige.

Speaking at the annual meeting of the American College of Mohs Surgery, Dr. Kunishige, a dermatologist in private practice in Pittsburgh, said that since

several studies have shown a 5-mm margin to be inadequate, she and her colleagues gathered the latest evidence on clearance rates to update previous National Institutes of Health guidelines, set in 1992 (NIH Consens. Statement 1992 Jan 27-29;10[1]:1-26). The goal was to clear at least 97% of tumors.

They evaluated all primary melanoma in situ cases that were collected as part of a prospective database started in 1982

at the practice. The database included 1,072 patients with 1,120 primary tumors. Of the patients, 675 (63%) were male, and mean age was 65 years, and mean follow-up was 4.7 years. A total of 593 (53%) of the lesions were on the face, 235 (21%) were on the extremities, and 201 (18%) were on the trunk, with the remainder in other locations.

All lesions were excised using the fresh tissue technique of Mohs, with frozen

section examination of the margin.

Using 6-mm margins, 86% of the tumors were cleared. With a 9-mm margin, there was a 98% clearance rate; and with a 12-mm margin, a 99.4% clearance rate, said Dr. Kunishige.

The 9-mm margin was equally effective regardless of sex, location, or diameter of the lesion. The overall 5-year survival was 93%; the 5-year melanoma in situ survival was 99.5%. Three patients died of melanoma in situ. Two died from a separate invasive melanoma and 90 died of other causes, free of melanoma, she said.

The investigators concluded that a 9-mm margin was superior to 6 mm.

She reported no disclosures. ■

VECTICAL™ (calcitriol) OINTMENT, 3 mcg/g
For topical use only.
Not for oral, ophthalmic, or intravaginal use.
Not to be applied to the eyes, lips, or facial skin.

BRIEF SUMMARY INDICATIONS AND USAGE:

VECTICAL Ointment is a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Effects on Calcium Metabolism

In controlled clinical trials with VECTICAL Ointment, among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the upper limit of normal.

If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

Ultraviolet Light Exposure

Animal data suggest that the vehicle of VECTICAL Ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumors.

Subjects who apply VECTICAL Ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use VECTICAL Ointment.

Unevaluated Uses

The safety and effectiveness of VECTICAL Ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated. The safety and effectiveness of VECTICAL Ointment in patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated.

ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience

VECTICAL Ointment was studied in two vehicle-controlled studies (419 subjects), and in one open label study (324 subjects). The table below describes exposure to VECTICAL Ointment in 743 subjects, including 239 exposed for 6 months and 116 exposed for one year.

Four hundred and nineteen subjects were treated with VECTICAL Ointment twice daily for 8 weeks. The population included subjects ages 13 to 87, males (284) and females (135), Caucasians (372) and non-Caucasians (47); with mild (105) to moderate (313) chronic plaque psoriasis.

Selected Adverse Events Occurring in at least 1% of Subjects in the Two Pooled Vehicle-Controlled Studies

	VECTICAL Ointment (n=419)	Vehicle Ointment (n=420)
Discomfort skin	3%	2%
Pruritus	1%	1%

Among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle, however the elevations were less than 10% above the upper limit of normal. The open label study enrolled 324 subjects with psoriasis who were then treated for up to 52 weeks. Adverse events reported at a rate of greater than or equal to 3% of subjects treated with VECTICAL Ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hypercalciuria (3%), and pruritus (3%). Kidney stones were reported in 3 subjects and confirmed in two.

Postmarketing Experience

The following adverse reactions have been identified during worldwide post-approval use of VECTICAL Ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, and skin discomfort. Because these 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 drug exposure.

DRUG INTERACTIONS

VECTICAL Ointment should be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies for VECTICAL Ointment in pregnant women. VECTICAL Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcitriol were performed in which rats were treated orally at dosages up to 0.9 mcg/kg/day (5.4 mcg/m²/day) and in which rabbits received topical application of calcitriol ointment (3 ppm) to 6.4% of the body surface area. No effects on reproductive or fetal parameters were observed in rats. In rabbits, topically applied calcitriol induced a significantly elevated mean post-implantation loss and an increased incidence of minor skeletal abnormalities due to retarded ossification of the pubic bones. A slightly increased incidence of skeletal variation (extra 13th rib, reduced ossification of epiphyses) was also observed. These effects may have been secondary to maternal toxicity. Based on the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

Nursing Mothers

It is not known whether calcitriol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VECTICAL Ointment is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VECTICAL Ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcitriol was applied topically to mice for up to 24 months, no significant changes in tumor incidence were observed. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated.

A two-year carcinogenicity study was conducted in which calcitriol was orally administered to rats at dosages of approximately 0.005, 0.03, and 0.1 mcg/kg/day (0.03, 0.18, and 0.6 mcg/m²/day, respectively). The incidence of benign pheochromocytomas was significantly increased in female rats. No other significant differences in tumor incidence data were observed.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcitriol ointment, a reduction in the time required for UVR to induce the formation of skin tumors was observed in all groups that received the ointment base, including the vehicle-treated control group, relative to animals that received no ointment but which were exposed to UVR. The time required for UVR to induce the formation of skin tumors did not differ between animals that received plain vehicle and those that received vehicle that contained calcitriol. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. These data suggest that the vehicle of VECTICAL Ointment may enhance the ability of UVR to induce skin tumors.

Calcitriol did not elicit genotoxic effects in the mouse lymphoma TK locus assay. Studies in which male and female rats received oral doses of calcitriol of up to 0.6 mcg/kg/day (3.6 mcg/m²/day) indicated no impairment of fertility or general reproductive performance.

Based upon the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposure in these studies.

PATIENT COUNSELING INFORMATION

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. Patients using VECTICAL Ointment should receive the following information:

Instructions for Use

This medication is to be used as directed by the physician. It is for external use only. This medication is to be applied only to areas of the skin affected by psoriasis, as directed. It should be gently rubbed into the skin so that no medication remains visible.

Adverse Reactions

Patients should report any signs of adverse reactions to their physician.

Marketed by:

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

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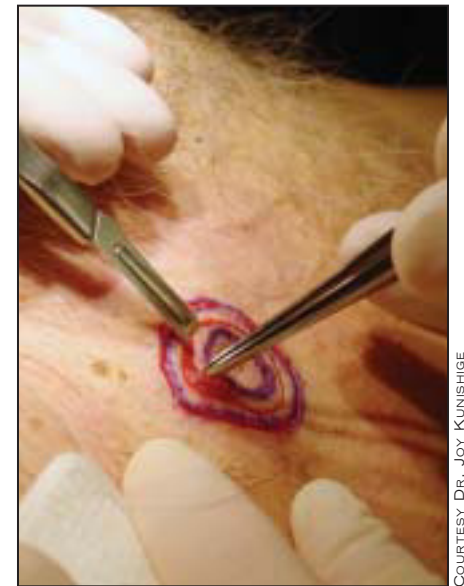
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A 5-mm margin may not be adequate for removing the majority of tumors.

COURTESY DR. JOY KUNISHIGE

Polymorphisms Show Potential In Melanoma

DENVER — Vascular endothelial growth factor provides a potential new target for the prevention and/or adjunct treatment of melanoma.

Several specific VEGF polymorphisms were strongly associated with primary tumor thickness and ulceration in a single nucleotide polymorphism genotyping study involving 778 patients with primary melanoma, Dr. Huey Liu reported at the annual meeting of the American Association for Cancer Research.

Median tumor thickness was 1.1 mm; 22% of the melanomas were ulcerated.

Patients with the VEGF -2578 C polymorphism had significantly thinner tumors than did patients without it: 1.2 mm, as compared with 1.3 mm.

In contrast, the VEGF +936 T polymorphism was associated with significantly thicker tumors: a median of 1.4 mm, compared with 1.1 mm in those without. In addition, 28% of melanomas in +936 T-positive patients were ulcerated, compared with 19% in those without +936 T, according to Dr. Liu of the M.D. Anderson Cancer Center, Houston.

—Bruce Jancin