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 non-productive 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.

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 non-refrigerated. 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.

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

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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.

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.

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Zirgan®
ganciclovir ophthalmic gel 0.15%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all 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 ocular antiviral agent that is indicated for the treatment of acute herpetic keratitis (herpetic ulcers) (1)

DOSEAGE AND ADMINISTRATION
The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 3 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)

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

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
ZIRGAN (ganciclovir ophthalmic gel) 0.15% is indicated for the treatment of acute herpetic keratitis (herpetic ulcers). (2)

2 DOSAGE AND ADMINISTRATION
The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 3 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)

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

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
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 65% of rabbits and mice administered 60 mg/kg/day and 10 lg/kg/day (approximately 10,000x and 1700x the human ocular dose of 0.25 mg/kg/day, respectively), assuming complete absorption. Effects observed in rabbits included fetal growth retardation, emphysema, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachycephaly. In mice, effects observed were maternal toxicity and embroyotoxicity. 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 male-old offspring, as well as pathologic changes in the non-glandular portion 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 ocular ganciclovir administration could result in sufficient systemic absorption to produce detectable amounts 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 agent for ophthalmic use. The chemical name is 9-[2-(hydroxy-1-hydroxyethyl)ethoxyethyl]guanine (CAS number: 82410-32-0). Ganciclovir is represented by the following structural formula:

\[
\text{Ganciclovir} = \text{C}_{16}\text{H}_{25}\text{N}_{2}\text{O}_{5}\]

Each gram of gel contains: ACTIVE: ganciclovir 13 mg (0.15%), N A T I V E S: carbon, water for injection, sodium hydroxide (to adjust the pH to 7.4), mannitol PRESERVATIVE: benzalkonium chloride 0.075 mg.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
ZIRGAN is indicated for topical ophthalmic use only. (1)

Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN. (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 1-800-723-0000 or FDA 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

8 Supplied
STERILE AMPOULES: Ganciclovir ophthalmic gel contains 0.015% of ganciclovir in a polyoxymethylene tube with a white polyethylene tip and cap protective band (NDC 24203-335-35).

Storage
Store at 5°C-25°C (41°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 Blinking or rubbing, or any other contact lenses are worn, the patient should be advised to consult a physician. Patients should be advised not to wear contact lenses when using ZIRGAN.

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