



Bosentan group patients had 2.3 new ulcers versus 4.4 new lesions in the control group.

COURTESY DR. JAMES R. SEIBOLD

# Bosentan Prevents Scleroderma Ulcers

BY NANCY WALSH  
New York Bureau

SAN DIEGO — A second randomized clinical trial has confirmed that treatment with bosentan can help prevent the formation of digital ulcers in patients with scleroderma, Dr. James R. Seibold reported at the annual meeting of the American College of Rheumatology.

A total of 188 patients from 41 cen-

ters in North America and Europe were enrolled in the Randomized Placebo-Controlled Investigation of Digital Ulcers in Scleroderma (RAPIDS-2). All had scleroderma and at least one recent active digital ulcer, and their mean disease duration was 8.7 years.

At baseline, patients randomized to the placebo and bosentan groups had a mean of 3.6 and 3.7 digital ulcers, respectively. By 24 weeks, a mean of 2.7 new ulcers were seen in the placebo

group, compared with a mean of 1.9 in the active treatment group, Dr. Seibold said in a late-breaking poster session. This difference was statistically significant.

Statistically significant differences were already apparent by week 12, at which time the placebo group had a mean of 1.3 new digital ulcers, whereas the bosentan group had a mean of 0.8 new ulcers.

The effects were particularly marked in patients with more severe peripheral vascular injury, said Dr. Seibold, director of the University of Michigan Scleroderma Program, Ann Arbor.

Among patients who had more than 3 ulcers at baseline, those receiving placebo developed 4.4 new ulcers during the 24 weeks of the trial, while those receiving bosentan had 2.3 new ulcers, which was a statistically significant difference, he said.

"These data suggest that if a patient with scleroderma were to present at a physician's office with three digital ulcers, he or she would be likely to develop an additional four to five ulcers over the next 24 weeks, and the risk of that occurring would be reduced by nearly 50% on bosentan," Dr. Seibold said in a discussion of the trial at a satellite symposium.

Bosentan treatment did not, however, shorten the time to healing of active digital ulcers. In 6 months, only 50% of ulcers had healed despite treatment with topical and systemic antibiotics and adjustments to therapy for Raynaud's phenomenon. "These data are quite instructive in terms of getting a handle on how intractable this problem is. We are treating the untreatable," he said.

The study also evaluated the effects of treatment on hand functionality as measured by the Scleroderma Health Assessment Questionnaire. Most notable was a significant improvement in patients' ability to dress. On this domain, change from baseline was -0.35 in the bosentan group; a change of -0.22 is considered clinically meaningful.

The findings of this study are in agreement with those in RAPIDS-1, which evaluated bosentan in 122 patients with scleroderma for 16 weeks, and found a 48% reduction in the mean number of new ulcers (Arthritis Rheum. 2004;50:3985-93).

Serious adverse events were uncommon. As in RAPIDS-1, more patients in the active treatment group had elevations of liver enzymes greater than 3 times the upper limit of normal (10.5%) than in the placebo group (1.1%).

Bosentan (Tracleer) is a dual endothelin receptor antagonist. Endothelin-1 and its receptors, particularly the ET<sub>B</sub> receptor, are overexpressed in scleroderma, and the vasoconstrictive and pro-proliferative effects of endothelin-1 contribute to the vasculopathy associated with the disease. The RAPIDS data "support the contention that chronic endothelin receptor antagonism has an important effect on vascular integrity and function in systemic sclerosis," he said.

Dr. Seibold disclosed that he has received research grants and consulting fees from Actelion Pharmaceuticals Ltd., the sponsor of the trial.

## ZOVIRAX® (acyclovir) Cream 5% Soothes at the Site to Heal Herpes Fast

- Targeted treatment soothes at the site<sup>1</sup>
- Significantly shortens lesion duration vs placebo\*<sup>1</sup>
- Significantly shortens pain duration vs placebo\*<sup>1</sup>

\* Shorter duration of episode: in study 1, acyclovir (n=324) 4.3 days vs vehicle (n=346) 4.8 days (P=0.010). In study 2, acyclovir (n=328) 4.6 days vs vehicle (n=343) 5.2 days (P=0.007). Shorter duration of pain: in study 1, acyclovir (n=334) 2.9 days vs vehicle (n=352) 3.2 days (P=0.024). In study 2, acyclovir (n=348) 3.1 days vs vehicle (n=351) 3.5 days (P=0.027).

Reference: 1. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T, for The Acyclovir Cream Study Group. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother.* 2002;46:2238-2243.

### ZOVIRAX® (acyclovir) Cream 5%

#### INDICATIONS AND USAGE

ZOVIRAX Cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

#### CONTRAINDICATIONS

ZOVIRAX Cream is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.

#### PRECAUTIONS

**General:** ZOVIRAX Cream is intended for cutaneous use only and should not be used in the eye or inside the mouth or nose. ZOVIRAX Cream should only be used on herpes labialis on the affected external aspects of the lips and face. Because no data are available, application to human mucous membranes is not recommended. ZOVIRAX Cream has a potential for irritation and contact sensitization (see ADVERSE REACTIONS). The effect of ZOVIRAX Cream has not been established in immunocompromised patients.

**Drug Interactions:** Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with ZOVIRAX Cream.

**Carcinogenesis, Mutagenesis, Impairment or Fertility:** Systemic exposure following topical administration of acyclovir is minimal. Dermal carcinogenicity studies were not conducted. Results from the studies of carcinogenesis, mutagenesis and fertility are not included in the full prescribing information for ZOVIRAX Cream due to the minimal exposures of acyclovir that result from dermal application. Information on these studies is available in the full prescribing information for ZOVIRAX Capsules, Tablets, and Suspension and ZOVIRAX for Injection.

**Pregnancy: Teratogenic Effects:** Pregnancy Category B. Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects

or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Systemic acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether topically applied acyclovir is excreted in breast milk. Systemic exposure following topical administration is minimal. After oral administration of ZOVIRAX, acyclovir concentrations have been documented in breast milk in 2 women and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Nursing mothers who have active herpetic lesions near or on the breast should avoid nursing.

**Geriatric Use:** Clinical studies of acyclovir cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic absorption of acyclovir after topical administration is minimal (see CLINICAL PHARMACOLOGY).

**Pediatric Use:** Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

#### ADVERSE REACTIONS

In 5 double-blind, placebo-controlled trials, 1,124 patients were treated with ZOVIRAX Cream and 1,161 with placebo (vehicle) cream. ZOVIRAX Cream was well tolerated; 5% of patients on ZOVIRAX Cream and 4% of patients on placebo reported local application site reactions.

The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each event occurred in less than 1% of patients receiving ZOVIRAX Cream and vehicle. Three patients on ZOVIRAX Cream and 1 patient on placebo discontinued treatment due to an adverse event.

An additional study, enrolling 22 healthy adults, was conducted to evaluate the dermal tolerance of ZOVIRAX Cream compared with vehicle using single occluded and semi-occluded patch testing methodology. Both ZOVIRAX Cream and vehicle showed a high and cumulative irritation potential. Another study, enrolling 251 healthy adults, was conducted to evaluate the contact sensitization potential of ZOVIRAX Cream using repeat insult patch testing methodology. Of 202 evaluable subjects, possible cutaneous sensitization reactions were observed in the same 4 (2%) subjects with both ZOVIRAX Cream and vehicle, and these reactions to both ZOVIRAX Cream and vehicle were confirmed in 3 subjects upon rechallenge. The sensitizing ingredient(s) has not been identified.

The safety profile in patients 12 to 17 years of age was similar to that observed in adults.

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir cream. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to acyclovir cream.

**General:** Angioedema, anaphylaxis.

**Skin:** Contact dermatitis, eczema, application site reactions including signs and symptoms of inflammation.

#### OVERDOSAGE

Overdosage by topical application of ZOVIRAX Cream is unlikely because of minimal systemic exposure (see CLINICAL PHARMACOLOGY).

#### DOSAGE AND ADMINISTRATION

ZOVIRAX Cream should be applied 5 times per day for 4 days. Therapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear). For adolescents 12 years of age and older, the dosage is the same as in adults.

#### HOW SUPPLIED

Each gram of ZOVIRAX Cream 5% contains 50 mg acyclovir in an aqueous cream base. ZOVIRAX Cream is supplied as follows:

2-g tubes (NDC 64455-994-42).

5-g tubes (NDC 64455-994-45).

Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

Manufactured by

GlaxoSmithKline  
Research Triangle Park, NC 27709

for

**BIOVAIL**  
Pharmaceuticals, Inc.

Bridgewater, NJ 08807

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**Soothes the Outbreak**



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