

Nanoemulsion Speeds Herpes Labialis Healing

BY MICHAEL KAUFMAN

SAN FRANCISCO — NB-001, a novel topical antiviral nanoemulsion, significantly improved time to healing of herpes labialis by more than 1 day, judging from the findings of a randomized, double-blind, vehicle-controlled trial of more than 900 people.

“The improvement in time to healing [defined as the difference in hours be-

tween first treatment and healing, divided by 24 hr/day] was similar to that reported for oral nucleoside analogues,” reported Dr. Terry Jones, a dermatologist who is an investigator with J and S Studies Inc. of Bryan, Tex., which conducted the study for NanoBio Corp., the developer of NB-001.

Although oral nucleoside analogues—including ganciclovir, acyclovir, and famciclovir—have been shown to be ef-

fective, they are infrequently prescribed because of concerns over the potential development of drug resistance, said Dr. Jones at the annual meeting of the American Academy of Dermatology.

Dr. Jones and his associates assessed the clinical efficacy of three concentrations of NB-001, which is designed to permeate to the site of infection and kill virus by fusing with the viral envelope, causing disruption and viral lysis.

The novel mechanism of action renders the emergence of drug resistance “highly unlikely,” said Dr. Jones, who also is in private practice in College Station, Tex. The size of the nanoemulsion droplets (180 nm) prevents them from entering the tight junctions of epithelial cells, minimizing the potential for irritation or systemic absorption, he noted.

The 919 subjects enrolled in the study were 18-80 years old and had a history of three cold-sore outbreaks per year. They were randomized to receive one of four treatments (NB-001 0.1%, 0.3%, or 0.5%, or vehicle) and were instructed to apply 200 mcL five times daily at the first sign of recurrence for up to 4 days. The subjects returned to the clinic within 12 hours of the onset of symptoms, and daily thereafter, for assessments of lesion stage. Lesions were considered to be healed when the skin had returned to normal and no scabs remained.

Of the 919 subjects, 482 had a recurrence and started treatment. “All treatments were well tolerated with no safety concerns or systemic absorption,” Dr. Jones said. Of the three active regimens, the 0.3% formulation provided the highest tissue levels of NB-001 and resulted in a significant improvement in time to healing (1.3 days, compared with vehicle).

A subset analysis of subjects considered by the investigator to be at the prodromal or erythematous stage at baseline indicated a time to healing of 3.6 days for subjects who were treated with 0.3% NB-001. This, said Dr. Jones, was nearly 2 days improvement over vehicle.

“In subjects with no lesion at baseline, NB-001 provides a significant clinical advantage over current topical and systemic agents,” he said.

The same patients were included in the safety population for an evaluation of the safety, tolerability, and pharmacokinetics of topical NB-001, results of which were reported by Dr. Michael Jarratt, an investigator for DermResearch Inc. in Austin, Tex., which conducted the study. A subset of subjects had pharmacokinetic sampling following application of medication to an open lesion. The samples were analyzed for circulating levels of cetylpyridinium chloride (CPC), a marker for the nanoemulsion.

The study subjects experienced few adverse events, and those observed were generally mild to moderate “as expected for the population,” said Dr. Jarratt, who also presented the data at the annual meeting of the AAD. One subject experienced “facial burning” at the application site, but that was considered to be unrelated to the study medication. Two subjects discontinued early because of adverse events that were also considered to be unrelated to NB-001.

Investigators found no detectable CPC in 99% of the plasma samples. Four samples had minimally detectable levels; two of those were obtained from subjects who had been randomized to the vehicle.

Both Dr. Jones and Dr. Jarratt reported receiving research support from NanoBio Inc. ■

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

Manufactured by:

Galderma Production Canada Inc.
Baie d'Urfé, QC, H9X 3S4 Canada
Made in Canada.

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