CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

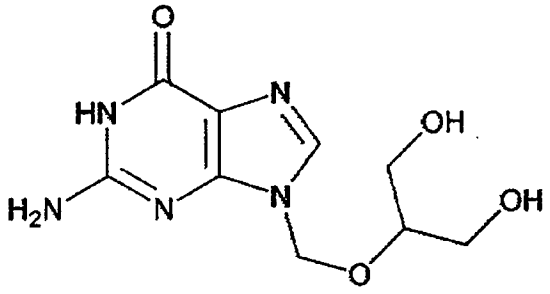
22-211

CHEMISTRY REVIEW(S)

NDA 22-211

Sirion Therapeutics, Inc.

Zirgan®(Ganciclovir Ophthalmic Gel), 0.15%



Milton J. Sloan, Ph.D.
ONDQA Pre-Marketing Assessment Division II Branch IV

For Division of Anti-Infective and Ophthalmology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA #22-211

2. REVIEW #: 2

3. REVIEW DATE: September 2, 2009

4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 25,082	
Original	25-Jun-2008
Resubmission (RS)	14-Nov-2008
Amendment (BC)	06-Jan-2009
Amendment (BC)	06-Aug-2009
Review #1	27-Aug-2009
Review Memorandum	31-Aug-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Email Response Amendment (BC)	31-Aug-2009
Email Response Amendment (BC)	02-Sep-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Sirion Therapeutics, Inc.
Address:	9314 East Broadway Avenue Tampa, FL 33619
Representative:	Jeremy Brace, VP Regulatory Affairs
Telephone:	(813) 496-7325

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zirgan; (Virgan)
b) Non-Proprietary Name (USAN): Ganciclovir
c) Code Name/# (ONDC only): ST-605
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-infective / Antiviral

11. DOSAGE FORM: Ophthalmic Gel

12. STRENGTH/POTENCY: 0.15%

13. ROUTE OF ADMINISTRATION: Ocular

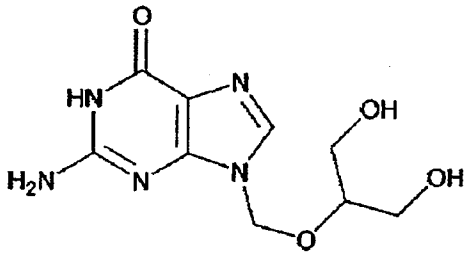
14. Rx/OTC DISPENSED: _X__R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine [*82410-32-0*].



$C_9H_{13}N_5O_4$
255.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		4	N/A	N/A	N/A
[redacted]		[redacted]		4	N/A	N/A	N/A

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-661	Ganciclovir
IND	25,082	Ganciclovir

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Overall Acceptable	Aug. 28, 2009	-
Pharm/Tox	Approval	June 25, 2009	Conrad Chen
Biopharm	N/A	-	-
LNC	N/A	-	-
Methods Validation	Not requested per ONDQA policy	-	-
EA	Request for Categorical Exclusion-Acceptable	-	Milton Sloan
Quality Microbiology	Approvable Approval	July 29,2009 Sept 01 2009	Vinayak Pawar

19. ORDER OF REVIEW N/A

The Chemistry Review for NDA 22-211

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from Chemistry, Manufacturing, and Controls (CMC) perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Sirion will attempt to identify any specified unidentified related substances in the drug product occurring at a level greater than 0.1% consistent with ICH Q3B(R2).

2. Sirion will analyze a recent lot of drug substance using the related substances method for the drug product and report the presence of any detected impurities as a relative retention time (RRT) of ganciclovir. Any detected impurity's RRT will be compared to the specified unidentified related substance RRT's.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Ganciclovir is a synthetic guanine derivative. Ganciclovir is chemically known as 9-[[(2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, an antiviral that is active *in vitro* and *in vivo* against herpes simplex virus (HSV). The efficacy and safety of ganciclovir as an antiviral agent is well established. In the United States, ganciclovir has been approved for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS (Cytovene®-IV, NDA 19,661, Cytovene® capsules, and Vitrasert®) and for the prevention of CMV disease in patients with kidney, heart, and kidney-pancreas transplants (Valcyte®, NDA 21-304). Ganciclovir is transformed in infected cells into ganciclovir triphosphate, the active form of the active substance. Preferential phosphorylation takes place in the infected cells, with ganciclovir triphosphate concentrations being 100 times lower in noninfected cells. Ganciclovir triphosphate exerts an antiviral activity by inhibiting synthesis of viral DNA by two mechanisms: competitive inhibition of viral DNA-polymerases and direct incorporation into viral DNA, which blocks its elongation.

Drug Product

Zirgan®(ganciclovir ophthalmic gel), 0.15% (ST-605) is a sterile topical ophthalmic aqueous gel containing the antiviral ingredient ganciclovir. ST-605 is the Sponsor's code name for ganciclovir ophthalmic gel, 0.15%. This product is currently marketed outside the United States by Laboratoires Théa of France for the treatment of acute

herpetic keratitis as Virgan®. The name Virgan® was not acceptable by DMETS. The sponsor subsequently, proposed Zirgan and [redacted] as proprietary names. The new proprietary name Zirgan® was found acceptable by DMETS (see review of Proprietary name). b(4)

The proposed aqueous gel formulation (B*) is contains carbopol as the [redacted], benzalkonium chloride as a preservative, mannitol as a [redacted] sodium hydroxide as pH adjuster, and [redacted] water (water for injection quality) as [redacted] The topical gel is packaged in a multidose polyfoil tube for ophthalmic administration. After preparation of the aqueous gel, the drug product is [redacted] and processed into multidose polyfoil tubes. ST-605 is contained in a [redacted] mL multidose polyfoil tube made of [redacted], a polyethylene nozzle, and a polyethylene stopper, with a useful content volume equivalent to 5 g of gel. The multidose polyfoil tubes are sterilized [redacted] filling operation. The multidose polyfoil tube is placed in a secondary container closure packaging system consisting of a cardboard box with a package insert. b(4)

B. Description of How the Drug Product is Intended to be Used

Zirgan®(ganciclovir ophthalmic gel), 0.15% was developed as a treatment for acute herpetic keratitis (dendritic ulcers) as an improvement over the earlier antivirals, e.g., idoxuridine, vidarabine, and trifluridine. The clinical trials were conducted in Europe with acyclovir 3% as the active control. Zirgan®(ganciclovir ophthalmic gel), 0.15% is indicated for topical ophthalmic use only. Zirgan® is supplied as 5 grams in a polycoated aluminum tube. For patient use, the protective band on the tube cap is removed and the cap is unscrewed exposing the tip of the tube, drops are dispensed, and the cap is re-applied to the tip of the tube. One drop of the gel is placed in the conjunctival sac of the affected eye five times a day until the corneal ulcer heals. Then instill one drop three times a day for an additional 7 days after healing. Treatment does not usually exceed [redacted] days. The proposed commercial packaging consists of a 5 gm polyfoil tube containing 0.15% of ganciclovir sterile preserved topical ophthalmic gel. ST-605 contains 1.5 mg of ganciclovir per gram of gel. Two presentations are available in the following sizes: 1 gm polyfoil tube – physicians sample and a 5 gm polyfoil tube. The tube is embossed with the lot number and expiration date as the tube is [redacted] sealed. Storage at 25°C (77°F) excursions permitted to [redacted] [see USP Controlled Room Temperature is usually recommended however, for this ophthalmic drug 15-25°C is the recommended statement. Do not freeze statement is also included. b(4)

C. Basis for Approvability or Not-Approval Recommendation

Zirgan®(ganciclovir ophthalmic gel), 0.15% (ST-605) was developed by Transphyto SA (now Laboratoires Théa) as a topical aqueous ophthalmic gel containing ganciclovir for the treatment of herpetic keratitis. ST-605 is currently marketed outside the US by Laboratoires Théa of France for the treatment of acute herpetic keratitis. Ganciclovir is approved in the US and Europe as both an oral and intravenous antiviral agent (Valcyte®, NDA 21-304 and Cytovene®, NDA 19-661). Sirion Therapeutics, Inc. (Sponsor) licensed ST-605 from Laboratoires Théa for the purpose of seeking approval

to market the product in the US. Zirgan®(ganciclovir ophthalmic gel), 0.15% will be manufactured by Alliance Medical Products, Inc. (AMP) for Sirion Therapeutics, Inc.. Alliance has provided data on three batches manufactured at the site. Part of the pharmaceutical development package provided by Laboratoires Théa included long-term (up to 36 months) stability testing on multiple lots of ST-605 (Laboratoires Théa Stability Report). The formulation of the ST-605 stability batches manufactured for Laboratoires Théa is similar to the intended US commercial ST-605 formulation. The source of the active pharmaceutical ingredient is the same in the batches manufactured for Laboratoires Théa as will be used in the Zirgan®(ganciclovir ophthalmic gel), 0.15% drug product. The manufacturing method for the product is very similar, — used in manufacturing. Table P.4 and Table P.5 of this review provide an overview of the formulation development and variations for ST-605 from the initial clinical trial materials to the formulation proposed for production in the US. Please note that all of the clinical studies of ST-605 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 US marketing. The mL capacity polyfoil multidose tube used by Laboratoires Théa is identical to the current container closure system (CCS) obtained from the same vendor (—) and proposed for Zirgan®(ganciclovir ophthalmic gel), 0.15%.

b(4)

A request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The quality microbiology consult review was found acceptable and approval is recommended. The analytical method, and labeling issues are all resolved and adequate. The impurity specification and acceptance criteria have been revised and results of analysis studies have been accepted as post approval commitment of Sirion. Therefore, this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product and from the CMC perspective, this NDA is recommended for approval.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D. Date: 04-Sept-09

Branch Chief: Norman Schmuff, Ph.D. Date:

C. CC Block

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

Chemistry Assessment Section

ATTACHMENT 1

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22211/000	**Action Goal:**	
Stamp Date:	26-JUN-2008	**District Goal:**	19-JUL-2009
Regulatory:	17-SEP-2009		
Applicant:	SIRION THERAPEUTICS 1400 SOUTH ORANGE AVE ORLANDO, FL 32806	**Brand Name:** **Estab. Name:** **Generic Name:**	ZIRGAN (GANCICLOVIR OPHTHALMIC GEL)0.15% GANCICLOVIR
Priority:	3S	**Product Number; Dosage Form; Ingredient; Potency**	
Org. Code:	520		

Application Comment: JUST AS A NOTE, THE CORRECT SPELLING FOR THE DRUG SUBSTANCE IS GANCICLOVIR. (on 18-AUG-2008 by M. SLOAN () 301-796-1464)

FDA Contacts:	L. GORSKI	Project Manager	(HFD-520)	301-796-0722
	M. SLOAN	Review Chemist		301-796-1464
	N. SCHMUFF	Team Leader		301-796-1454

Overall Recommendation:	ACCEPTABLE	on 28-AUG-2009	by M. STOCK	(HFD-320)	301-796-4753

ATTACHMENT 1con'td

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: 2027189 FEI: 2027189

ALLIANCE MEDICAL PRODUCTS INC

9342 JERONIMO RD
IRVINE, CA 926181903

DMF No: **AADA:** b(4)

Responsibilities:

Estab. Comment: RESPONSE IS EXPECTED TO BE SENT BY JULY 1, 2009 (PER DISCUSSION WITH RENA ONG, AT ALLIANCE MEDICAL PRODUCTS). FIRM WAS REQUESTED TO SEND A COPY TO CDER (ATTN COKI CRUZ). (on 10-JUN-2009 by C. MCNAB (HFR-PA250) 949-608-4472)

Profile: OPHTHALMIC/STERILE NON-INJECTABLE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	18-AUG-2008				SLOANM
SUBMITTED TO DO	18-AUG-2008	10-Day Letter			KIEL
REQUEST CANCELLED	27-AUG-2008				SLOANM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	17-DEC-2008				SLOANM
SUBMITTED TO DO	17-DEC-2008	10-Day Letter			KIEL
ASSIGNED INSPECTION TO IB	03-APR-2009	Product Specific			CEVERLY
INSPECTION SCHEDULED	03-APR-2009		24-APR-2009		CEVERLY
INSPECTION PERFORMED	05-MAY-2009		05-MAY-2009		CEVERLY
INSPECTION PERFORMED	26-MAY-2009				CARYN.MCNAB
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED					
DO RECOMMENDATION	10-JUN-2009			WITHHOLD	CEVERLY
A PRODUCT SPECIFIC AND GMP INSPECTION WAS PERFORMED 4/20 - 5/5/09 AND DISCLOSED THE FOLLOWING DEFICIENCIES SPECIFIC TO NDA 22-211: 1. NO VALIDATED [redacted] LOAD SPECIFIC TO THE GANCICLOVIR GEL [redacted] FILLING PROCESS FOR STERILIZATION OF FILL TUBING SETS AND MISCELLANEOUS ITEMS. 2. NO ESTABLISHED AUTOCLAVE LOADING PATTERNS. 3. NO MAXIMUM NUMBER OF ITEMS THAT CAN BE PLACED IN AN [redacted] LOAD. 4. [redacted] FILLED VIALS WERE REJECTED AT THE 100% INSPECTION (PRE-INCUBATION) WITHOUT DOCUMENTATION OF REASON FOR THE REJECT. OF THE THREE LOTS REVIEWED FOR THIS PROCESS THE NUMBER OF REJECTS WAS [redacted], AND [redacted] 5. ACTIVE MONITORING FOR VIABLES IN THE FILL ROOM CONDUCTED ONLY AT THE END OF THE FILL (NOT BEFORE, DURING SET UP, DURING FILL, OR DURING [redacted] CONNECTIONS). 6. PERSONNEL ARE NOT MONITORED WITH PLATES EACH TIME THEY EXIT THE FILL ROOM. 7. THE FIRM HAS NO SOP FOR RESPONDING TO AND INVESTIGATING PRESSURE DIFFERENTIAL ALARMS. 8. [redacted] USED FOR VIALS FOR THIS PRODUCT HAVE NOT BEEN LEAK TESTED SINCE 2005. 9. NO SOP FOR PREVENTIVE MAINTENANCE OF THE TUBE FILLER USED TO FILL THIS PRODUCT.				EQUIPMENT QUALIFICATION INADEQUATE ENVIRONMENT CONTROL LACK OF/INADEQUATE SOPS b(4)	

ATTACHMENT 1 con'td
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

10. NO EQUIPMENT LOGS.
11. NO MIXING HOMOGENEITY STUDY USING ASSAY THAT SHOWS THE PROPOSED PROCESS PARAMETERS FOR THE COMMERCIAL SCALE BATCH ARE ADEQUATE.
12. FINISHED PRODUCT SAMPLING IS NOT REPRESENTATIVE OF THE LOT (ONLY 1 SAMPLE REQUIRED FOR ASSAY AND RELATED SUBSTANCES).
13. THE BATCH RECORD FOR THE ENGINEERING BATCH WHICH STUDIED THE USE OF THE CLARIFYING FILTER WAS LOST AND THE FIRM COULD PROVIDE NO RAW DATA FROM THIS STUDY.

LOS-DO RECOMMENDS WITHHOLDING APPROVAL.
CARYN MCNAB, PAI MANAGER

OC RECOMMENDATION	28-AUG-2009	ACCEPTABLE	GOULDS

FIRM RESPONSE TO 483 HAS BEEN EVALUATED AND DISCUSSED WITH THE DISTRICT OFFICE. WE ARE IN AGREEMENT THAT THIS APPLICATION IS NOW ACCEPTABLE.
/S GOULD 8/28/09

FIRM RESPONSE TO DEFIC. ADEQUA

ATTACHMENT 1 con'td

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

b(4)

DMF No: **AADA:** [redacted]

Responsibilities: [redacted]

Estab. Comment:

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	18-AUG-2008				SLOANM
REQUEST CANCELLED	27-AUG-2008				SLOANM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	17-DEC-2008				SLOANM
OC RECOMMENDATION	15-JAN-2009			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	

ATTACHMENT 1 con'td
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

[redacted] b(4)

DMF No: [redacted] **AADA:**

Responsibilities: [redacted]

Estab. Comment:

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	18-AUG-2008				SLOANM
SUBMITTED TO DO	19-AUG-2008	10-Day Letter			KIEL
REQUEST CANCELLED	27-AUG-2008				SLOANM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	17-DEC-2008				SLOANM
OC RECOMMENDATION	17-DEC-2008			ACCEPTABLE	KIEL
				BASED ON PROFILE	

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/

MILTON J SLOAN
09/09/2009

NORMAN R SCHMUFF
09/14/2009

Food & Drug Administration

Memorandum

Date : August 31, 2009

From: Linda Ng, Ph.D.
Pharmaceutical Assessment Lead

Subject: N22-211, Sirion Therapeutics Inc

To: The File

Content

This memo is to complement chemistry review #1 placed in DARRTS on August 27, 2008 for Zirgan (ganciclovir ophthalmic gel) 0.15%. Dr. Milton Sloan, chemistry reviewer, has recommended not approval in his review. In addition to his concern for "analytical method, impurity and labeling" stated in his Executive Summary, II.C, the inspection EES overall recommendation is still outstanding as of August 27.

Dr. Sloan's list of comments still outstanding is in Attachment A. Since the NDA is ready for approval pending CMC, a final condensed list will be formulated to replace Attachment A. The intent is to finalize any outstanding issues for approval from CMC. The drug product specification from the August 6, 2009 amendment is included as Attachment B below. The PDUFA date for this NDA is September 17, 2009.

Here is the recommended list of revised comments to the applicant. Dr. Sloan is in agreement with these comments.

1. Confusion is caused in equation 8.3 of analytical methods for the determination of ganciclovir assay and for BAC as

compared to the drug product specification. This may affect the strength of the drug product. Please revise to express it as percent weight per volume. This should be consistent with the analytical method calculations, acceptance criteria in the drug product specification and labeling.

2. The acceptance criterion for the particulate analysis test in the drug product specification should be modified from ——— throughout shelf life.
3. The acceptance criteria for the Related Substances Assay for Unknown Individual impurity should be set at NMT —; and Total Impurities at NMT —.
4. An updated drug product specification should be submitted.
5. In the Stability Protocol, a statement to inform the Review Division of failures and also to reference CFR 314.81(b)(1) for reporting to the District Office.
6. An expiry dating period for 18 months will be granted.

b(4)

Item 3 addressed the reviewer's concern for impurities in his comments 2, 3, 6 and 7. Comment 5 was excluded because a pH difference of — will not have an effect in the eye and is close to the assay variation of pH meter. Item 10 on granularity of the document is not a hold deficiency.

In the immediate container label and carton, the font size of the established name should be at least ½ the size of the trade name. The storage condition in the carton should be, "Store between 15°C to 25°C (59°F to 77°F).

The Office of Compliance has provided the overall recommendation of Acceptable dated August 28, 2009. See Attachment C below.

File: C:/MyDocuments/Reviews/Memos/N22211.doc

Attachment A. Outstanding Deficiencies from NDA 22-211 Review #1

1. The sponsor should revise the analytical method equation 8.3 for the determination of ganciclovir assay with a conversion factor and/or provide a qualification to the acceptance criterion percentage term. Only for a solid does it imply %w/w, without qualification. For a solution or suspension of solids in liquids, the term implies percent weight per volume. This should be consistent with the analytical method calculations, acceptance criteria and labeling.

2. The specification acceptance criteria have been relaxed to provide for greater impurities as compared to the European version of the drug product with no justification provided.

3. The sponsor has not provided a discussion of the difference in impurity profile as compared to earlier formulations.

4. Conversely, the equation of 8.3 provides for the concentration of BAK in the gel to result in %w/v as the acceptance criteria is specified in % w/w (i.e.). The sponsor should either revise the equation with a conversion factor and/or provide acceptance percentage criterion range, this should be consistent with analytical method calculations, acceptance criteria and labeling. b(4)

5. The chemistry test method (CTM-200001) describes the determination of pH. Again, the sponsor has relaxed the pH (from acceptance criterion with no justification provided. The pH is a critical process control test. b(4)

6. The sponsor has not provided a discussion on the drug product impurities. It is not clear if some are the same or drug product process related. No discussion on levels and the identification of the known drug substance impurities that may be in the drug product was provided, only has been listed.

7. The representative chromatogram for the manufactured batch above shows an additional peak with an RRT approximately in the finished drug product as compared to listed peaks. The sponsor should provide a rationale for exclusion of the unidentified impurity. Please also compare this impurity to the other unknowns category shown in primary stability data and not listed in Table 2.

Other Comments

8. A — -month expiration period is not recommended based on the stability data of the primary batches (formula B*). b(4)
9. The particulate analysis test provided in the specifications should also relate to USP <788> test injectables. The criterion should be that the product is "free of particulate matter" through out shelf life as is appropriate.
10. The NDA submission is too granular and does not facilitate review with GS Submit. There are too many one and two page documents with each having a "Table 1", etc..

Attachment B Drug Product Specification Sheet

Attachment C EES Overall Recommendation for NDA

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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/

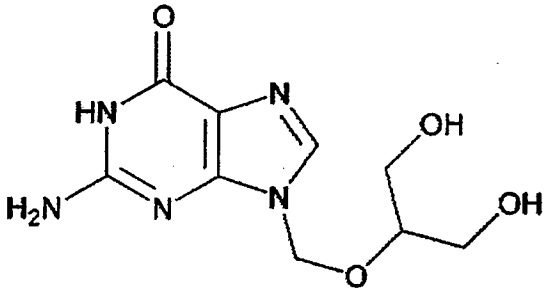
LINDA L NG
08/31/2009
Complements CMC Original NDA Review #1

CHEMISTRY REVIEW

NDA 22-211

Sirion Therapeutics, Inc.

Zirgan®(Ganciclovir Ophthalmic Gel), 0.15%



Milton J. Sloan, Ph.D.
ONDQA Pre-Marketing Assessment Division II Branch IV

For Division of Anti-Infective and Ophthalmology Drug Products

Table of Contents

b(4)

Chemistry Review Data Sheet

1. NDA #22-211

2. REVIEW #: 1

3. REVIEW DATE: April 1, 2009

4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 25,082 Original	25-Jun-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (RS)	14-Nov-2008
Amendment (BC)	06-Jan-2009
Amendment (BC)	06-Aug-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Sirion Therapeutics, Inc.
Address:	9314 East Broadway Avenue Tampa, FL 33619
Representative:	Jeremy Brace, VP Regulatory Affairs
Telephone:	(813) 496-7325

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zirgan; (Virgan)
b) Non-Proprietary Name (USAN): Ganciclovir
c) Code Name/# (ONDC only): ST-605
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-infective / Antiviral

11. DOSAGE FORM: Ophthalmic Gel

12. STRENGTH/POTENCY: 0.15%

13. ROUTE OF ADMINISTRATION: Ocular

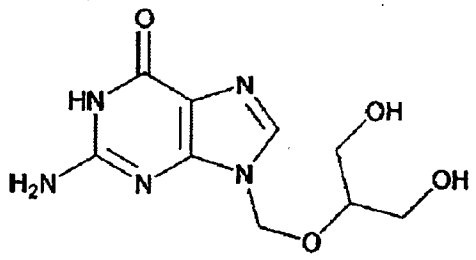
14. Rx/OTC DISPENSED: _X__ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

6*H*-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-.
9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine [*82410-32-0*].



$C_9H_{13}N_5O_4$
255.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		4	N/A	N/A	N/A
[redacted]		[redacted]		4	N/A	N/A	N/A

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-661	Ganciclovir
IND	25,082	Ganciclovir

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Acceptable		Conrad Chen
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not requested per ONDQA policy		
EA	Request for Categorical Exclusion-Acceptable		
Quality Microbiology	Acceptable		Vinne Padwar

19. ORDER OF REVIEW N/A

The Chemistry Review for NDA 22-211

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. Therefore, from the CMC perspective, this application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance overall recommendation has not been made as of date of this review. Three facilities were requested for inspection approval, Alliance Medical Products, Inc., the contract manufacturing site responsible for the finished dosage manufacturing, [redacted] has not been found acceptable. The District Office has given a withhold recommendation against the contracted drug product facility. However, specification and labeling issues are still pending. Approval is not recommended for this NDA until all issues are resolved and all supporting sites have an acceptable recommendation. b(4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Ganciclovir is a synthetic guanine derivative. Ganciclovir is chemically known as 9-[[(2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, an antiviral that is active *in vitro* and *in vivo* against herpes simplex virus (HSV). The efficacy and safety of ganciclovir as an antiviral agent is well established. In the United States, ganciclovir has been approved for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS (Cytovene®-IV, NDA 19,661, Cytovene® capsules, and Vitrasert®) and for the prevention of CMV disease in patients with kidney, heart, and kidney-pancreas transplants (Valcyte®, NDA 21-304). Ganciclovir is transformed in infected cells into ganciclovir triphosphate, the active form of the active substance. Preferential phosphorylation takes place in the infected cells, with ganciclovir triphosphate concentrations being 100 times lower in noninfected cells. Ganciclovir triphosphate exerts an antiviral activity by inhibiting synthesis of viral DNA by two mechanisms: competitive inhibition of viral DNA-polymerases and direct incorporation into viral DNA, which blocks its elongation.

Drug Product

Zirgan®(ganciclovir ophthalmic gel), 0.15% (ST-605) is a sterile topical ophthalmic aqueous gel containing the antiviral ingredient ganciclovir. ST-605 is the Sponsor's code name for ganciclovir ophthalmic gel, 0.15%. This product is currently marketed outside the United States by Laboratoires Théa of France for the treatment of acute herpetic keratitis as Virgan®. The name Virgan® was not acceptable by DMETS. The sponsor subsequently, proposed Zirgan and —— as proprietary names. The new proprietary name Zirgan® was found acceptable by DMETS (see review of Proprietary name). b(4)

The proposed aqueous gel formulation (B*) is contains carbopol as the ——, benzalkonium chloride as a preservative, mannitol as a —— sodium hydroxide as pH adjuster, and —— water (water for injection quality) as —— The topical gel is packaged in a multidose polyfoil tube for ophthalmic administration. After preparation of the aqueous gel, the drug product is —— sterilized and processed into multidose polyfoil tubes. ST-605 is contained in a —mL multidose polyfoil tube made of ——, a polyethylene nozzle, and a polyethylene stopper, with a useful content volume equivalent to 5 g of gel. The multidose polyfoil tubes are sterilized —— filling operation. The multidose polyfoil tube is placed in a secondary container closure packaging system consisting of a cardboard box with a package insert. b(4)

B. Description of How the Drug Product is Intended to be Used

Zirgan®(ganciclovir ophthalmic gel), 0.15% was developed as a treatment for acute herpetic keratitis (dendritic ulcers) as an improvement over the earlier antivirals, e.g., idoxuridine, vidarabine, and trifluridine. The clinical trials were conducted in Europe with acyclovir 3% as the active control. Zirgan®(ganciclovir ophthalmic gel), 0.15% is indicated for topical ophthalmic use only. Zirgan® is supplied as 5 grams in a polycoated aluminum tube. For patient use, the protective band on the tube cap is removed and the cap is unscrewed exposing the tip of the tube, drops are dispensed, and the cap is re-applied to the tip of the tube. One drop of the gel is placed in the conjunctival sac of the affected eye 5 times a day until the corneal ulcer heals. Then instill one drop 3 times a day for an additional 7 days after healing. Treatment does not usually exceed—days. The proposed commercial packaging consists of a 5 gm polyfoil tube containing 0.15% of ganciclovir sterile preserved topical ophthalmic gel. ST-605 contains 1.5 mg of ganciclovir per gram of gel. Two presentations are available in the following sizes: 1 gm polyfoil tube – physicians sample and a 5 gm polyfoil tube. The tube is embossed with the lot number and expiration date as the tube is ——sealed. Storage at 25°C (77°F) excursions permitted to —— [see USP Controlled Room Temperature is recommended. Do not freeze statement is also included. b(4)

C. Basis for Approvability or Not-Approval Recommendation

Zirgan®(ganciclovir ophthalmic gel), 0.15% (ST-605) was developed by Transphyto SA (now Laboratoires Théa) as a topical aqueous ophthalmic gel containing ganciclovir for the treatment of herpetic keratitis. ST-605 is currently marketed outside the US by Laboratoires Théa of France for the treatment of acute herpetic keratitis. Ganciclovir is approved in the US and Europe as both an oral and intravenous antiviral agent (Valcyte®, NDA 21-304 and Cytovene®, NDA 19-661). Sirion Therapeutics, Inc. (Sponsor) licensed ST-605 from Laboratoires Théa for the purpose of seeking approval to market the product in the US. Zirgan®(ganciclovir ophthalmic gel), 0.15% will be manufactured by Alliance Medical Products, Inc. (AMP) for Sirion Therapeutics, Inc.. Alliance has provided data on three batches manufactured at the site. Part of the pharmaceutical development package provided by Laboratoires Théa included long-term (up to 36 months) stability testing on multiple lots of ST-605 (Laboratoires Théa Stability Report). The formulation of the ST-605 stability batches manufactured for Laboratoires Théa is similar to the intended US commercial ST-605 formulation. The source of the active pharmaceutical ingredient is the same in the batches manufactured for Laboratoires Théa as will be used in the Zirgan®(ganciclovir ophthalmic gel), 0.15% drug product. The manufacturing method for the product is very similar, only ——— used in manufacturing. Table P.4 and Table P.5 of this review provide an overview of the formulation development and variations for ST-605 from the initial clinical trial materials to the formulation proposed for production in the US. Please note that all of the clinical studies of ST-605 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 US marketing. The—mL polyfoil multidose tube used by Laboratoires Théa is identical to the current container closure system (CCS) obtained from the same vendor ——— and proposed for Zirgan®(ganciclovir ophthalmic gel), 0.15%.

b(4)

A request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The quality microbiology consult review was found acceptable and approval is recommended.

This NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, analytical method, impurity, and labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D. Date: 26-June-09
Final Draft: 24-August-09

Branch Chief: Norman Schmuff, Ph.D. Date:

C. CC Block

62 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

Chemistry Assessment Section

ATTACHMENT 2

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22211/000	**Action Goal:**	
Stamp Date:	26-JUN-2008	**District Goal:**	19-JUL-2009
Regulatory:	17-SEP-2009		
Applicant:	SIRION THERAPEUTICS	**Brand Name:**	ZIRGAN (GANCICLOVIR OPHTHALMIC GEL)0.15%
	1400 SOUTH ORANGE AVE	**Estab. Name:**	
	ORLANDO, FL 32806	**Generic Name:**	GANCICLOVIR
Priority:	3S	**Product Number; Dosage Form; Ingredient; Potency**	
Org. Code:	520		

Application Comment: JUST AS A NOTE, THE CORRECT SPELLING FOR THE DRUG SUBSTANCE IS GANCICLOVIR. (on 18-AUG-2008 by M. SLOAN () 301-796-1464)

FDA Contacts:	L. GORSKI	Project Manager	(HFD-520)	301-796-0722
	M. SLOAN	Review Chemist		301-796-1464
	N. SCHMUFF	Team Leader		301-796-1454

Overall Recommendation:

Chemistry Assessment Section

ATTACHMENT 2con'td

DETAIL REPORT

Establishment: CFN: 2027189 FEI: 2027189

ALLIANCE MEDICAL PRODUCTS INC

9342 JERONIMO RD
IRVINE, CA 926181903

DMF No: **AADA:** b(4)

Responsibilities:

Estab. Comment: RESPONSE IS EXPECTED TO BE SENT BY JULY 1, 2009 (PER DISCUSSION WITH RENA ONG, AT ALLIANCE MEDICAL PRODUCTS). FIRM WAS REQUESTED TO SEND A COPY TO CDER (ATTN COKI CRUZ). (on 10-JUN-2009 by C. MCNAB (HFR-PA250) 949-608-4472)

Profile: OPHTHALMIC/STERILE NON-INJECTABLE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	18-AUG-2008				SLOANM
SUBMITTED TO DO	18-AUG-2008	10-Day Letter			KIEL
REQUEST CANCELLED	27-AUG-2008				SLOANM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	17-DEC-2008				SLOANM
SUBMITTED TO DO	17-DEC-2008	10-Day Letter			KIEL
ASSIGNED INSPECTION TO IB	03-APR-2009	Product Specific			CEVERLY
INSPECTION SCHEDULED	03-APR-2009		24-APR-2009		CEVERLY
INSPECTION PERFORMED	05-MAY-2009		05-MAY-2009		CEVERLY
INSPECTION PERFORMED	26-MAY-2009				CARYN.MCNAB
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED					
DO RECOMMENDATION	10-JUN-2009			WITHHOLD	CEVERLY
A PRODUCT SPECIFIC AND GMP INSPECTION WAS PERFORMED 4/20 - 5/5/09 AND DISCLOSED THE FOLLOWING DEFICIENCIES SPECIFIC TO NDA 22-211: 1. NO VALIDATED [redacted] LOAD SPECIFIC TO THE GANCICLOVIR GEL [redacted] FILLING PROCESS FOR STERILIZATION OF FILL TUBING SETS AND MISCELLANEOUS ITEMS. 2. NO ESTABLISHED [redacted] LOADING PATTERNS. 3. NO MAXIMUM NUMBER OF ITEMS THAT CAN BE PLACED IN AN / [redacted] LOAD. 4. [redacted] FILLED VIALS WERE REJECTED AT THE 100% INSPECTION (PRE-INCUBATION) WITHOUT DOCUMENTATION OF REASON FOR THE REJECT. OF THE THREE LOTS REVIEWED FOR THIS PROCESS THE NUMBER OF REJECTS WAS [redacted], AND [redacted] 5. ACTIVE MONITORING FOR VIABLES IN THE FILL ROOM CONDUCTED ONLY AT THE END OF THE FILL (NOT BEFORE, DURING SET UP, DURING FILL, OR DURING [redacted] CONNECTIONS). 6. PERSONNEL ARE NOT MONITORED WITH PLATES EACH TIME THEY EXIT THE FILL ROOM. 7. THE FIRM HAS NO SOP FOR RESPONDING TO AND INVESTIGATING PRESSURE DIFFERENTIAL ALARMS. 8. [redacted] USED FOR VIALS FOR THIS PRODUCT HAVE NOT BEEN LEAK TESTED SINCE 2005. 9. NO SOP FOR PREVENTIVE MAINTENANCE OF THE TUBE FILLER USED TO FILL THIS PRODUCT.				EQUIPMENT QUALIFICATION INADEQUATE ENVIRONMENT CONTROL LACK OF/INADEQUATE SOPS	

b(4)

ATTACHMENT 2con'td

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

10. NO EQUIPMENT LOGS.
11. NO MIXING HOMOGENEITY STUDY USING ASSAY THAT SHOWS THE PROPOSED PROCESS PARAMETERS FOR THE COMMERCIAL SCALE BATCH ARE ADEQUATE.
12. FINISHED PRODUCT SAMPLING IS NOT REPRESENTATIVE OF THE LOT (ONLY 1 SAMPLE REQUIRED FOR ASSAY AND RELATED SUBSTANCES).
13. THE BATCH RECORD FOR THE ENGINEERING BATCH WHICH STUDIED THE USE OF THE CLARIFYING FILTER WAS LOST AND THE FIRM COULD PROVIDE NO RAW DATA FROM THIS STUDY.

LOS-DO RECOMMENDS WITHHOLDING APPROVAL.
CARYN MCNAB, PAI MANAGER

Chemistry Assessment Section

ATTACHMENT 2con'td

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

[redacted]

[redacted]

b(4)

DMF No: **AADA:** [redacted]

Responsibilities: [redacted]

Estab. Comment:

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	18-AUG-2008				SLOANM
REQUEST CANCELLED	27-AUG-2008				SLOANM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	17-DEC-2008				SLOANM
OC RECOMMENDATION	15-JAN-2009			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	

Chemistry Assessment Section

ATTACHMENT 2con'td

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

[redacted]

[redacted] b(4)

DMF No: [redacted] **AADA:**

Responsibilities: [redacted]

Estab. Comment:

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	18-AUG-2008				SLOANM
SUBMITTED TO DO	19-AUG-2008	10-Day Letter			KIEL
REQUEST CANCELLED	27-AUG-2008				SLOANM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	17-DEC-2008				SLOANM
OC RECOMMENDATION	17-DEC-2008			ACCEPTABLE	KIEL
				BASED ON PROFILE	

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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/

MILTON J SLOAN
08/27/2009

LINDA L NG
08/31/2009
See Memo to the File dated August 31, 2009 to complement this review.
Sign off review as Acting Branch Chief