CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21478Orig1s008

Trade Name: **ZOVIRAX**

Generic Name: **Acyclovir**

Sponsor: **Valeant**

Approval Date: 01/28/2015

Indications: ZOVIRAX Cream 5% is a herpes simplex virus (HSV) nucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21478Orig1s008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21478Orig1s008

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21478/S-008

APPROVAL LETTER

Valeant International Bermuda
Attention: Lori a. Fiorentino, MSc., RA
Associate Director, Regulatory Affairs, CMC
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Fiorentino:

Please refer to your Supplemental New Drug Application (sNDA) dated September 30, 2014, received September 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zovirax (acyclovir) Cream 5%.

This "Prior Approval" supplemental new drug application provides for the following:

1. An alternate drug product manufacturer (Valeant Pharmaceuticals International Inc. [VPII], Laval, Quebec, Canada);
2. An alternate drug substance manufacturer ((b) (4));
3. An alternate compendial testing facility ((b) (4) (b) (4)).

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

Thomas F. Oliver, Ph.D.
Branch Chief, Branch VI
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21478Orig1s008

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div II, Branch VI and HFD-530	**021478**

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE	
Valeant International Bermuda Claredon House 2 Church Street Hamilton, Bermuda HM11	**SCM-008** SDN 275 Letter Date Goal Date	**PA** 09/30/14 01/30/15

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
ZOVIRAX	Acyclovir Cream	N/A

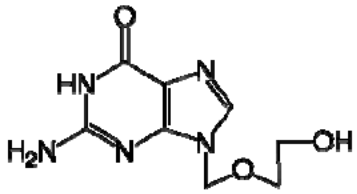
8. SUPPLEMENT PROVIDES FOR:

an alternate drug product manufacturing and testing site (Valeant Pharmaceuticals International Inc. [VPII], Laval Quebec) including process changes, an alternate drug substance manufacturing site ((b) (4)), and an alternate compendial testing site ((b) (4) (b) (4)).

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Antiviral	Rx	DMF (b) (4) LoA 09/03/13
12. DOSAGE FORM	**13. POTENCY**	
Cream	5%	

14. CHEMICAL NAME AND STRUCTURE

Chemical Name: 2-amino-9-(propoxymethyl)-1*H*-purin-6(9*H*)-one
Molecular Formula: $C_8H_{11}N_5O_3$
Molecular Wt.: 225.21
CAS No.: [59277-89-3]
Chemical Structure:



15. COMMENTS

Overall Manufacturing Inspection Recommendation from OC Approved (b) (4). The Biopharm consult for review of *In-vitro* comparative data (V. Kolhatkar) dated 01/27/15 recommends Approval. The applicant makes reference to DMF (b) (4) for all information pertaining to the drug substance manufacturing. DMF (b) (4) has been judged Adequate in the review by J. Salemme, dated (b) (4).

16. CONCLUSION AND RECOMMENDATION

Approved

17. REVIEWER	18. REVIEWER'S SIGNATURE	19. DATE COMPLETED
Brian Rogers	See appended electronic signature sheet	01/27/15

The subject of this review is PA supplement 021478/SCM-008 (09/30/14) which supports an alternate drug product manufacturing and testing site (Valeant Pharmaceuticals International Inc. [VPII], Laval Quebec) including process changes, an alternate drug substance manufacturing site ([redacted]), and an alternate compendial testing site ([redacted]

Alternative Drug Substance Manufacturing Site
The applicant makes reference to DMF [redacted] for all information pertaining to manufacture and control of acyclovir from the proposed alternate drug substance supplier ([redacted]). An LoA to reference DMF [redacted] dated [redacted], is provided.

The details of the proposed site of drug substance manufacturing are as follows:

[redacted]

Evaluation
Satisfactory. DMF [redacted] for the drug substance manufacturing has been found Adequate in the review by J. Salemme dated [redacted].

The proposed manufacturing site has been submitted for inspection. Overall Manufacturing Inspection Recommendation from OC Approved [redacted]. Output from Panorama is duplicated at the end of this review.

Characterization and Control of the Drug Substance:
The applicant compared the results of characterization studies (FTIR, XRPD, Raman Spectroscopy, and SEM) from three batches manufactured at the current site (ACP5870811, 27005726, and 27010091) with those from three batches from the proposed site (14071220010, 14071220012, and 14071220013). See section 3.2.S.3.1 for additional details.

The applicant makes reference to the appropriate section of DMF [redacted] for comparative chemical analytical data.

The applicant affirms that the specification for Acyclovir USP remains unchanged with the following exceptions: Removal of [redacted]; removal of control of [redacted] level as a residual solvent; **addition of controls for [redacted] as residual solvents**.

The methods are unchanged with the exception of the method for Assay and related impurities by HPLC ((b) (4)) which includes the following changes:

(b) (4)

The updated analytical method is provided.

The drug substance specification is duplicated at the end of this review. A comparison table between the approved specification and that proposed for the new manufacturing site is reproduced on the following pages.

Evaluation

Satisfactory. The removal of the (b) (4) is acceptable since the USP does not require a (b) (4) for acyclovir.

Control of (b) (4) level was removed from the specification for residual solvents as this solvent is not used by the manufacturer in the synthesis of acyclovir. However, (b) (4) were added to the specification to monitor these solvents since they are used during the manufacturing process.

The reported changes in analytical test method numbers were necessary to reflect the method number required by the change in site.

The changes to the analytical method for Assay and related impurities by HPLC are acceptable since they improve the quality of the system suitability testing and quantitation of the impurities.

The physical characterization data show equivalency of the proposed site ((b) (4)) to that of the approved ((b) (4) site. All analytical results show no differences in physical properties.

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Comparative Release Data

The applicant has submitted comparative release analytical data from three lots of (proposed supplier) Uquifa drug substance, and three lots of (current supplier) Mylan drug substance.

The following table provides the lot numbers and manufacturing dates from the tested batches:

Table 3.2.S.4.4–1: Acyclovir USP Batch Information

Supplier	Supplier Lot No.	Manufacturing Date
	ACP5870811	August 2011
	27005726	September 26, 2012
	27010091	December 11, 2012
	14071220010	March 27, 2012
	14071220012	July 19, 2012
	14071220013	July 5, 2012

Evaluation

Satisfactory. The two sites produce equivalent drug substance. The data show no differences between the two sites in *Description*, *ID*, *Color* (All comply), *Water Content*, *Ordinary impurities* (ND), or *Assay* or *Related impurities* (with the exception of which were lower in all batches from the proposed site, i.e., , respectively). All data were within acceptance criteria.

There were small differences between the two sites in *Particle Size Distribution* (b) (4) but this difference is not significant for this dosage form, particularly since they easily met the acceptance criterion (b) (4) .

Comparative Physical Properties

The physical properties of three batches of drug substance from either supplier ((b) (4)) were compared using characterization data from FTIR, XRPD, Raman spectroscopy, Scanning Electron Microscope, and PSD. The characteristics of the tested drug substance lots are provided in the above table.

Evaluation

Satisfactory. The FTIR spectra from all lots were identical from (b) (4)

The location and relative intensities of the peaks in the XRPD data from all lots were identical within reasonable expectations.

The Raman spectra were all identical in peak position and relative intensities from (b) (4) (b) (4)

The images from the SEM were reasonably similar from all lots. The surface conditions of the particles from all lots were similar to the extent discernable at the provided magnification.

Drug Substance Stability Testing

The applicant makes reference to DMF (b) (4) for all information pertaining to stability studies. The proposed retest period is (b) (4). The applicant states that acyclovir is stable when stored in (b) (4)

Evaluation

Satisfactory. DMF (b) (4) has been found Adequate in the review by J. Salemme dated (b) (4) .

Alternate compendial testing facility ((b) (4)).

The following site is proposed as an alternate compendial testing facility:

(b) (4)

(b) (4)

Evaluation

Satisfactory. The proposed compendial testing site has been submitted for inspection. Overall Manufacturing Inspection Recommendation from OC Approved (b) (4). The site is acceptable since there is no issue with performing compendial testing. Output from Panorama is duplicated at the end of this review.

Additional Drug Product Manufacturing and Packaging Site

The applicant proposes to use the following site for drug product manufacturing, packaging, release and stability testing (approved site is GlaxoSmithKline (GSK) in Mississauga, Ontario):

Valeant Pharmaceuticals International, Inc.
2150 boul Saint-Elzear O.
Laval, Quebec, H7L 4A8, Canada
FEI: 3002807186
DUNS: 245141858

Evaluation

Satisfactory. The proposed drug product manufacturing and packaging site has been submitted for inspection. Overall Manufacturing Inspection Recommendation from OC Approved 11/19/14. Output from Panorama is duplicated at the end of this review.

Manufacturing Process Comparison

Differences between the GSK process and the process at the proposed site (VPII) are described in Table 3.2.P.2.3–1 which is reproduced below.

The manufacturing process at VPII is reportedly based upon the process that is currently approved at the Glaxo Smith Kline (GSK) site. The applicant states that some minor process changes were necessary in order to adapt to the equipment available at VPII; however the overall flow of the process did not change. (b) (4), however both the composition and the order of addition of the ingredients remains the same. Mixing speeds and mixing times were adjusted to ensure that the finished product met the same specification and had the same quality attributes.

Equipment at the proposed site are of the same operating principle and design as those from the currently approved site (GSK) as described in Table 3.2.P.2.3–2 (reproduced following Table 3.2.P.2.3-1).

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Evaluation

Satisfactory. The changes in equipment are all within the same operating principles and class/subclass as defined in SUPAC-SS.

Comparative Drug Product Batch Test Results

The applicant manufactured one full scale, validation batch of Zovirax Cream 5%, using acyclovir from (b) (4) The applicant placed this batch (#8072412) in their stability program Data from Batch 8072412 consists of 9 months long-term (25ºC/60% RH), and 6 months accelerated (40ºC/75% RH) testing.

Release test data for batch 8072412 are provided in section 3.2.P.5.4 *Batch Analysis*. All data met specifications.

Comparative *In-Vitro* Release Testing

The applicant provided comparative *in-vitro* release profile data of the product manufactured at the currently approved site (GSK) and that of the product manufactured at VPII. The applicant also provided the details of the study performed in the report "*Method Development and Evaluation of In-Vitro Release (SUPAC-SS) of Acyclovir (5%) in 2 Formulations under GLP*", (see Attachment 1).

In this study, a recent batch of Zovirax Cream manufactured at GSK (Batch No. L3004) was compared to the first validation batch (Batch No. 8072412) manufactured at VPII.

A Biopharm consult was issued to evaluate the comparative *In-vitro* data and the comparison method.

Evaluation

Satisfactory. The Biopharm review dated 01/27/15, by V. Kolhatkar had the following Recommendation:

> ***"The IVRT comparison data support the approval of the proposed new manufacturing site. From the Biopharmaceutics perspective, NDA 21478/S-008 for Zovirax® (Acyclovir) cream, 5% is recommended for approval."***

The Holder provided post-approval stability protocol and commitment in section 3.2.P.8.2. These are duplicated below:

The stability studies for the first three validation lots will continue in accordance with the stability protocol presented in 3.2.P.8.1 Stability Summary and Conclusion. Thereafter, one batch will be placed in a stability program annually in accordance with the protocol presented below in Table 3.2.P.8.2–1. Samples will be stored in the horizontal orientation and tested according to the specification provided in 3.2.P.5.1 Specification.

Table 3.2.P.8.2–1 Stability testing protocol applied to Zovirax Cream 5%

Storage Condition	Test Intervals (Months)				
	0	12	24	36	48[a]
25°C ± 2°C/60 ± 5% RH (horizontal orientation)	X, M	X	X	X,M	X,M

a: Optional test interval.

Stability information will be submitted periodically as required by 21 CFR §314.81(b)(2)(iv).

Table 3.2.P.8.1–1 Stability Protocol applied to first three validation batches

Storage Condition	Test Interval (months)										
	0	1	2	3	6	9	12	18	24	36	48[a]
25°C ± 2°C/ 60 ± 5%RH (horizontal)	X,M	NT	NT	X	X	X	X	X	X	X,M	X,M
30°C ± 2°C/ 65 ± 5%RH (horizontal)	X,M	NT	NT	X	X	X	X	NT	NT	NT	NT
40°C ± 2°C/ 75 ± 5%RH (horizontal)	X,M	X	X	X	X	NT	NT	NT	NT	NT	NT

NT=not tested

a: Optional test point

X: Physical and chemical tests (description, pH, viscosity, particle size, assay, related substances) are performed.

M: Microbiological tests are performed.

Evaluation

Satisfactory. The long-term and accelerated stability data from exhibit batch 8072412 are all within specification. There are no trends noted with the exception that the accelerated data show a slight drop in pH from 6.4 -5.6 over the length of the study.

The post-approval stability protocol and commitment are acceptable.

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Tolerances: NLT 85% (Q) of the labeled amount of $C_{21}H_{26}O_3$ is dissolved.

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE: LIMIT OF DEGRADATION PRODUCTS**

Diluent, Mobile phase, System suitability solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay.*

Analysis

Sample: *Sample solution*

Calculate the percentage of each degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each individual impurity

r_T = sum of the responses of all the peaks

Acceptance criteria

Individual impurities: See *Impurity Table 1.*

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acitretin related compound A[a]	0.84	0.5
Acitretin	1.0	—
9-*cis* isomer[b]	1.09	—
Any unspecified impurity	—	0.4
Total unspecified impurities	—	0.8

[a] [(2*Z*,4*E*,6*E*,8*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid] ($C_{21}H_{26}O_3$ 326.43).

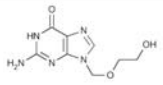
[b] (*E*,*E*,*Z*,*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Acitretin RS

Acyclovir



$C_8H_{11}N_5O_3$ 225.20

6*H*-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-.

9-[(2-Hydroxyethoxy)methyl]guanine [59277-89-3].

» Acyclovir contains not less than 98.0 percent and not more than 101.0 percent of $C_8H_{11}N_5O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers. Store at room temperature. Protect from light and moisture.

USP Reference standards ⟨11⟩—

USP Acyclovir RS

Identification—

A: *Infrared Absorption ⟨197K⟩.*

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay and limit for guanine.*

Water, *Method I ⟨921⟩*: not more than 6.0%.

Ordinary impurities ⟨466⟩—

Test solution: dimethyl sulfoxide.

Standard solution: dimethyl sulfoxide.

Eluant: a mixture of chloroform, methanol, and ammonium hydroxide (80:20:2).

Visualization: 1.

Application volume: 5 µL.

Limit: 1%.

Assay and limit for guanine—

Mobile phase—Prepare a filtered and degassed solution of glacial acetic acid in water (1 in 1000). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

System suitability solution 1—Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 0.1 mg of each per mL.

System suitability solution 2—Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.7 µg per mL.

Guanine standard preparation—Transfer about 8.75 mg of guanine, accurately weighed, to a 500-mL volumetric flask. Dissolve in 50 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a 50-mL volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having a concentration of about 0.7 µg per mL.

Standard preparation—Dissolve about 25 mg of USP Acyclovir RS, accurately weighed, in 5 mL of 0.1 N sodium hydroxide in a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having a known concentration of about 0.1 mg of USP Acyclovir RS per mL.

Assay preparation—Dissolve about 100 mg of Acyclovir, accurately weighed, in 20 mL of 0.1 N sodium hydroxide in a 200-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph *System suitability solution 1,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between acyclovir and guanine is not less than 2.0; the tailing factor for the analyte peak is not more than 2; and the relative standard deviation for replicate injections for the acyclovir peak is not more than 2.0%. Chromatograph *System suitability solution 2,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation,* the *Guanine standard preparation,* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all

the peaks. Calculate the quantity, in µg, of guanine in the portion of Acyclovir taken by the formula:

$$1000C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of guanine in the *Guanine standard preparation;* and r_U and r_S are the peak responses due to guanine in the *Assay preparation* and the *Guanine standard preparation,* respectively: not more than 0.7% of guanine is found. Calculate the quantity, in mg, of $C_8H_{11}N_5O_3$ in the portion of Acyclovir taken by the formula:

$$1000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Acyclovir RS in the *Standard preparation;* and r_U and r_S are the peak responses due to acyclovir in the *Assay preparation* and the *Standard preparation,* respectively.

Acyclovir Capsules

DEFINITION

Acyclovir Capsules contain NLT 93.0% and NMT 107.0% of the labeled amount of acyclovir ($C_8H_{11}N_5O_3$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution,* as obtained in the *Assay.*

ASSAY

- **PROCEDURE**

Mobile phase: 0.02 M acetic acid

System suitability solution A: 0.1 mg/mL each of USP Acyclovir RS and guanine. Dissolve in 0.1 N sodium hydroxide, and dilute with water.

System suitability solution B: 2.0 µg/mL of guanine. Dissolve in 0.1 N sodium hydroxide, and dilute with water.

Standard solution: 0.1 mg/mL of USP Acyclovir RS. Dissolve in 0.1 N sodium hydroxide, and dilute with water.

Sample solution: Nominally 0.1 mg/mL of acyclovir prepared as follows. Transfer the contents of Capsules equivalent to 10 mg of acyclovir (NLT 10 Capsules) to a 100-mL volumetric flask. Dissolve in 10 mL of 0.1 N sodium hydroxide, dilute to volume with water, and filter.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability.*)

Mode: LC

Detector: UV 254 nm

Column: 4.2-mm × 25-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution A* and *System suitability solution B*

[NOTE—The relative retention times for guanine and acyclovir are about 0.6 and 1.0, respectively, in *System suitability solution A.*]

Suitability requirements

Resolution: NLT 2.0 between guanine and acyclovir, *System suitability solution A*

Relative standard deviation: NMT 2.0% for the acyclovir peak, *System suitability solution A*

Relative standard deviation: NMT 2.0%, *System suitability solution B*

Analysis: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acyclovir ($C_8H_{11}N_5O_3$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of the *Sample solution*
r_S = peak response of the *Standard solution*
C_S = concentration of USP Acyclovir RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of acyclovir in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Detector: UV 254 nm

Standard solution: USP Acyclovir RS in *Medium*

Sample solutions: Dilute with *Medium* to a concentration that is similar to the *Standard solution.*

Analysis: Determine the amount of acyclovir ($C_8H_{11}N_5O_3$) dissolved from UV absorption at the wavelength of maximum absorption on filtered portions of the solution under test.

Tolerances: NLT 75% (Q) of the labeled amount of acyclovir ($C_8H_{11}N_5O_3$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements for *Content Uniformity*

IMPURITIES

- **PROCEDURE**

Mobile phase, System suitability solution A, System suitability solution B, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay.*

Analysis: *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity
r_T = sum of the responses for all of the peaks

Acceptance criteria

Guanine: NMT 2.0%

Any individual impurity: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store between 15° and 25°. Protect from light and moisture.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Acyclovir RS

Acyclovir for Injection

DEFINITION

Acyclovir for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of acyclovir ($C_8H_{11}N_5O_3$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution,* as obtained in the *Assay.*

ASSAY

- **PROCEDURE**

Mobile phase: 0.02 M acetic acid

System suitability solution A: 0.1 mg/mL each of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide

USP Monographs

Inspection View

#	Task Name	Task Instructions	Assigned To	Pln Comp	Act Comp	Task Status	Task Actions
	Parent: Profile Evaluation for VALEANT PHARMACEUTICALS INTERNATIONAL INC. - OIN OINTMENT,NONSTERILE (INCLUDES CREAM, JELLY, PASTE) | FEI: 3002807186(1)						
1 2	Office of Process and Facilities Recommendation OIN OINTMENT,NONSTERILE (INCLUDES CREAM, JELLY, PASTE)		Derek Smith	11/9/14	11/19/14	Complete	
	[redacted]						
	Parent: Manufacturing Facility Inspection(1)						
3 8	Overall Manufacturing Inspection Recommendation		Derek Smith	1/17/15	11/19/14	Complete	

(b) (4)

NDA-021478-SUPPL-8: Overall Manufacturing Inspection Recommendation http://panorama.fda.gov/atask/taskView.cmd?ID=542cb723001019b7e4d816222d49d1d9

Overall Manufacturing Inspection Recommendation | Next task »

NDA-021478-SUPPL-8

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Facility Inspection - Overall Application Re-evaluation Date
7/20/15

What's New? | TeamHome »

[redacted] PM

Initial Quality Assessment and Triage

ONDQA Branch VI

OND Division: HFD-530 (DAVP)
NDA: 21-478
Supplement: S-008
DARRTS Document Number: SDN275
Applicant: Valeant Pharmaceuticals, North America
Letter Date: 9-30-2014
Stamp Date: 9-30-2014
ONDQA Receipt Date: notified to CMC lead electronically on 10-10-2014
ONDQA CMC Lead triage date: 10-10-2014
Application Type: electronic
Proprietary Name: Zovirax® (acyclovir) cream 5%
Established Name: acyclovir cream
Dosage Form: cream
Route of Administration: topical
Submission Type: Prior-Approval Supplement (PAS)
Recommended submission type: PAS

This electronic PAS provides for the addition of three alternate manufacturing facilities:

- [redacted], for drug substance manufacture --- the applicant refers to DMF [redacted]
- Valeant Pharmaceuticals, International, Inc., Laval, Quebec, Canada, for drug product manufacture
- [redacted], for compendial testing

- These facilities need to be submitted for cGMP evaluation.
- DMF [redacted] has been reviewed recently and was found adequate to support NDA 18-604/S-025 (Zovirax® Ointment) for the drug substance, acyclovir, see quality review dated [redacted], J. Salemme.
- This application corresponds to a SUPAC-SS Level 3 site change. The applicant performed IVRT studies and claim that the topical drug product, as manufactured at Valeant/Laval Quebec is equivalent to the current drug product, as manufactured at GSK, Mississauga, Ontario, Canada. This application requires a consult to the ONDQA biopharmaceutics staff.

Alternate facilities to be submitted for inspection:

(b) (4)

[redacted]

Facility	Operation
Valeant Pharmaceuticals International, Inc. 2150 boul Saint-Elzear O. Laval, Quebec, H7L 4A8, Canada FEI: 3002807186 DUNS: 245141858 Contact: Thomas Laing, Director, Quality and Compliance Telephone: 905-305-0998 Fax: 905-305-0996 Email: thomas.laing@valeant.com	Manufacturing, packaging, release and stability testing

(b) (4)

[redacted]

The applicant provides manufacturing process description, controls of critical steps and intermediates, and process validation. Release data is provided for one batch as manufactured at Valeant Laval, PQ, Canada. Stability data is provided through 9 months at 25/60 and through 6 months at 40/75.

The following statement is provided in the CTD (Module 2.2):

Drug Product

In order to support both the drug substance and drug product manufacturing site changes, VPII has manufactured one full scale, validation batch of Zovirax Cream 5%, using acyclovir from Uquifa. This batch (#8072412) was placed in a stability program and was tested against one lot of drug product manufactured by the currently approved site, GlaxoSmith Kline (GSK), for in-vitro release testing, per the SUPAC guidelines for Nonsterile Semisolid Dosage Forms. Validation and stability data, as well as in-vitro release test results demonstrate that the quality of the drug product is not impacted as a result of the drug substance and drug product manufacturing site changes.

The IVRT study and results are provided in Module 3.2.P.2 (manufacturing Pharmaceutical Development).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21478Orig1s008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 021478/**S-008**	**Reviewer:** Vidula R. Kolhatkar, Ph.D.	
Submission Date:	September 29, 2014		
Division:	Division of Antiviral Products	**Acting Biopharmaceutics Lead:** Kelly M. Kitchens Ph.D.	
Applicant:	Valeant Pharmaceuticals	**Acting Supervisor:** Tapash Ghosh, Ph.D.	
Trade Name:	Zovirax	**Date Assigned:**	October 31, 2014
Established Name:	Acyclovir Cream 5%	**Date of Review:**	January 23, 2015
Indication:	Management of recurrent genital herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.	**Type of Submission:** Prior approval supplement	
Formulation/ strengths	Cream/5%		
Route of Administration	Topical		
Type of Review:	IVRT data to qualify manufacturing site change		

SUMMARY:

Background: Zovirax® (acyclovir) Cream 5% was approved on December 30, 2002 for the management of recurrent genital herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older. The applicant is seeking approval for an alternate manufacturing and packaging site.

Submission: To support the level 3 change the applicant developed in vitro release testing (IVRT) method and conducted comparative IVRT of Acyclovir cream, 5% manufactured by GlaxoSmithKline (GSK) in Mississauga, Ontario vs. Acyclovir cream, 5% manufactured by Valeant Pharmaceuticals International, Inc. (VPII)) in Laval, Quebec.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the IVRT method and data supporting the approval of the new manufacturing site.

RECOMMENDATION:

The IVRT comparison data support the approval of the proposed new manufacturing site. From the Biopharmaceutics perspective, NDA 21478/S-008 for Zovirax® (Acyclovir) cream, 5% is recommended for approval.

Signature	**Signature**
Vidula R. Kolhatkar, Ph.D. Biopharmaceutics Reviewer Office of New Drug Products	Kelly M. Kitchens, Ph.D. Biopharmaceutics Quality Assessment Lead Office of New Drug Products
cc. TGhosh; PSeo.	

Assessment of Biopharmaceutics information

- Zovirax® (acyclovir) Cream 5% is indicated for the management of recurrent genital herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.
- Zovirax is currently manufactured and packaged by GlaxoSmithKline (GSK) in Mississauga, Ontario.
- This prior approval supplement is submitted for
  1. Alternate drug manufacturer (Valeant Pharmaceuticals International Inc. [VPII], Laval Quebec)
  2. Alternate drug substance manufacturer (b) (4)
  3. Alternate compendial testing facility (b) (4)
- Manufacturing process at VPII is based on the process currently approved at GSK. Although there are some minor changes there is no change in overall flow of the process. (b) (4). Both composition and order of addition of the ingredients remains the same. Composition of Acyclovir cream 5% is described in Table 1.

Table 1. Batch formula for current GSK manufacturing site (500 kg) and the proposed VPII site (400kg)

Component	Reference to Quality Standard	Purpose	% Formula (w/w)	(b) (4)
Acyclovir				(b) (4)
Poloxamer 407				
Cetostearyl alcohol				
Sodium Lauryl Sulfate				
White petrolatum				
Mineral oil				
Propylene glycol				
(b) (4) water				

Table Table 3.2.P.3.2–1 from submission

- To support this level 3 change the applicant has submitted IVRT method development and validation report.

IVRT method development report

- (b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

IVRT Results

- The applicant obtained the following results:

Table 4. Statistical comparison of two batches of Zovirax® Cream 5 %

Formulation 1	Formulation 2	Limits of the 90 % confidence interval		
		Lower-limit / 8th value (corresponds to 75 % of the confidence interval)	Upper-limit / 29th value (corresponds to 133.33 % of the confidence interval)	Significant difference
Zovirax® Cream 5 % batch L3004	Zovirax® Cream 5 % batch 8072412	0.849	1.120	No

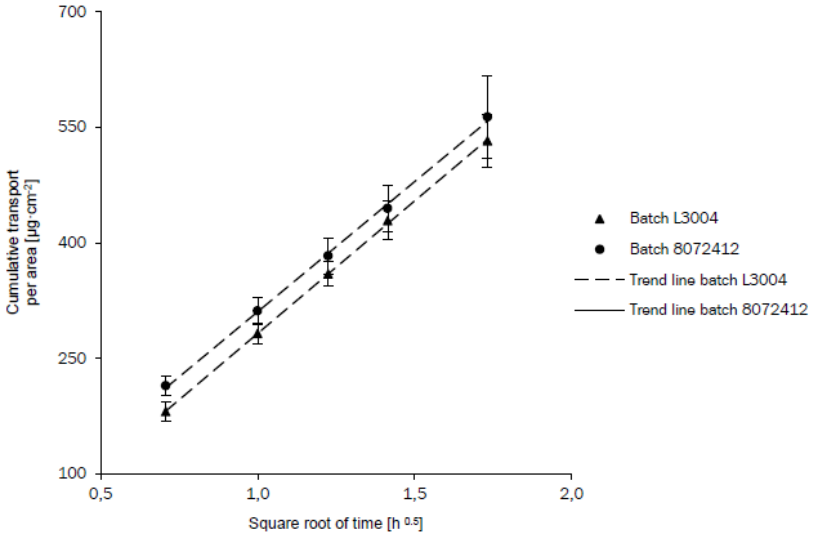


Fig. 25: Higuchi plot of the release of Acyclovir from Zovirax® Cream 5 % batches L3004 and 8072412. The values shown are the mean values from the experiment in six-fold. The cumulative transport into the acceptor compartment is expressed in µg per cm² of membrane area against the square root of time.

- The Applicant reported the 8th and 29th ordered test/reference ratios were 84.9% and 112%, respectively.

Comments on IVRT results:
On January 23, 2015, the following Information Request (IR) was submitted to the Applicant:

Please submit the raw acyclovir release data for Zovirax Cream Batch L3004. Submit the data in the same format that you submitted the data for Zovirax Cream Batch 8072412 in Tables 113, 114, 115 and 116 of your report no. 40293-2573-0814 "Method development and evaluation of in vitro release (SUPAC-SS) of acyclovir (5 %) in 2 formulations under GLP." We request this data by COB January 27, 2015.

The Applicant responded to the IR on January 26, 2015. In the response, the applicant clarified that the raw data for acyclovir release from Zovirax is included in the current submission (section 10.2.3 in Method Validation of release experiments, tables 97 to 100 in report no. 40293-2573-0814 "Method development and evaluation of in vitro release (SUPAC-SS) of acyclovir (5 %) in 2 formulations under GLP").

Reviewer's results
This Reviewer verified the Applicant's results per the submitted data for Zovirax cream:

Table 5: Reviewer calculated slope data

Acyclovir Release Rates ($\mu g.cm^{-2}\ hr^{-1/2}$)	
Reference product (Batch L3004)	Test product (Batch 8072412)
360.1	323.0
380.2	341.4
353.9	403.4
448.4	338.4
312.0	359.0
294.8	273.2

Table 6. Reviewer calculated T/R values

	360.1	**380.2**	**353.9**	**448.4**	**312.0**	**294.8**
323.0	**0.8969**	**0.8495**	**0.9126**	**0.7202**	**1.0351**	**1.0956**
341.4	**0.9482**	**0.8980**	**0.9647**	**0.7614**	**1.0943**	**1.1581**
403.4	**1.1202**	**1.0609**	**1.1398**	**0.8995**	**1.2928**	**1.3683**
338.4	**0.9397**	**0.8900**	**0.9562**	**0.7546**	**1.0845**	**1.1478**
359.0	**0.9970**	**0.9442**	**1.0144**	**0.8006**	**1.1506**	**1.2178**
273.2	**0.7586**	**0.7184**	**0.7719**	**0.6091**	**0.8755**	**0.9266**

Table 7. Reviewer calculated rank order of individual T/R values

Rank Order	T/R Ratios
1	0.60914941
2	0.71844801
3	0.72022241
4	0.75459985
5	0.7585946
6	0.76136919
7	0.77185824
8	0.80055439
9	0.84945063
10	0.87547941
11	0.88999636
12	0.89691759
13	0.89798031
14	0.8995297
15	0.91259975
16	0.92659782
17	0.939729
18	0.94419644
19	0.94815908
20	0.95615969
21	0.96473717
22	0.99695776
23	1.01438907
24	1.03511531
25	1.06093072
26	1.08452313
27	1.09425213
28	1.09555471
29	1.12021509
30	1.1398015
31	1.14784741
32	1.15056974
33	1.15814447
34	1.21775042
35	1.29281866
36	1.36830511

Reviewer's comments on IVRT results:
Per the SUPAC Guidance for nonsterile semisolid dosage forms, the 90% confidence intervals (8^{th} and 29^{th} ordered individual ratios) should fall within 75% to 133.33% at the first stage. The 90% confidence intervals for Acyclovir (80.05%, 112.02%) meet the acceptance criteria for IVRT. These values are slightly different than the applicant calculated values (84.9%, 112%) but are within acceptable range.

Recommendation:
The IVRT comparison data support the approval of the proposed new manufacturing site. From the Biopharmaceutics perspective, NDA 21478/S-008 for Zovirax® (Acyclovir) cream, 5% is recommended for approval.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21478Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21478/S-008

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Valeant International Bermuda
Attention: Lori a. Fiorentino, MSc., RA
Associate Director, Regulatory Affairs, CMC
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Fiorentino:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21478

SUPPLEMENT NUMBER: S-008

PRODUCT NAME: Zovirax (acyclovir) Cream 5%

DATE OF SUBMISSION: SEPTEMBER 30, 2014

DATE OF RECEIPT: SEPTEMBER 30, 2014

This supplemental application proposes the following changes: 1) an alternate drug product manufacturer (Valeant Pharmaceuticals International Inc. [VPII], Laval, Quebec, Canada), 2) an alternate drug substance manufacturer (Uquifa Inc., Sant Celoni, Barcelona), and an alternate compendial testing facility (QCL Quality Compliance Laboratories Inc., Markham, Ontario, Canada).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 29, 2014, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be January 30, 2015.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Althea Cuff, MS
Regulatory Health Project Manager
Branch V, Office of New Drug Quality Assessment
Center for Drug Evaluation and Research