

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-211**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA 22-211  
Submission Number 000  
Submission Code Original

Letter Date November 14, 2008  
Stamp Date November 17, 2008  
PDUFA Goal Date September 17, 2009

Reviewer Name Lucious Lim, M.D., M.P.H.  
Review Completion Date September 9, 2009

Established Name ganciclovir ophthalmic gel  
0.15%  
(Proposed) Trade Name Zirgan  
Therapeutic Class antiviral  
Applicant Sirion Therapeutics, Inc.

Priority Designation S

Formulation Active ingredient: ganciclovir (a  
synthetic guanine derivative, 9-  
[[[2-hydroxy-1-(hydroxymethyl)  
ethoxy]methyl]guanine)  
Dosing Regimen 1 drop in the affected eye 5 times  
per day (approximately every 3  
hours while awake) until the



**Table of Contents**

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>5</b>
1.1	Recommendation on Regulatory Action.....	5
1.2	Risk Benefit Assessment .....	5
1.3	Recommendations for Postmarketing Risk Management Activities .....	5
1.4	Recommendations for other Post Marketing Study Commitments .....	5
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND.....</b>	<b>5</b>
2.1	Product Information.....	5
2.2	Currently Available Treatments for Proposed Indications .....	6
2.3	Availability of Proposed Active Ingredient in the United States .....	6
2.4	Important Safety Issues With Consideration to Related Drugs .....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission.....	7
2.6	Other Relevant Background Information .....	7
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>7</b>
3.1	Submission Quality and Integrity .....	7
3.2	Compliance with Good Clinical Practices .....	7
3.3	Financial Disclosures.....	7
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b>	<b>8</b>
4.1	Chemistry Manufacturing and Controls .....	8
4.2	Clinical Microbiology.....	8
4.3	Preclinical Pharmacology/Toxicology.....	8
4.4	Clinical Pharmacology .....	9
4.4.1	Mechanism of Action.....	9
4.4.2	Pharmacokinetics .....	9
<b>5</b>	<b>SOURCES OF CLINICAL DATA .....</b>	<b>10</b>
5.1	Tables of Clinical Studies.....	10
5.2	Review Strategy.....	12
5.3	Discussion of Individual Studies .....	12
5.3.1	Study 7 – Protocol Nos. 64.GV550/04.92 and 66.GV550/06.92 – Open multicenter comparative study on the effect of the instillation of Zirgan in superficial corneal herpes .....	12
5.3.2	Studies 4, 5, and 6 – Comparative multicenter single blind clinical study on the effect of the instillation of ganciclovir eye gel in the treatment of superficial corneal herpes. ....	14
<b>6</b>	<b>REVIEW OF EFFICACY.....</b>	<b>14</b>
6.1	Indication.....	14
6.1.1	Methods .....	14
6.1.2	Demographics .....	14
6.1.3	Patient Disposition.....	15
6.1.4	Analysis of Primary Endpoint(s) .....	15
6.1.5	Analysis of Secondary Endpoints(s).....	18
6.1.6	Other Endpoints .....	19
6.1.7	Subpopulations .....	19
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations .....	19
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	19
6.1.10	Additional Efficacy Issues/Analyses.....	19
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>19</b>
7.1	Methods .....	19

7.1.1	Clinical Studies Used to Evaluate Safety.....	19
7.1.2	Adequacy of Data .....	20
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence.....	20
7.2	Adequacy of Safety Assessments .....	20
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	20
7.2.2	Explorations for Dose Response.....	20
7.2.3	Special Animal and/or In Vitro Testing.....	20
7.2.4	Routine Clinical Testing.....	20
7.2.5	Metabolic, Clearance, and Interaction Workup .....	21
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .....	21
7.3	Major Safety Results .....	21
7.3.1	Deaths .....	21
7.3.2	Nonfatal Serious Adverse Events .....	21
7.3.3	Dropouts and/or Discontinuations .....	21
7.3.4	Significant Adverse Events.....	22
7.3.5	Submission Specific Primary Safety Concerns.....	22
7.4	Supportive Safety Results.....	22
7.4.1	Common Adverse Events .....	23
7.4.2	Laboratory Findings.....	24
7.4.3	Vital Signs .....	24
7.4.4	Electrocardiograms (ECGs).....	24
7.4.5	Special Safety Studies.....	24
7.4.6	Immunogenicity.....	24
7.5	Other Safety Explorations .....	24
7.5.1	Dose Dependency for Adverse Events.....	24
7.5.2	Time Dependency for Adverse Events .....	24
7.5.3	Drug-Demographic Interactions .....	24
7.5.4	Drug-Disease Interactions.....	25
7.5.5	Drug-Drug Interactions.....	25
7.6	Additional Safety Explorations.....	25
7.6.1	Human Carcinogenicity.....	25
7.6.2	Human Reproduction and Pregnancy Data.....	25
7.6.3	Pediatrics and Effect on Growth.....	25
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	25
7.7	Additional Submissions .....	25
<b>8</b>	<b>POSTMARKETING EXPERIENCE.....</b>	<b>25</b>
<b>9</b>	<b>APPENDICES.....</b>	<b>26</b>
9.1	Literature Review/References .....	26
9.2	Advisory Committee Meeting .....	26
9.3	Labeling Recommendations .....	26

## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

It is recommended that NDA 22-211 be approved with the labeling revisions found in this review.

The application supports the safety and effectiveness of ganciclovir ophthalmic gel 0.15% for the treatment of acute herpetic keratitis (dendritic ulcers).

### **1.2 Risk Benefit Assessment**

There is adequate information in the literature to demonstrate that the active ingredient, ganciclovir, a synthetic guanine derivative antiviral agent, inhibits replication of herpes viruses both in vitro and in vivo. Sensitive human viruses include cytomegalovirus (CMV), herpes simplex virus (HSV, types 1 and 2), Epstein-Barr virus, and varicella zoster virus.

Ganciclovir has been shown to be active against CMV and HSV in human clinical studies. Ganciclovir is approved in the United States for the treatment of CMV retinitis in patients with AIDS (Cytovene -IV, Cytovene capsules, and Vitrasert implant) and for the prevention of CMV disease in patients with kidney, heart, and kidney-pancreas transplants (Valcyte). Ganciclovir ophthalmic gel 0.15% is approved in over 30 countries outside of the United States for the treatment of acute herpetic keratitis. The submitted studies in this NDA support a favorable risk benefit profile regarding the safety and efficacy of ganciclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer). The most common adverse events were blurred vision (59%) and eye irritation (18%).

### **1.3 Recommendations for Postmarketing Risk Management Activities**

There are no recommended Phase 4 clinical study commitments.

### **1.4 Recommendations for other Post Marketing Study Commitments**

There are no optional or recommended Phase 4 requests.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

The drug product (ganciclovir ophthalmic gel, 0.15%) is a sterile topical ophthalmic gel containing the active ingredient ganciclovir, a synthetic guanine derivative antiviral agent. The

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

aqueous gel is a \_\_\_\_\_, preserved, \_\_\_\_\_ solution. The topical gel is packaged in a multi-dose polyfoil tube. This formulation is for topical ophthalmic use only.

b(4)

The chemical name is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine. Its structural formula is:



MW 255.23 with a molecular formula of C<sub>9</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>.

**Quantitative and Qualitative Composition for Drug Product**

Component	Quantity (%w/w)	Function	Quality Standard
Ganciclovir	0.15%	Active ingredient	USP
Carbomer _____			NF
Mannitol			USP
Benzalkonium chloride _____			USP/NF
Sodium hydroxide	As needed	pH adjustment	NF
Water for injection	qs	Aqueous vehicle	USP

b(4)

NF, National Formulary; qs, quantum sufficient (a sufficient quantity); USP, United States Pharmacopeia; w/w, weight in weight  
 Source: Sirion Table 2.3.P.1 Composition of the ST-605 Drug Product

**2.2 Currently Available Treatments for Proposed Indications**

Trifluridine ophthalmic solution 1% (NDA 18-299) is approved and marketed for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2.

**2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient, ganciclovir, is a synthetic guanine derivative, which has antiviral activity against HSV. In the United States, ganciclovir is approved for the treatment of CMV retinitis in patients with AIDS (Cytovene -IV, Cytovene capsules, and Vitrasert ocular implant) and for the prevention of CMV disease in patients with kidney, heart, and kidney-pancreas transplants (Valcyte).

## **2.4 Important Safety Issues With Consideration to Related Drugs**

Animal studies indicate that ganciclovir is a potential carcinogen and may cause infertility in humans and birth defects in pregnant women.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

Orphan drug status for NDA 22-211 (IND 75,762) was granted on March 22, 2007.

The Agency provided responses to questions contained in a request for a Pre-IND/NDA meeting for NDA 22-211 on May 22, 2007. Agency responses to additional questions were provided on June 11, 2007, and October 29, 2007.

NDA 22-211 was originally filed on with the Agency on June 26, 2008, with a formulation (i.e. Formulation C) that was different from that used in the clinical trials. The application was withdrawn on August 26, 2008, and resubmitted on November 17, 2008, with a formulation more consistent with that used in the clinical trials (i.e. Formulation B\*).

## **2.6 Other Relevant Background Information**

Ganciclovir has been shown to be active against CMV and HSV in human clinical studies.

Ganciclovir ophthalmic gel 0.15% was originally approved in 1995 in France for the treatment of acute herpetic keratitis with the same database that has been submitted to support NDA 22-211. Since the initial approval, the drug product has been approved in over 30 countries outside of the United States for this indication.

# **3 Ethics and Good Clinical Practices**

## **3.1 Submission Quality and Integrity**

There is no evidence that the submitted studies were not conducted in accordance with acceptable clinical ethical standards.

## **3.2 Compliance with Good Clinical Practices**

The clinical studies included in this application conformed to Good Clinical Practices.

## **3.3 Financial Disclosures**

All clinical studies included in this application were conducted in Europe, Africa, and Asia between 1990 and 1994 and were originally sponsored by Laboratoires Thea formerly (TRANSPHYTO S.A.). Laboratoires Thea, a pharmaceutical company based in Clermont-

Ferrand, France, was not required to collect financial disclosure information from the investigators in those studies.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

See Section 2.1 this review.

### **4.2 Clinical Microbiology**

Not applicable to this review.

### **4.3 Preclinical Pharmacology/Toxicology**

From the Pharmacology/Toxicology review dated July 8, 2009:

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1,000 mg/kg/day (approximately 3,200x and 160,000x the human ocular dose of 6.25 µg/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 histiocytic 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 µg/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 µg/mL.

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryoletality in female mice following intravenous doses of 90 mg/kg/day (approximately 14,400x the human ocular dose of 6.25 µg/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 (32x to 1,600x the human ocular dose).

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 (9,600x and 17,280x the human ocular dose of 6.25 µg/kg/day, assuming complete absorption), respectively. Effects observed in rabbits included: fetal growth retardation, embryoletality, 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 embryoletality.

Daily intravenous doses of 90 mg/kg (14,400x 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.

Ganciclovir may be teratogenic or embryotoxic at dose levels recommended for human systemic use. There are no adequate and well-controlled studies in pregnant women. ZIRGAN should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

#### **4.4 Clinical Pharmacology**

##### **4.4.1 Mechanism of Action**

Ganciclovir is a synthetic guanine derivative antiviral drug 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 two ways: competitive inhibition of viral DNA-polymerase and direct incorporation into viral primer strand DNA, resulting in DNA chain termination and prevention of replication.

##### **4.4.2 Pharmacokinetics**

Systemic exposure to ganciclovir following ophthalmic administration of ganciclovir 0.15% gel is expected to be minimal. The estimated maximum daily dose of ganciclovir following 1 drop 5 times per day is 0.375 mg, compared to maintenance doses for 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 and IV doses, respectively, thus minimal systemic exposure is expected.

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 060  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

## 5 Sources of Clinical Data

### 5.1 Tables of Clinical Studies

Type of Study	Study Identifier (Study Period)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen: Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
efficacy/safety phase 2	<b>Study 4</b> Protocol No.: 42-2.GV550 /02.90 (April 1990-May 1992)	to evaluate the efficacy and safety of Gan 0.15% and Gan 0.05% vs acyclovir 3% in the treatment of herpetic keratitis	multicenter, randomized, stratified by center, comparison of Gan 0.15% and Gan 0.05% vs acyclovir 3%	Gan 0.15% or Gan 0.05% or acyclovir 3% 1 drop 5x/day until ulcer healed, then 3x/day for 7 days	N=67 Gan 0.15%=23 Gan 0.05%=22 acyclovir 3%=23	herpetic keratitis with dendritic or geographic ulcers	1 drop 5x/day until ulcer healed, then 3x/day for 7 days for a maximum duration of 21 days
efficacy/safety phase 2	<b>Study 5</b> Protocol Nos.: 44.GV 550/12.90 and 46.GV 550/07.90 (Dec 1990-May 1992)	to evaluate the efficacy and safety of Gan 0.15% vs acyclovir 3% in treatment of herpetic keratitis	multicenter, randomized, stratified by center, comparison of Gan 0.15% vs acyclovir 3%	Gan 0.15% or acyclovir 3% 1 drop 5x/day until ulcer healed, then 3x/day for 7 days	N=37 Gan 0.15%=19 acyclovir 3%=18	herpetic keratitis with dendritic or geographic ulcers	1 drop 5x/day until ulcer healed, then 3x/day for 7 days for a maximum duration of 21 days
efficacy/safety phase 2	<b>Study 6</b> Protocol No.:	to evaluate the efficacy and safety of Gan 0.15%	randomized, single-masked comparison	Gan 0.15% or Gan 0.05% or acyclovir 3%	N=109 Gan 0.15%=	herpetic keratitis with dendritic	1 drop 5x/day for 10 days

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

efficacy/ safety phase 3	47.GV 550/ 09.90 (May 1991- Oct 1992)	and Gan 0.05% vs acyclovir 3% in treatment of herpetic keratitis	of Gan 0.15% and Gan 0.05% vs acyclovir 3%	1 drop 5x/day for 10 days	36 Gan 0.05%= 35 acyclovir 3%=38 N=164 dendritic =138 geo- graphic= 26 Gan 0.15%= 84 dendritic =71 geo- graphic= 13 acyclovir 3%=80 dendritic =67 geo- graphic =13	or geo- graphic ulcers	1 drop 5x/day until ulcer healed, then 3x/day for 7days
Study 7 Protocol Nos.: 64.GV 550/ 04.92 And 66.GV 550/06.92 (Sept 1992- Sept 1994)	to evaluate the efficacy and safety of Gan 0.15% vs acyclovir 3% in treatment of herpetic keratitis by ulcer type	open-label, multicenter, randomized, stratified by center and ulcer type, comparison of Gan 0.15% vs Acyclovir 3%	Gan 0.15% or acyclovir 3%  1 drop 5x/day until ulcer healed, then 3x/day for 7 days			herpetic keratitis with dendritic or geo- graphic ulcers	

Gan=ganciclovir  
 Source: Sirion Table 5.2 - Tabular Listing of All Clinical Studies

All clinical studies were conducted in Europe, Africa, and Asia between 1990 and 1994 and were originally sponsored by Laboratoires  
 Thea formerly (TRANSPHYTO S.A.). Full study reports are included in this application.

## 5.2 Review Strategy

The November 18, 2008, submission was submitted electronically. All subsequent amendments were submitted electronically. All study reports and literature were reviewed. The included clinical study reports, post-marketing safety reports, literature review, and package inserts for the reference active ingredient ganciclovir formed the basis for the review of efficacy and safety for ganciclovir ophthalmic gel 0.15% for the proposed indication.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Sirion in this application for this indication.

## 5.3 Discussion of Individual Studies

This 505(b)(1) application relies on four clinical studies conducted in Europe, Africa, and Asia between 1990 and 1994 which were originally sponsored by Laboratoires Thea formerly TRANSPHYTO S.A. to support efficacy and safety of ganciclovir ophthalmic gel 0.15% for the proposed indication, treatment of acute herpetic keratitis (dendritic ~~ulcers~~ ulcers). b(4)

### 5.3.1 Study 7 – Protocol Nos. 64.GV550/04.92 and 66.GV550/06.92 – Open multicenter comparative study on the effect of the instillation of Zirgan in superficial corneal herpes

#### Primary objectives

- Evaluation of the clinical efficacy and local tolerance of ganciclovir ophthalmic gel 0.15% (Zirgan) on superficial herpetic corneal ulcers (dendritic and geographic) versus acyclovir 3% ophthalmic ointment

#### A. Study Design

Open-label, controlled, parallel group, randomized, multi-center clinical trial.

#### B. Major Eligibility Criteria

- Age  $\geq$  18 years.
- Patients of acute superficial keratitis whose clinical appearance strongly suggests a herpetic origin.

#### C. Treatment Groups

- Zirgan (ganciclovir ophthalmic gel 0.15%)
- Zovirax (acyclovir 3% ophthalmic ointment)

#### D. Duration of Treatment

- Dendritic ulcer: 3 weeks maximum

- Geographic ulcer: 5 weeks maximum

#### **E. Main Efficacy Outcomes**

Primary: Time to healing of dendritic or geographic ulcer (clinical disappearance of ulcer)

Secondary:

- Symptoms
- Physical indications, and in particular occurrences of profound herpetic damage (stromal keratitis, uveitis)

#### **F. Main Safety Outcomes**

Local tolerance: Presence (and intensity) of visual disturbances, tingling or burning on instillation, presence of conjunctival or palpebral reaction, superficial punctate keratitis of a toxic nature, other impairment of corneal epithelium or lacrimal punctum abnormalities.

#### **G. Sample Size**

The number of patients was chosen to enable a precise estimation of the recovery rate in both treatment groups. The sample size was increased from 100 patients presenting with dendritic ulcers to 130 patients in an amendment dated May, 1994. The calculation was based on the following:

In the control group B (Zovirax group), a recovery rate of 20% in 6 days is expected. A 20% improvement on the recovery rate, i.e. a recovery rate of 40%, is desired for group A (Zirgan group). Hence the failure rate at time  $t=6$ days can be deduced.

$$S_B(t) = 0.80$$

$$S_A(t) = 0.60$$

Relative risk  $r$  is therefore approximately 0.44 ( $r = \ln(S_B(t)) / \ln(S_A(t))$ ). Hence, as  $n = m / [2 - S_A(t) - S_B(t)]$ , the number of patients necessary for each randomized category is approximately 64, or 128 patients to be included in the study. It is therefore anticipated that the total recruitment of the study will be stopped when a recruitment of 130 patients presenting a dendritic ulcer has been achieved.

The patients presenting with geographic ulcer were recruited in addition to this number.

#### **H. Study Visits**

Dendritic ulcers: after 3, 7, 10 and 14 days, then if required, after 3 weeks of treatment.

Geographic ulcers: after 3, 7, 10 and 14 days, plus after 4 and 5 weeks of treatment.

#### **I. Statistical Analysis**

For each type of ulcer (dendritic or geographic), a difference will be considered statistically significant if the level of significance of the two-sided test is lower than 0.05.

5.3.2 Studies 4, 5, and 6 – Comparative multicenter single blind clinical study on the effect of the instillation of ganciclovir eye gel in the treatment of superficial corneal herpes.

Studies 4, 5, and 6 were phase 2 studies that were conducted in Africa, Europe, and Pakistan, respectively. The treatment groups in study 5 were ganciclovir 0.15% and acyclovir 3%. The treatment groups in studies 4 and 6 were ganciclovir 0.15%, ganciclovir 0.05%, and acyclovir 3%. The study design for all three studies was similar; single-blind, controlled, parallel group, randomized, multi-center clinical trial. The primary efficacy endpoint was time to cicatrisation of the ulcer (absence of coloration after instillation of fluorescein). The visit schedule in study 4 was Days 2, 7, 10, and 14. The visit schedule for studies 5 and 6 was Days 3, 7, 10, and 14.

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

The proposed indication is for the treatment of acute herpetic keratitis (dendritic ulcers). b(4)

##### 6.1.1 Methods

The major sources of clinical data utilized in this review include:

- One phase 3 clinical trial – Study 7.
- Three phase 2 clinical trials – Studies 4, 5, and 6.
- Literature search that identified published clinical articles involving placebo control and the active control acyclovir 3% trials.

##### 6.1.2 Demographics

**Study 7 - Demographics (Age, Sex) – ITT Population**

		Treatment	
		Ganciclovir 0.15%	Acyclovir 3%
Age (yrs)	N	84	80
	Mean	47.31	44.35
	Std	18.4	17.2
	Median	45.5	42.0
	Min	18	4
	Max	88	83
Sex			

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

Male	n (%)	58 (69.0)	56 (70.0)
Female	n (%)	26 (31.0)	24 (30.0)

Source: Sirion Table 4.1.1 – Demographics (Age, Sex) – ITT Population

#### Studies 4, 5, and 6 Combined - Demographics (Age, Sex) – ITT Population

		Treatment		
		Ganciclovir 0.15%	Acyclovir 3%	Ganciclovir 0.05%
Age (yrs)	N	77	77	57
	Mean	38.32	40.43	38.35
	Std	17.6	17.9	17.7
	Median	37.0	40.0	39.0
	Min	2	11	5
	Max	81	81	80
Sex				
Male	n (%)	48 (62.3)	51 (66.2)	43 (75.4)
Female	n (%)	29 (37.7)	26 (33.8)	14 (24.6)

Source: Sirion Table 5.1.1 – Demographics (Age, Sex) – ITT Population

#### 6.1.3 Patient Disposition

##### Study 7 - Disposition – ITT Population

Reason		Treatment		Total
		Ganciclovir 0.15%	Acyclovir 3%	
Adverse Event	n (%)	2 (2.4)	1 (1.3)	3 (1.8)
Completed	n (%)	61 (72.6)	62 (77.5)	123 (75.0)
Lack of Efficacy	n (%)	11 (13.1)	9 (11.3)	20 (12.2)
Lost to Follow-up	n (%)	10 (11.9)	8 (10.1)	18 (11.0)
Total	N	84	80	164

Source: Sirion Table 4.1.2 – Disposition – ITT Population

##### Studies 4, 5, and 6 Combined Disposition – ITT Population

Reason		Ganciclovir 0.15%	Acyclovir 3%	Ganciclovir 0.05%	Total
		Completed	n (%)	61 (79.2)	
Lack of Efficacy	n (%)	7 (9.1)	22 (28.6)	9 (15.8)	38 (18.0)
Lost to Follow-up	n (%)	9 (11.7)	6 (7.8)	3 (5.3)	18 (8.5)
Total	N	77	77	57	211

Source: Sirion Table 5.1.2 – Disposition ITT Population

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7. This review analyzed the submitted clinical data as though the phase 2 and phase 3 studies were designed as non-inferiority trials.

6.1.4.1 Efficacy Findings for Study 7 – Protocol Nos. 64.GV550/04.92 and 66.GV550/06.92

**Median Time to Recovery (Days) – ITT Population**

Treatment	Median
Ganciclovir 0.15%	7.0
Acyclovir 3%	7.0

Source: Sirion 5.3.5.1 Integrated Summary of Efficacy, 4.2.5 Median Time to Recovery (Days) – ITT Population

**Reviewer’s Comments:** *Although time to healing of ulcer (dendritic or geographic) was the specified primary efficacy endpoint, the primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7.*

*The statistical plan was written without an understanding of how to write a non-inferiority statistical plan. The assumption of a cure rate of 20% in 6 days for acyclovir and a 20% improvement for ganciclovir on this cure rate is not supported by the literature or the results from the ganciclovir phase 2 clinical trials. The cure rate for acyclovir is approximately 80%. This review analyzed the submitted clinical data as though study 7 was designed as non-inferiority trial. There is sufficient data in the literature to justify a non-inferiority margin for dendritic ulcers, but not for geographic ulcers.*

**Idoxuridine (IDU) vs Placebo – Day 7 Cure (Dendritic Ulcers)**

First Author	Year	Control	IDU Cures n/N (%)	Control Cures n/N (%)
Burns	1963	Water ± Mydriatics, Steroids	15/23 (65)	5/15 (33)
Davidson	1964	Gamma globulin 1%	12/25 (48)	8/25 (32)
Hart	1965	Neosporin 0.3% with 0.5% Chlorbutol	14/19 (74)	2/13 (15)
Laibson	1964	Water + Thimersol	15/22 (66)	7/26 (27)
Markham	1977	Ointment and Homatropine	4/20 (20)	4/19 (21)
Lutz	1963	Neosporin 1%	3/11 (27)	5/11 (45)
Patterson	1963	Culture medium	5/10 (50)	5/13 (38)
Patterson	1963	Phenyl mercuric nitrate	13/17 (76)	2/15 (13)
Patterson	1963	Occlusive dressing	11/16 (69)	0/14 (0)
Average (95% CI)			92/163 (56) (49%-64%)	38/151 (25) (18%-32%)

**Reviewer’s Comments:** *IDU is superior to placebo for the treatment of dendritic ulcers.*

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

**Acyclovir vs IDU – Day 7 Cure (Dendritic Ulcers)**

First Author	Year	Control	Acyclovir Cures n/N (%)	IDU Cures n/N (%)
Colin	1981	IDU	19/25 (76)	11/27 (41)
Collum	1980	IDU	29/30 (97)	6/30 (20)
Coster	1980	IDU	27/28 (96)	22/26 (85)
Klauber	1982	IDU	8/10 (80)	5/10 (50)
McCulley	1982	IDU	16/26 (62)	16/26 (62)
Average (95% CI)			99/119 (83) (76%-90%)	60/119 (50) (41%-59%)

**Reviewer's Comments:** *Acyclovir 3% is superior to IDU for the treatment of dendritic ulcers. The data supports a non-inferiority margin of 10% for the active control, acyclovir 3%.*

**Study 7 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)	95 % CI
Ganciclovir 0.15%	55/71 (77)	68%-87%
Acyclovir 3%	48/67 (72)	64.2%-85.0%
Difference	5.8%	(-9.6%-18.3%)

**Reviewer's Comments:** *The non-inferiority analysis showed that the lower 95% confidence interval around the difference between ganciclovir 0.15% and acyclovir 3% (9.6%) was no greater than the non-inferiority margin (10%).*

6.1.4.2 Efficacy Findings for Studies 4, 5, and 6

**Study 4 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)
Acyclovir 3%	11/17 (65)
Ganciclovir 0.15%	13/20 (65)
Ganciclovir 0.05%	13/20 (65)

**Study 5 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)
Acyclovir 3%	10/17 (59)
Ganciclovir 0.15%	14/17 (82)

**Study 6 – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)
Acyclovir 3%	13/15 (87)
Ganciclovir 0.15%	14/20 (70)

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

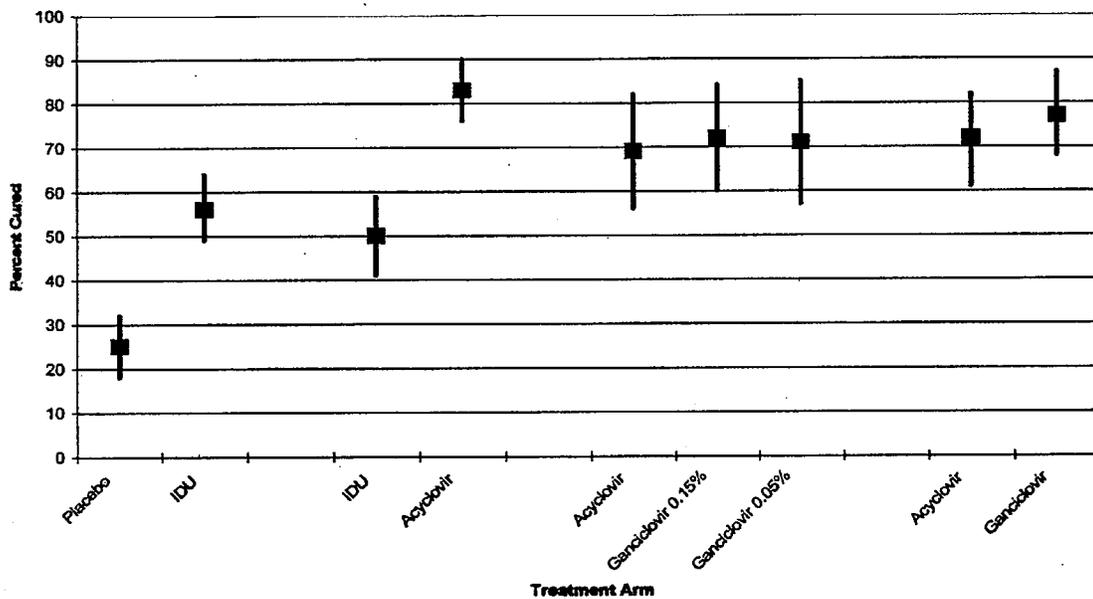
Ganciclovir 0.05%	16/21 (76)
-------------------	------------

**Combined Phase 2 Studies – Cure Rate at Day 7 (Dendritic Ulcers)**

Treatment	n/N (%)	95 % CI
Acyclovir 3%	34/49 (69)	56%-82%
Ganciclovir 0.15%	41/57 (72)	60%-84%
Ganciclovir 0.05%	29/41 (71)	57%-85%
Difference between Acyclovir and ganciclovir 0.15%	2.5%	-15.6%-20.9%

**Reviewer’s Comments:** *The cure rate at Day 7 (dendritic ulcers) for ganciclovir and acyclovir 3% are similar. The phase 2 studies data demonstrate that ganciclovir is not inferior to acyclovir 3% for dendritic ulcers.*

**Day 7 Cure Rate with 95% Confidence Intervals**



**Reviewer’s Comments:** *IDU is superior to placebo; acyclovir is superior to IDU; and ganciclovir is not inferior to acyclovir.*

**6.1.5 Analysis of Secondary Endpoints(s)**

The secondary endpoints in the phase 3 trial (study 7) included recovery rate (healed ulcer at any time during study), number of relapses, and global end-of-study assessment of efficacy.

**Study 7 - Secondary Endpoints (Dendritic Ulcers) – ITT Population**

Endpoint	Ganciclovir 0.15%	Acyclovir 3%	P-value
Recovery rate	88.73%	91.04%	P=0.65
Number of Relapses	2	2	
% efficacy very satisfactory	67.6	71.7	

**6.1.6 Other Endpoints**

No other efficacy endpoints were evaluated.

**6.1.7 Subpopulations**

No subgroup analyses were conducted.

**6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

The optimal frequency of administration was based on the results of the clinical studies. The dosing regimen utilized in studies 4, 5, and 7 was 1 drop instilled into the conjunctival sac 5 times a day until the ulcer has healed, then 3 times a day for 7 days. The dosing regimen utilized in study 6 was 1 drop instilled into the conjunctival sac 5 times a day for 10 days.

**6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

There is no persistence of efficacy or tolerability issue.

**6.1.10 Additional Efficacy Issues/Analyses**

There are no additional efficacy issues/analyses.

**7 Review of Safety**

**Safety Summary**

**7.1 Methods**

**7.1.1 Clinical Studies Used to Evaluate Safety**

The major sources of clinical data utilized in this review include:

- One phase 3 clinical trial – Study 7

- Three phase 2 clinical trials – Studies 4, 5, and 6
- Worldwide marketing experience

### 7.1.2 Adequacy of Data

The patient exposure and safety assessments were adequate.

A total of 161 and 57 subjects were exposed to ganciclovir 0.15% and ganciclovir 0.05%, respectively in three phase 2 (studies 4, 5, and 6) and one phase 3 studies (study 7). The mean days of exposure was 11.5 days for ganciclovir 0.15% and 9.1 days for ganciclovir 0.05%.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Pooled data is presented because of the small number of adverse events reported.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 161 and 57 subjects were exposed to ganciclovir 0.15% and ganciclovir 0.05%, respectively in three phase 2 (studies 4, 5, and 6) and one phase 3 studies (study 7). The mean days of exposure were 11.5 days for ganciclovir 0.15% and 9.1 days for ganciclovir 0.05%.

### 7.2.2 Explorations for Dose Response

The nonclinical studies established a range of doses that were safe and effective. The results indicated that ganciclovir 0.15% was more effective than ganciclovir 0.05%. This was confirmed in clinical studies 4 and 5 which showed that the higher ganciclovir concentration (0.15%) was more effective than ganciclovir 0.05%.

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal and in vitro testing is necessary.

### 7.2.4 Routine Clinical Testing

The clinical testing performed in the studies was adequate for evaluation of the new drug product.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The passage of ganciclovir into the systemic circulation is very low after repeated topical administration in subjects with ulcerated corneas. Measurements of metabolism, clearance, and interaction are insignificant.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Oral and IV ganciclovir are contraindicated in patients with hypersensitivity to ganciclovir or acyclovir.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths were reported for subjects treated with ganciclovir 0.15%.

### 7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious adverse events were reported for subjects treated with ganciclovir 0.15%.

### 7.3.3 Dropouts and/or Discontinuations

#### Drop-outs for Studies 4, 5, 6, and 7

Study	Treatment		
	Ganciclovir 0.15% n/N (%)	Acyclovir 3% n/N (%)	Ganciclovir 0.05% n/N (%)
4	3/23 (13.0)	7/22 (31.8)	6/22 (27.3)
5	2/18 (11.1)	7/17 (41.2)	
6	2/36 (5.6)	8/38 (22.2)	4/35 (11.4)
7	11/71 (15.5)	8/67 (11.9)	

Source: Sirion 5.3.5.1 Integrated Summary of Efficacy, Study 7-Table 3, Study 6-Table 4.A, Study 5-Table 4.A, Study 4-Table 4.A

#### Drop-outs Due to Adverse Event

Study	Treatment		
	Ganciclovir 0.15% n/N (%)	Acyclovir 3% n/N (%)	Ganciclovir 0.05% n/N (%)
4	0/23 (0.0)	0/22 (0.0)	0/22 (0.0)
5	0/18 (0.0)	0/17 (0.0)	
6	0/36 (0.0)	0/38 (0.0)	0/35 (0.0)
7	2/71 (2.8)	1/67 (1.5)	

Source: Sirion 2.7.4.6.2 Treatment-Related Withdrawals Due to Adverse Events

### 7.3.4 Significant Adverse Events

#### Study 7 – Drop-outs Due to Adverse Event

Subject No.	Ganciclovir 0.15%	Acyclovir 3%
074	Foreign body in eye, resulting in palpebral and conjunctival disorders, superficial punctate keratitis (SPK), and epithelial abrasion	
537	Bilateral conjunctival hyperemia recorded 48 hours after cessation of treatment (so it was not possible at the study visit to determine whether the subject applied the product to both eyes), minimal SPK, burning	
032		SPK, initial signs of punctuate keratitis

Source: Sirion 2.7.4.6.2 Summary of Clinical Safety, Table 4. Withdrawal Due to Adverse Events

### 7.3.5 Submission Specific Primary Safety Concerns

There are no specific safety issues related to this drug product.

## 7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Adverse Events – Studies 4, 5, 6 & 7 Pooled – Safety Population**

Measure	Study 4		Study 5		Study 6			Study 7		Total		
	GAN 0.15%  N=23	ACY  N=22	GAN 0.05%  N=22	GAN 0.15%  N=18	ACY  N=17	GAN 0.15%  N=36	ACY  N=38	GAN 0.05%  N=35	GAN 0.15%  N=84	ACY  N=80	GAN 0.15% & 0.05% N=218	ACY  N=167
<b>Ocular</b>												
Vision blurred	3 13%	3 13.6%	3 13.6%	14 77.8%	16 94.1%	33 91.7%	37 97.4%	33 94.3%	43 51.2%	56 70%	129 59.2%	112 71.3%
Eye irritation	4 17.4%	10 45.5%	5 22.7%	3 16.7%	10 58.8%	1 2.8%	2 5.3%	1 2.9%	25 29.8%	35 43.8%	39 17.9%	55 46.2%
Punctate keratitis	3 13%	2 9.1%	0	0	0	0	0	0	8 9.5%	17 21.3%	11 5.0%	19 11.4%
Conjunctival hyperemia	1 4.3%	0	1 4.5%	4 22.2%	2 11.8%	0	0	2 5.7%	2 2.4%	4 5%	10 4.6%	6 3.6%
Erythema of the eyelid	1 4.3%	0	1 4.5%	2 11.1%	2 11.8%	0	0	0	1 1.2%	2 2.5%	5 2.3%	4 2.4%
Corneal disorder	0	0	0	0	1 5.9%	0	0	0	1 1.2%	0	1 0.5%	1 0.6%
Eye pain	0	0	0	0	0	0	1 2.6%	1 2.9%	0	0	1 0.5%	1 0.6%
Dry eye	0	0	0	0	0	0	0	1 2.9%	0	0	1 0.5%	0
Lacrimation increased	0	0	0	0	0	0	0	1 2.9%	0	0	1 0.5%	0
Foreign body sensation	0	0	0	0	0	0	0	1 2.9%	0	0	1 0.5%	0
<b>Non-ocular</b>												
Dysgeusia	0	0	0	0	0	0	0	0	1 1.2%	0	0	1 0.6%
Headache	0	0	0	0	0	0	1 2.6%	0	0	0	0	1 0.6%

GAN=ganciclovir, ACY=acyclovir 3%

Source: Sirion 2.7.4.4.4 – Summary of Clinical Safety, Tables 2 and 3

**Reviewer's Comments:** *The most common ocular adverse events were blurred vision (59%) and eye irritation (18%). No non-ocular adverse events occurred at a rate of 5% or more.*

#### 7.4.2 Laboratory Findings

No clinical chemistry was performed. Hematology results did not show any significant clinical findings. Urinalysis showed there was no detectable ganciclovir in the urine samples.

The mean plasma ganciclovir concentration was very low,  $12.7 \pm 3.7$  ng/mL (average of 57 instillations of the product before sampling).

#### 7.4.3 Vital Signs

No vital signs were collected in the studies performed.

#### 7.4.4 Electrocardiograms (ECGs)

No ECG was collected in the studies performed.

#### 7.4.5 Special Safety Studies

No special safety studies were performed.

#### 7.4.6 Immunogenicity

Ganciclovir is not expected to be immunogenic.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

No dose dependency for adverse events was identified.

#### 7.5.2 Time Dependency for Adverse Events

No time dependency for adverse events was identified.

#### 7.5.3 Drug-Demographic Interactions

No studies were performed specifically to analyze responses to the drug in different demographic subsets.

#### 7.5.4 Drug-Disease Interactions

There is no evidence of drug-disease interactions.

#### 7.5.5 Drug-Drug Interactions

No formal drug interaction studies were performed with topical ophthalmic ganciclovir.

### 7.6 Additional Safety Explorations

#### 7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted.

#### 7.6.2 Human Reproduction and Pregnancy Data

No studies in humans on the effects of topical ophthalmic ganciclovir on reproduction or pregnancy were conducted.

#### 7.6.3 Pediatrics and Effect on Growth

This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). No studies of the effect on growth have been performed.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose experience is available. There is no drug abuse potential, no withdrawal effect, and no rebound effect with this drug product.

### 7.7 Additional Submissions

There were no additional submissions.

## 8 Postmarketing Experience

Ganciclovir is approved in over 30 countries outside of the United States and marketed under the brand name, Virgan. Since the launch of the product in 1996, no actions relating to safety has been taken; no article concerning case report of adverse reaction with ganciclovir has been found in the literature. Two cases of spontaneous report of adverse event were submitted to the marketing authorization holder.

## **9 Appendices**

### **9.1 Literature Review/References**

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Sirion in this application for this indication.

### **9.2 Advisory Committee Meeting**

No Advisory Committee was necessary or convened for this drug product.

### **9.3 Labeling Recommendations**

NDA 22-211, Zirgan (ganciclovir ophthalmic gel) 0.15% is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the labeling submitted on September 9, 2009, and found here at the end of this Medical Officer review.

Clinical Review  
Lucious Lim, M.D., M.P.H.  
NDA 22-211 000  
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 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2009

---

**FULL PRESCRIBING INFORMATION:  
CONTENTS\***

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
  - 5.1 Topical Ophthalmic Use Only
  - 5.3 Avoidance of Contact Lenses
- 6 ADVERSE REACTIONS
- 8 USE IN SPECIFIC POPULATIONS
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use

- 8.5 Geriatric Use
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
  - 12.1 Mechanism of Action
  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
  - 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
- 14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

\*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, embryoletality, 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 embryoletality. 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 has not been established.

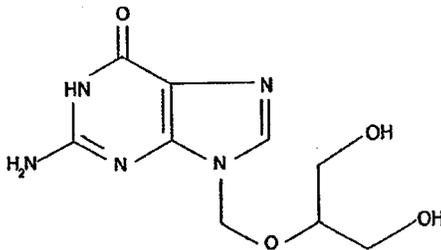
#### **8.5 Geriatric Use**

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

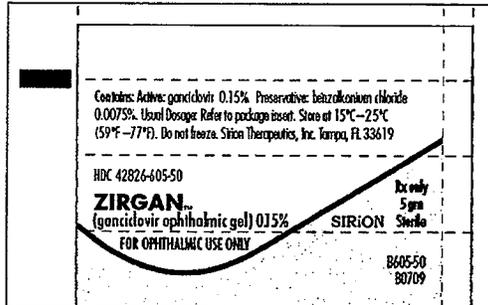
By: Alliance Medical Products, Inc., Irvine,  
CA 92688

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

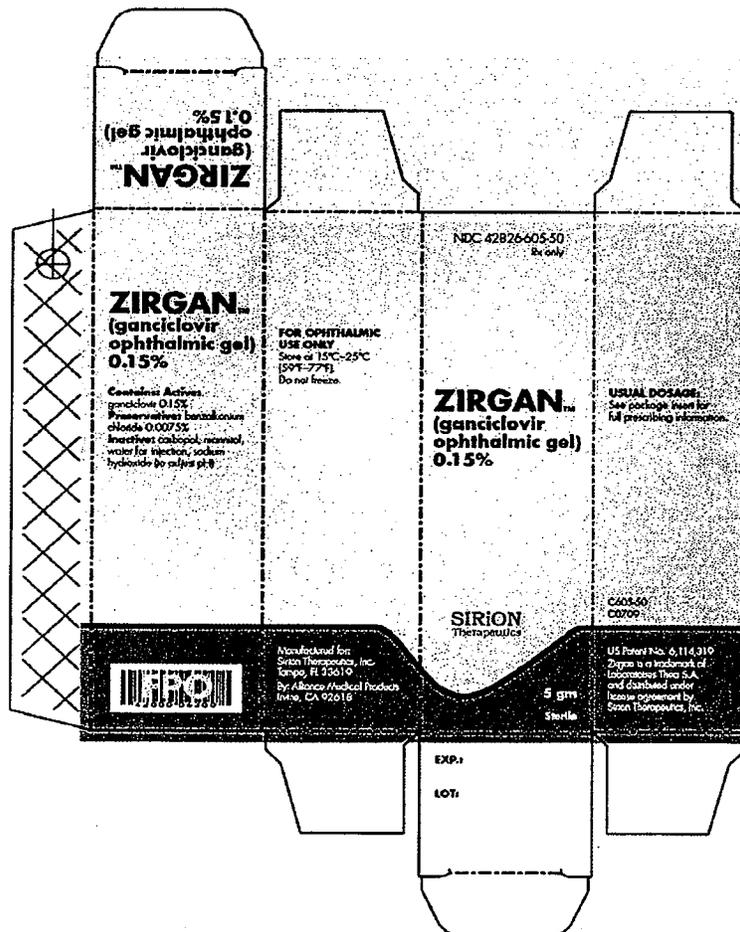
© 2009, Sirion Therapeutics, Inc. All Rights  
Reserved. PI605

Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

**Commercial 5 gm container label**

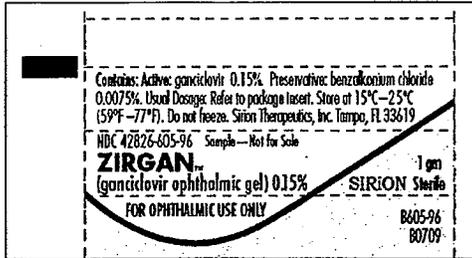


**Commercial 5 gm carton**



Clinical Review  
 Lucious Lim, M.D., M.P.H.  
 NDA 22-211 000  
 Zirgan (ganciclovir ophthalmic gel) 0.15%

**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 OPTHALMIC 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/

---

LUCIOUS LIM  
09/11/2009

WILLIAM M BOYD  
09/11/2009