DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-211

NDA APPROVAL

Sirion Therapeutics, Inc
Attention: Jeremy Brace
Vice President, Regulatory Affairs
9314 E Broadway Avenue
Tampa, FL 33619

Dear Mr. Brace:

Please refer to your new drug application (NDA) dated November 14, 2008, received November 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zirgan (ganciclovir ophthalmic gel) 0.15%.

We acknowledge receipt of your submissions dated January 6, February 2, 3, 5, and 19, March 19 and 25, June 24, August 6 and 31, and September 10 (two), 2009.

This new drug application provides for the use of Zirgan (ganciclovir ophthalmic gel) 0.15% for the treatment of acute herpetic keratitis (dendritic ulcers).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling, text for the package insert, submitted September 10, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-211**."

We acknowledge your September 10, 2009, submission containing final printed carton and container labels.

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted September 10, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative

purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-211.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with Final Printed Labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product for this indication has an orphan drug designation, and therefore, you are exempt from this requirement.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

In addition, we request that you submit one copy of the introductory promotional materials you propose to use for this product to this division. Please submit one market package of the drug product when it is available.

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori Marie Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert, Carton and Container labels

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 US 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 Sirion Therapeutics at 1-866-4SIRION (1-866-474-7466) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2009

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, 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

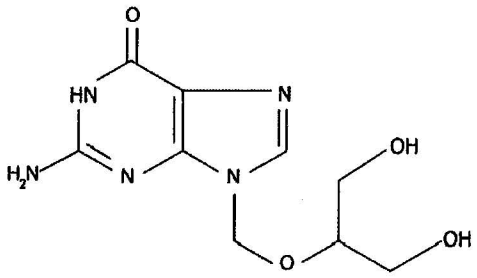
Safety and efficacy in pediatric patients below the age of 2 years have not been established.

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 42826-605-50).

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: September 2009

SIRiON
Therapeutics

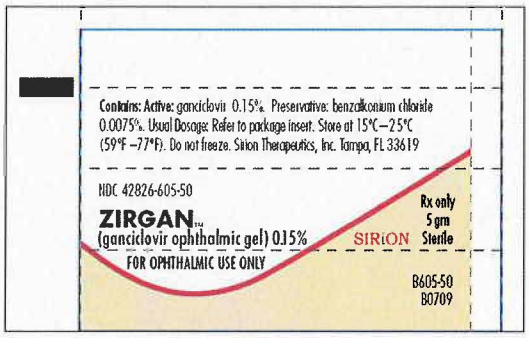
Manufactured for: Sirion Therapeutics, Inc., Tampa, FL 33619

By: Alliance Medical Products, Inc., Irvine, CA 92688

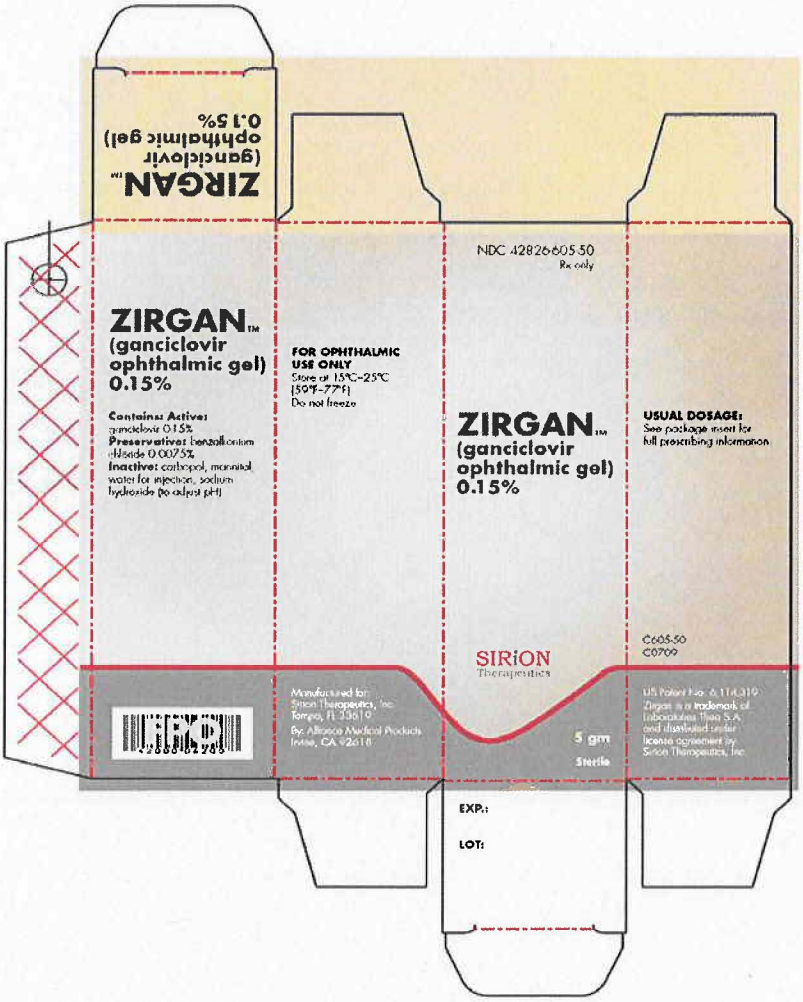
Zirgan™ is the trademark of Laboratoires Thea S.A., and is distributed under license agreement by Sirion Therapeutics, Inc.

 PI605

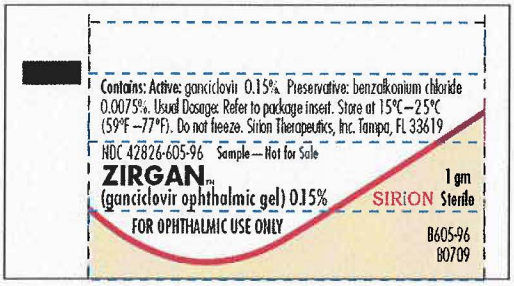
Commercial 5 gm container label



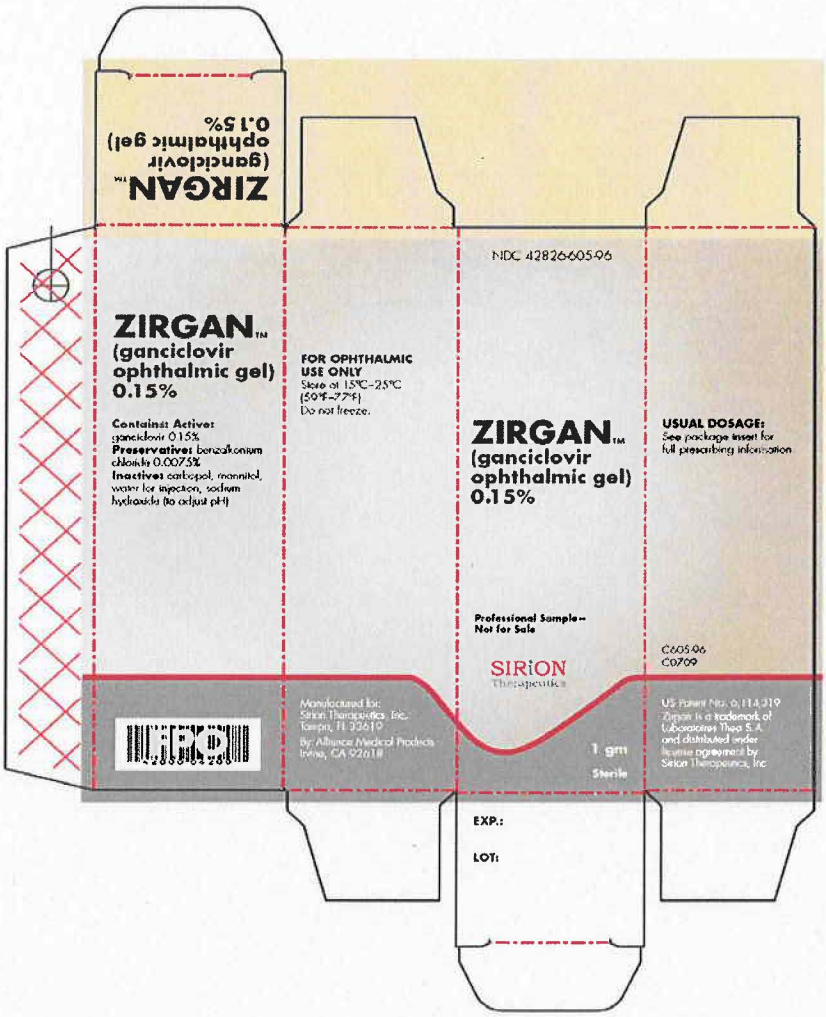
Commercial 5 gm carton



Professional Sample 1 gm container label



Professional Sample 1 gm carton



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22211	ORIG-1	SIRION THERAPEUTICS	ZIRGAN (GANCICLOVIR OPHTHALMIC GEL)0.15%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
09/15/2009