ZIRGAN (ganciclovir ophthalmic gel) 0.15% Treats Herpetic Dendritic Ulcers

To watch a video of these cases, visit Eyetube.net and enter the keyword "Zirgan" in the search bar.

BY JAY S. PEPOSE, MD, PHD

Recently, I was presented with a case of acute herpes simplex epithelial keratitis that I was able to successfully treat with ZIRGAN, or ganciclovir ophthalmic gel 0.15% (Bausch + Lomb, Rochester, NY; recently made available in the United States). ZIRGAN is a topical ophthalmic antiviral gel that is indicated for the treatment of acute herpetic keratitis or dendritic ulcers.

IMPORTANT RISK INFORMATION

ZIRGAN gel is indicated for topical ophthalmic use only. Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN. The most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%). See the brief summary of the ZIRGAN full prescribing information on page 3.

CASE STUDY

A 27-year-old female presented with a history of fever for 5 days, a nonproductive cough, and a red left eye for 2 days. I detected follicular conjunctivitis and some epiphora. I made the diagnosis of dendritic keratitis (Figure 1) and started her on ZIRGAN 0.15% gel five times per day. The dendritic lesion resolved within 6 days, after which I lowered the dose to t.i.d. for another week. The patient was pleased with the outcome and very comfortable with using the drug. I was glad to see a clinical resolution of the infection.

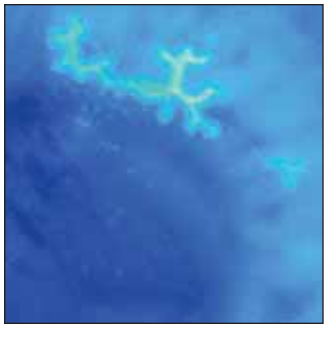


Figure 1. Dendritic keratitis that resolved after 2 weeks of treatment with ZIRGAN gel 0.15%.

I chose to use ZIRGAN 0.15% gel because it has proven efficacy, a low toxicity profile, and is well tolerated by my patients. Compared to trifluridine 1% drops (dosed one drop every 2 waking hours until re-epithelialization, then every 4 waking hours for 1 week), ZIRGAN offers a lower dosing regimen (1 drop 5 times per day until the ulcer heals, and then 1 drop 3 times per day for 7 days) and comes nonrefrigerated. Trifluridine 1% requires refrigeration, which can be challenging for patients who must take it with them when they leave the house to instill it every 2 hours. In addition, trifluridine is one of the few remaining ophthalmic drugs that are preserved with thimerosal.

MECHANISMS OF ACTION

ZIRGAN gel 0.15% works in two ways. It is phosphorylated primarily by the viral enzyme thymidine kinase, which allows the formulation to selectively target cells infected with herpes simplex virus. Also, ganciclovir, the active molecule in ZIRGAN, inhibits the synthesis of viral DNA by (1) competitive inhibition—activated ganciclovir directly inhibits viral DNA polymerase, thus preventing viral replication; and (2) chain termination—the activated ganciclovir incorporates into viral DNA, inhibiting DNA synthesis.

ACCURATE DIAGNOSIS

Other ocular disorders, such as medicamentosa, can mimic herpetic keratitis and complicate a definitive diagnosis. Referred patients who have been diagnosed incorrectly may be on antiviral, antibiotic, and antifungal medications that contain preservatives and can mimic a dendritic lesion. Other diseases that can mimic herpetic keratitis include acanthamoeba and varicella-zoster. I find it most helpful to make a differential diagnosis of the dendritic lesion. The word *dendritic* comes from the Latin root for *many fingers*, and dendritic ulcers have several delicate branches and are sometimes likened in appearance to a tree. The zoster lesions are more coarse and truncated. In addition, herpes simplex is a true ulcer, which means the entire lesion will stain with fluorescein. Zoster lesions are more elevated and will stain negatively or just in small parts.

Prior to the approval of ZIRGAN 0.15% gel in the United States, trifluridine was my topical drug of choice. It is satisfying to have ZIRGAN as a topical ophthalmic treatment option that has proven efficacy combined with a low toxicity profile and thus allows me to treat a localized disease locally in my appropriate patients as indicated. ◆

Jay S. Pepose, MD, PhD, is the director of the Pepose Vision Institute and a professor of clinical ophthalmology and visual sciences at the Washington University School of Medicine in St. Louis. Dr. Pepose may be reached at (636) 728-0111; jpepose@peposevision.com.

Treating Herpes Simplex Virus With a Low Risk of Toxicity

BY PAUL KARPECKI, OD

Both herpes zoster ophthalmicus and herpes simplex keratitis can be very painful conditions, due to the fact that they directly impact the ocular nerves. Herpes simplex keratitis can range from a simple, uncomfortable infection to a severe condition that can cause blindness. The National Eye Institute estimates that 400,000 Americans have experienced some form of ocular herpes, with close to 50,000 new and recurring cases occurring each year.

ZIRGAN (ganciclovir ophthalmic gel) 0.15% (Bausch + Lomb, Rochester, NY) was made available commercially in the United States in April 2010, and I immediately put it to work on a very challenging case. ZIRGAN is a topical ophthalmic antiviral gel that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

IMPORTANT RISK INFORMATION

ZIRGAN gel is indicated for topical ophthalmic use only. Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN. The most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

HERPES SIMPLEX CASE

A 68-year-old white woman was referred to me with a red, watery, burning, and painful right eye. She also had a history of lid disease and ocular allergies. Her general practitioner identified dendrites and correctly diagnosed the infection as herpes simplex virus. The patient was prescribed trifluridine, but after 3 weeks, she began to experience toxicity. The physician lowered the dose as much as possible to reduce the toxic effect, but the patient's symptoms remained substantial. The patient was instructed to cease use of the medication, but unfortunately, the dendritic ulcers that had disappeared reignited. Throughout this course, the patient's inflammation continued to increase.

When the patient presented to me, still exhibiting dendrites, I was able to offer her the approved ZIRGAN gel 0.15%. The eye's response to ZIRGAN dosed five times per day was dramatic; the dendrites resolved within 3 days. I instructed the patient to continue using ZIRGAN with t.i.d. dosing for 7 days following the resolution of the dendrites.

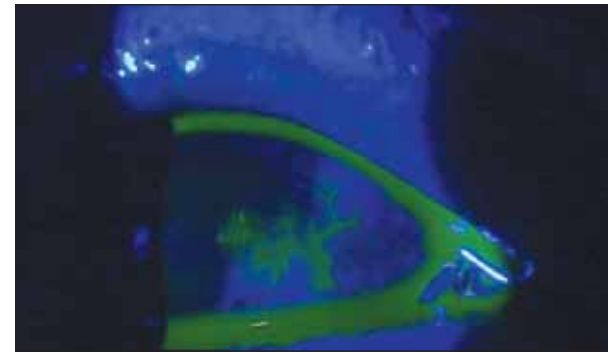


Figure 1. A case of herpes simplex virus, similar to the one described, resolved after 5 days of treatment with ZIRGAN gel 0.15%. Individual results may vary. In clinical trials, resolution (healed ulcers) at day 7 was achieved in 72% (41 of 57) to 77% (55 of 71) of patients with dendritic ulcers.

DISCUSSION

A major complicating factor in this case was the patient's hypersensitivity to the previous medication, which increased the eye's irritation and inflammation and complicated the disease state. ZIRGAN gel 0.15% is phosphorylated primarily by the viral enzyme thymidine kinase, meaning that it selectively targets the replication of DNA in the HSV viral particles and not the corneal epithelium. ZIRGAN has a neutral pH and an osmolarity that is very similar to that of human tears. ZIRGAN both soothed the eye and effectively cleared the dendrites.

EFFICACY AND CONVENIENCE

I have since used ZIRGAN 0.15% in a variety of cases of herpetic keratitis (dendritic ulcers) and have had positive results every time. I find the gel to be highly effective with a low toxicity profile. Additionally, the reduced dosing regimen and the fact that it does not require refrigeration provide a convenience factor that I was not able to offer my patients in the past. For me, it is now the only way to treat a herpetic ulcer or dendrite in the United States. ◆

Paul Karpecki, OD, is the clinical director of Corneal Services at Koffler Vision Group in Lexington, Kentucky. He is a paid consultant to Bausch + Lomb but stated that he holds no financial interest in the product mentioned herein. Dr. Karpecki may be reached at paul@karpecki.com.

Zirgan®

ganciclovir ophthalmic gel 0.15%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use ZIRGAN® safely and effectively. See full prescribing information for ZIRGAN.

ZIRGAN (ganciclovir ophthalmic gel) 0.15%
Initial U.S. approval: 1989

----------INDICATIONS AND USAGE----------

ZIRGAN is a topical ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers). (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days. (2)

----------DOSAGE FORMS AND STRENGTHS----------

ZIRGAN contains 0.15% of ganciclovir in a sterile preserved topical ophthalmic gel. (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- ZIRGAN is indicated for topical ophthalmic use only. (5.1)
- Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: June 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZIRGAN (ganciclovir ophthalmic gel) 0.15% is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

2 DOSAGE AND ADMINISTRATION

The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.

3 DOSAGE FORMS AND STRENGTHS

ZIRGAN contains 0.15% of ganciclovir in a sterile preserved topical ophthalmic gel.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

ZIRGAN is indicated for topical ophthalmic use only.

5.2 Avoidance of Contact Lenses

Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN.

6 ADVERSE REACTIONS

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Teratogenic Effects

Pregnancy Category C: Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (approximately 10,000x and 17,000x the human ocular dose of 6.25 mcg/kg/day), respectively, assuming complete absorption. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality. Daily intravenous doses of 90 mg/kg/day (14,000x the human ocular dose) administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

There are no adequate and well-controlled studies in pregnant women. ZIRGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic ganciclovir administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Caution should be exercised when ZIRGAN is administered to nursing mothers.

8.4 Pediatric Use

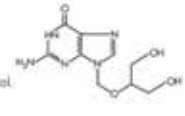
Safety and efficacy in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

ZIRGAN (ganciclovir ophthalmic gel) 0.15% contains a sterile, topical antiviral for ophthalmic use. The chemical name is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (CAS number 82410-32-0). Ganciclovir is represented by the following structural formula:



Ganciclovir has a molecular weight of 255.23, and the empirical formula is $C_9H_{13}N_5O_4$.

Each gram of gel contains: ACTIVE: ganciclovir 1.5 mg (0.15%). INACTIVES: carbopol, water for injection, sodium hydroxide (to adjust the pH to 7.4), mannitol. PRESERVATIVE: benzalkonium chloride 0.075 mg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZIRGAN (ganciclovir ophthalmic gel) 0.15% contains the active ingredient, ganciclovir, which is a guanosine derivative that, upon phosphorylation, inhibits DNA replication by herpes simplex viruses (HSV). Ganciclovir is transformed by viral and cellular thymidine kinases (TK) to ganciclovir triphosphate, which works as an antiviral agent by inhibiting the synthesis of viral DNA in 2 ways: competitive inhibition of viral DNA-polymerase and direct incorporation into viral primer strand DNA, resulting in DNA chain termination and prevention of replication.

12.3 Pharmacokinetics

The estimated maximum daily dose of ganciclovir administered as 1 drop, 5 times per day is 0.375 mg. Compared to maintenance doses of systemically administered ganciclovir of 900 mg (oral valganciclovir) and 5 mg/kg (IV ganciclovir), the ophthalmically administered daily dose is approximately 0.04% and 0.1% of the oral dose and IV doses, respectively, thus minimal systemic exposure is expected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1,000 mg/kg/day (approximately 3,000x and 160,000x the human ocular dose of 6.25 mcg/kg/day, assuming complete absorption). At the dose of 1,000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland, and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (160x the human ocular dose). Except for histocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2,000 mcg/mL, respectively.

In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV) (24,000x to 80,000x human ocular dose) but not 50 mg/kg (8,000x human ocular dose). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5,000 mcg/mL.

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 14,000x the human ocular dose of 6.25 mcg/kg/day). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg (30x to 1,600x the human ocular dose).

14 CLINICAL STUDIES

In one open-label, randomized, controlled, multicenter clinical trial which enrolled 164 patients with herpetic keratitis, ZIRGAN was non-inferior to acyclovir ophthalmic ointment, 3% in patients with dendritic ulcers. Clinical resolution (healed ulcers) at Day 7 was achieved in 77% (55/71) for ZIRGAN versus 72% (48/67) for acyclovir 3% (difference 5.8%, 95% CI - 9.6%-18.3%). In three randomized, single-masked, controlled, multicenter clinical trials which enrolled 213 total patients, ZIRGAN was non-inferior to acyclovir ophthalmic ointment 3% in patients with dendritic ulcers. Clinical resolution at Day 7 was achieved in 72% (41/57) for ZIRGAN versus 69% (34/49) for acyclovir (difference 2.5%, 95% CI - 15.6%-20.9%).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZIRGAN is supplied as 5 grams of a sterile, preserved, clear, colorless, topical ophthalmic gel containing 0.15% of ganciclovir in a polycoated aluminum tube with a white polyethylene tip and cap and protective band (NDC 24208-535-35).

Storage

Store at 15°C-25°C (59°F-77°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel. If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician. Patients should be advised not to wear contact lenses when using ZIRGAN.

Revised: June 2010

Bausch & Lomb Incorporated, Tampa, FL 33637

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