CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-211

SUMMARY REVIEW

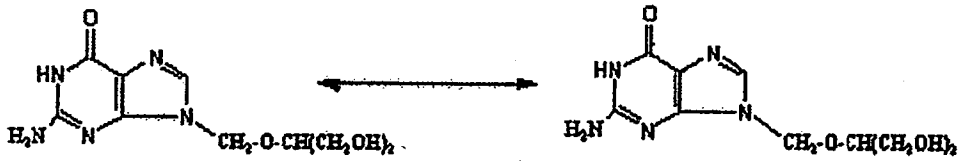
Division Director Review

Date	September 15, 2009
From	Wiley A. Chambers, M.D.
NDA #	22-211
Name	Zirgan (ganciclovir ophthalmic gel) 0.15%
Dosage forms	Topical ophthalmic gel
Applicant	Sirion Therapeutics, Inc.
Date of Submission	November 14, 2008
Type of Application	505(b)(1)
Proposed Indication(s)	Indicated for the treatment of acute herpetic keratitis (dendritic ulcers)
Action:	Approval

1. Introduction

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

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



is:

MW 255.23 with a molecular formula of $C_9H_{13}N_5O_4$.

This 505(b)(1) application includes four clinical studies conducted in Europe, Africa, and Asia between 1990 and 1994 which were sponsored by Laboratoires Théa formerly TRANSPHYTO S.A. to support efficacy and safety of ganciclovir ophthalmic gel 0.15% for the recommended indication, treatment of acute herpetic keratitis (dendritic ulcers). Laboratoires Théa has provided Sirion a right of reference to all of the clinical data and clinical study reports for Ganciclovir Ophthalmic Gel, 0.15%.

2. Background

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).

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.

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.

Orphan drug status for NDA 22-211 (IND 75,762) was granted on March 22, 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 that is consistent with that used in the clinical trials (i.e. Formulation B*).

3. CMC

Ganciclovir ophthalmic gel, 0.15% (ganciclovir) is currently marketed outside the U.S. by Laboratoires Théa of France for the treatment of acute herpetic keratitis. Ganciclovir administered as an oral drug product and an intravenous drug product is approved in the U.S. for the treatment of CMV retinitis (Valcyte, NDA 21-304 and Cytovene, NDA 19-661).

Four formulations of ganciclovir gel will be discussed. All of the clinical studies were conducted outside of the US, by Laboratoires Théa. Formulation A was used in the Phase 2 clinical trials, and Formulation B was used in the Phase 3 clinical trial and was the original commercially marketed formulation (first approved in 1995). Formulation C has been approved and marketed in Europe and internationally since 2001, and Formulation B* is proposed for U.S. marketing.

Formulation History

Parameter	Formulation/Variation			
	A	B	B*	C
Ganciclovir concentration	0.05% and 0.15%	0.15%		0.15%
Ganciclovir source				

b(4)

qs. quantity sufficient.

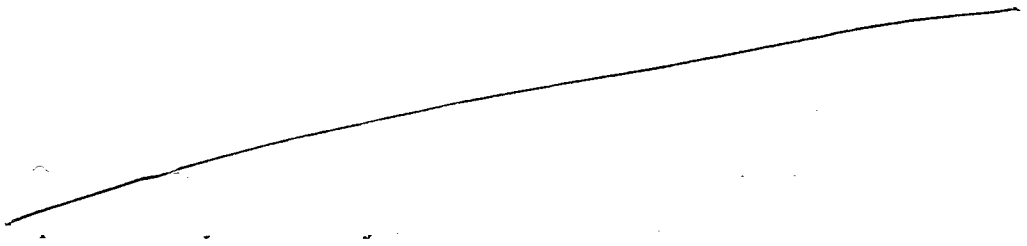
Formulation Usage

Purpose	Formulation/Variation			
	A	B	B*	C
Phase 1		X		
Phase 2	X			
Phase 3		X		
Commercial		X	X	X
	Clinical development	Clinical development and approved and marketed for use in Europe	Proposed for marketed product in the US	Current marketed product for European and international distribution
Used in Théa clinical studies	1, 4, 5, and 6	2, 3, and 7		

Formulation A: The formulation for Formulation A was identical for both dose strengths of ganciclovir evaluated (0.05% and 0.15%), with only the amount of ganciclovir in each formula varying. Both dose strengths of Formula A were used during the Phase 2 studies dose ranging conducted during clinical development.

Formulation B: On the basis of the clinical results obtained from the studies using Formulation A, the 0.15% strength was the dose strength selected for Phase 3 studies with Formulation B. During clinical development, the preservative used in the formulation was changed from sodium mercurothiolate at a concentration of 0.0060% to benzalkonium chloride 0.0075%. After the change to the antimicrobial preservative, additional Phase 1 and Phase 3 controlled clinical studies were performed. Marketing authorization in France was originally granted for Formulation B on August 10, 1995. In December 2000, a transfer of the marketing authorization from Transphyto to Laboratoires Théa occurred after the merging of the 2 companies.

Formulation C: Formulation C is the formula currently marketed in Europe. The transition from Formulation B to Formulation C occurred in 2001. The difference between Formulation B and Formulation C is as follows:



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The Formulation C change has been in effect since 2001.

Formulation B*: Formulation B* is the proposed formulation for marketing authorization in the U.S. Formulation B* will use water for injection instead of , as in the previous Laboratoires Théa formulations.

Quantitative and Qualitative Composition of U.S. Market Formula B*

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

qs. quantum sufficient, a sufficient quantity; USP, United States Pharmacopeia; NF, National Formulary

b(4)

PROPOSED REGULATORY SPECIFICATIONS (from Table 1, Section 3.2.P.5.1, September 9, 2009, submission):

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 1

FACILITIES INSPECTIONS:
The overall recommendation from the Office of Compliance is "Acceptable" in EES.

4. Nonclinical Pharmacology/Toxicology

Most of the non-clinical safety information in support of this NDA has been previously submitted for Cytovene (referenced with permission, ganciclovir sodium for injection – Roche Laboratories, NDA 19-661). The systemic toxicity of ganciclovir in animals was investigated in toxicity studies conducted by Syntex and Roche Pharmaceutical Companies, in support of ganciclovir for injection. Additional safety studies have been conducted by Laboratoires Théa to evaluate the safety and tolerability of the ganciclovir ophthalmic formulations.

The repeat-dose intravenous and oral toxicity studies in animals showed that ganciclovir caused anemia and testicular toxicity. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes *in vitro* at concentrations of 50 to 500 and 250 to 2000 µg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg but not 50 mg/kg. Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 µg/mL. Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 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, clitorial gland and vagina) and liver in females. No carcinogenic effect was observed in mice administered at 1 mg/kg/day.

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, respectively. 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.

Seven local ocular tolerance studies have been conducted with ganciclovir, when administered in the ganciclovir ophthalmic gel formulation. Three of the local tolerance studies compared the effects of ganciclovir eye gel containing either BAC 0.0075% as the preservative or sodium mercurothiolate 0.006% (thimerisol) as the preservative. The BAC preservative was selected prior to the Phase 3 clinical study and was also present in the initially marketed Virgan formulation. In these studies, there appeared to be no differences between gel formulations with respect to irritancy to the conjunctiva, iris or cornea, or corneal sensitivity after single instillation, or wound-healing time after repeat instillation. The ocular toxicity information from the above studies has been previously used in the marketing approval of ganciclovir ophthalmic formulation of ganciclovir (Virgan) in foreign countries. Two additional studies have been conducted evaluating the local tolerance and corneal toxicity of ganciclovir and trifluridine 1% in rabbits with intact corneas or with total corneal epithelial defects.

None of the ocular studies showed any systemic adverse reactions resulting from ocular topical instillation of ganciclovir, regardless of formulation tested. The only noted ocular finding was slight irritation and redness post instillation. However, each morning the signs of the previous day had disappeared, showing reversibility of the irritation.

The animal ocular tolerance studies with ganciclovir (0.15%) included regimen of 1 drop per eye, 5 times a day, for up to 42 days. It appears that there is a sufficient margin of safety.

5. Clinical Pharmacology/Biopharmaceutics

The application includes one pharmacokinetic study in subjects with acute herpetic keratitis (Study 1, based on a subset of the subjects in Study 4), two pharmacokinetic studies in healthy subjects (Studies 2 and 3), and one Phase 3 study with pharmacokinetic data in herpetic keratitis patients (Study 7). The clinical pharmacology findings from these studies are summarized as follows:

- The extent of local and systemic exposure to ganciclovir from topical ophthalmic administration of ganciclovir ganciclovir 0.15% was evaluated in four clinical studies: two multiple dose studies in healthy volunteers (Studies 2 and 3) and two studies in patients with acute herpetic keratitis as part of the Phase 2 and Phase 3 clinical development program (Studies 4 and 7). Systemic exposure to ganciclovir appears to be minimal following multiple administration of ganciclovir 0.15% gel, as evidenced by plasma and urine concentrations following multiple administration.

- In tear samples collected from six healthy volunteers following multiple dose administration of ganciclovir 0.15% gel, the concentrations of ganciclovir were below the limit of detection in 33% of samples. For the remaining samples, a high variability in ganciclovir concentrations was found within and between individuals. The clinical relevance of ganciclovir tear concentrations or their variability is unknown.

- Although urine samples collected from herpetic keratitis patients following multiple doses of ganciclovir 0.15% gel yielded no detectable ganciclovir, conclusions regarding systemic absorption following ophthalmic administration of ganciclovir gel cannot be made due to the lack of sensitivity of the urine assay (LLOQ of 100 ng/mL).

- A dose-response relationship for efficacy was suggested in both the phase 2 studies which compared ganciclovir 0.05% and 0.15%. Although numerical differences in response rates were observed, the sponsor's statistical analysis showed no statistically significant differences between the ganciclovir 0.05% and 0.15% treatments. No dose-response relationship for safety was observed in the phase 2 studies which compared ganciclovir 0.05% and 0.15%.

In comparison to systemic concentrations following IV administration of ganciclovir, plasma concentrations following ophthalmic administration are much lower; concentrations ranged

between 0 to 37 ng/mL with ganciclovir gel versus a reported mean Cmax value of 9.46 ± 2.02 µg/mL with the intravenous formulation. Similarly, systemic concentrations following instillation of ganciclovir gel are much lower than the reported mean ganciclovir Cmax value of 5.61 ± 1.52 µg/mL following oral administration of valganciclovir tablets.

Although the current application included multiple assessments of systemic exposure of ganciclovir 0.15% gel in both healthy subjects and acute herpetic keratitis patients, the Applicant did not submit adequate validation data to support the bioanalytical methods used in the pharmacokinetic studies. Thus, pharmacokinetic data from the ganciclovir 0.15% gel development program was used for informational purposes only and was not used for product labeling.

6. Sterility Assurance

The drug product was found to be acceptable from a sterility assurance prospective. It is formulated at 1.5 mg of ganciclovir per gram of clear colorless gel with benzalkonium chloride as preservative. The bulk formulation is sterilized [redacted] aluminum tubes. The container and closures are sterilized [redacted] b(4)

The primary Container Closure System (CCS) for US commercial ganciclovir consists of a [redacted] mL multidose polyfoil tube, a tip, and a cap. The polyfoil tube with tip and cap is supplied by [redacted] The tube contains little or no headspace due to the filling and is closed using a [redacted] process by the contract manufacturer, Allied Medical Products (AMP). Laboratoires Théa (European manufacturer of the same product), evaluated the antimicrobial effectiveness of benzalkonium chloride and found that benzalkonium chloride at a concentration of 0.0075% was capable of ensuring a level of antimicrobial protection that satisfied the efficacy of the antimicrobial preservation.

7. Clinical/Statistical - Efficacy

This application relies primarily on four clinical studies (Study 4, 5, 6, and 7) conducted in Europe, Africa, and Asia between 1990 and 1994. The primary efficacy endpoint used is cure rate (healed ulcers) at Day 7. The phase 2 and phase 3 studies were designed as non-inferiority trials. The original statistical plan appears to have been written without an understanding of how to write a non-inferiority statistical plan. The plan's 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 has been demonstrated in the literature to be approximately 80%. There is sufficient data in the literature to justify a non-inferiority margin for dendritic ulcers, [redacted] b(4)

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%)

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%)

IDU is superior to placebo for the treatment of dendritic ulcers. Acyclovir 3% is superior to IDU. The data from the literature supports a non-inferiority margin of at least 44% for the active control, acyclovir 3%, over vehicle and at least 17% for acyclovir over IDU (typically referred to as M1).

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%)

The non-inferiority analysis showed that the lower 95% confidence interval around the difference between ganciclovir 0.15% and acyclovir 3% was no greater than 9.6%.

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)

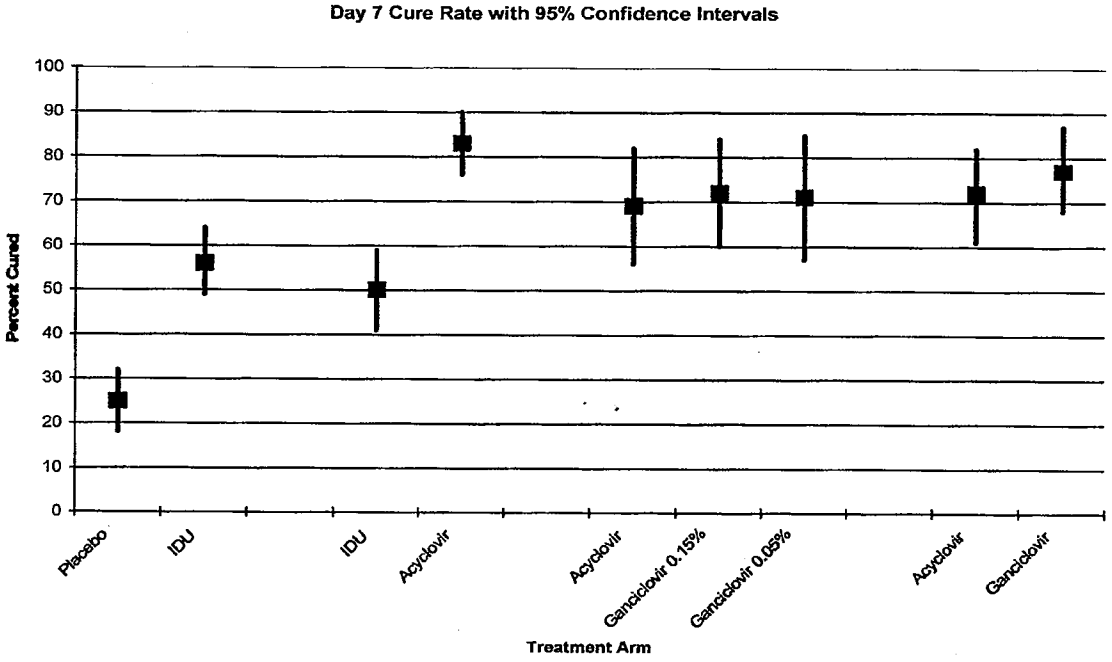
Treatment	n/N (%)
Acyclovir 3%	13/15 (87)
Ganciclovir 0.15%	14/20 (70)
Ganciclovir 0.05%	16/21 (76)

Combined Phase 2 Studies – Cure Rate at Day & (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%

The phase 2 study data (Study 4, 5, and 6) demonstrate that ganciclovir is not inferior to acyclovir 3% for dendritic ulcers, with a non-inferiority margin of at least 15.6%.

Each of these is less than the 17% value that acyclovir has demonstrated over IDU and the 44% that acyclovir has demonstrated over placebo, as shown in the graph below.



IDU is superior to placebo; acyclovir is superior to IDU; and ganciclovir is not inferior to acyclovir.

Substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Zirgan (ganciclovir ophthalmic solution) 0.15% is effective in the treatment of acute herpetic keratitis (dendritic ulcers) consists of Studies 4, 5, 6 and 7 which demonstrated that that ganciclovir 0.15% was not inferior to acyclovir 3%. There is not sufficient data in the literature to justify a non-inferiority margin for geographic ulcers.

8. Safety

The patient exposure and safety assessments were adequate for this orphan product. The product has been marketed in Europe for a number of years. In the submitted studies, 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).

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%). No non-ocular adverse events occurred at a rate of 5% or more.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for Zirgan (ganciclovir ophthalmic gel) 0.15%.

10. Pediatrics

This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). Safety and efficacy in pediatric patients below the age of 2 years have not been established.

11. Other Relevant Regulatory Issues

DSI
After discussion with the Division of Scientific Investigations (DSI), no audit was conducted. The NDA studies were not conducted under an IND, and the data was gathered solely from foreign sites. No irregularities were noted in the studies.

FINANCIAL DISCLOSURE
All clinical studies included in this application were conducted in Europe, Africa, and Asia between 1990 and 1994 and were originally sponsored by Laboratoires Théa formerly (TRANSPHYTO S.A.). Laboratoires Théa, a pharmaceutical company based in Clermont-Ferrand, France, was not required to collect financial disclosure information from the investigators in those studies.

DMEPA
The Division of Medication Error Prevention and Analysis objected to the Applicant's primary name, Virgan (OSE Review #2007-1171, dated June 14, 2007) due to potential orthographic and phonetic confusion with Veregen, an approved drug product in the U.S. Subsequently, DMEPA objected to the Applicant's second and third name choices, [redacted] due to the inclusion of the USAN stems –vir and –vir-, respectively, as well as potential orthographic confusion between [redacted] and Denavir and between [redacted] and Zovirax OSE Review # 2008-1300/2008-1302, dated April 6, 2009). Zirgan is the Applicant's fourth name choice. b(4)

DAIOP concurred with DMEPA's objection to the proposed names, [redacted], based on the orthographic similarity arguments. However, DAIOP disagreed with DMEPA's position regarding USAN stems. b(4)

The Proprietary Name Risk Assessment findings indicated that the proposed name, Zirgan, is not vulnerable to name confusion that could lead to medication errors. Thus the Division of Medication Error Prevention and Analysis (DMEPA) had no objection to the proprietary name,

Zirgan, for this product at this time. Additionally, DDMAC did not object to the proposed name, Zirgan, from a promotional perspective.

DMEPA also provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate. DMEPA was present at the wrap-up meeting/pre-approval safety meeting for this application, held on September 2, 2009. DMEPA was in agreement with the comments proposed to the applicant regarding the final package insert, carton, and container labeling.

DDMAC

DDMAC reviewed the proposed product labeling for Zirgan (ganciclovir ophthalmic gel) 0.15% submitted by the applicant in July 2009. Comments were reviewed and are discussed in the Cross Discipline Team Leader review. DDMAC was invited to the wrap-up meeting/pre-approval safety meeting for this application, held on September 2, 2009, but did not attend. Final labeling was discussed at this meeting.

BIOSTATISTICS

The Statisical Reviewer's post-hoc exploratory analysis in study 7 (phase-3) showed that ganciclovir is non-inferior to Acyclovir 3% ointment using a NI margin determined post-hoc, but the reviewer did not think that the current submission was adequate or that it provides substantial evidence of efficacy required for the approval of this indication in the US. The objections included that the pre-planned hypothesis of superiority using the pre-planned efficacy endpoint of time to healing, failed to demonstrate superiority using the data from an open label Phase 3 trial. Since the analysis used a post-hoc endpoint and a post-hoc non-inferiority hypothesis, the analysis had the same potential for multiple testing errors as any post-hoc exploratory analysis. The reviewer believes that to avoid multiple testing errors and bias, the choice of primary endpoint and hypothesis test should be pre-planned at the protocol stage and the non-inferiority margin should be pre-specified. Second, the active control used in the Phase 3 trial is not an FDA approved drug, nor the standard of care in the United States. Although the historical evidence may show that the active control used in this trial is effective, the historical evidence fails to shows that the active control is superior to the current standard of care in the United States: Trifluridine. Thus, this trial does not provide evidence that ganciclovir would be non-inferior, much less superior, to the standard of care Trifluridine. These objections were reinforced by the reviewer's derivation of the non-inferiority margin using heterogeneous historical trials which violate the constancy assumption and are sensitive to the subset of studies included.

Based on the objections cited above, the reviewer recommend that at least one prospectively designed, adequate and well-controlled study of ganciclovir be conducted for the treatment of acute herpetic keratitis with the comparator Trifluridine to demonstrate that the product is at least as effective as standard of care. The results from the reviewer's exploratory analysis could be used as supportive evidence. This new proposed study could be a dose-ranging superiority study or a non-inferiority study comparing ganciclovir to Trifluridine or Acyclovir 3% if a clinically meaningful margin can be agreed upon.

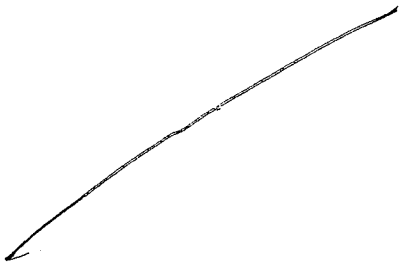
These conclusions by the Biostatistics Reviewer **are not in agreement** with the conclusions reached between Clinical and Biostatistics disciplines at the CDER Regulatory Briefing held

March 27, 2009. In a separate memorandum dated September 1, 2009, from the Director, Division of Biometrics IV/Office of Biostatistics/OTS outlined that the meta-analysis of historical trials of Acyclovir comparator suggests its efficacy (in comparison to placebo) at day 7 is in the range of 14% to 31%. If these results can be assumed to be clinically applicable to the current trial, then one can conclude that the Acyclovir was an effective treatment in the trial for the proposed endpoint and indication. In addition, the determination of margin M2, for the non-inferiority testing of ganciclovir to Acyclovir, is not a statistical issue. This is to be decided based on clinical considerations. If the value of M2 can be set at 10.5 for the day 7 endpoint and it is conservative enough for discounting the multiplicity issue raised for this trial, then the results of this trial suggest non-inferiority of ganciclovir (Ganciclovir Ophthalmic Gel, 0.15%) in comparison to the Acyclovir treatment for this endpoint.

The clinical team agrees that Study 7 is not the sole basis to support efficacy of Zirgan. Studies 4, 5, and 6 have also been considered and determined to be supportive of efficacy. The objections raised by the Statistical Reviewer are not considered by me to be consistent with the requirements of the Food Drug and Cosmetic Act. As identified above, Studies 4, 5, 6 and 7 are considered supportive of the safety and efficacy of the drug product for the treatment of dendritic keratitis.

12. Labeling

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.



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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 2

13. Regulatory Action

REGULATORY ACTION:
NDA 22-211, Zirgan (ganciclovir ophthalmic gel) 0.15% can be approved for the treatment of acute herpetic keratitis (dendritic ulcers). There is substantial evidence consisting of adequate and well controlled studies which demonstrate that Zirgan, dosed 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until corneal ulcer heals, and then 1 drop 3 times per day for 7 days, is safe and effective for the treatment of treatment of acute herpetic keratitis (dendritic ulcers). Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Wiley A. Chambers, MD
Acting Director
Division of Anti-infective and Ophthalmology Products

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/s/

WILEY A CHAMBERS
09/15/2009