CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-257s000

21-304s007

CHEMISTRY REVIEW(S)

NDA 22-257

VALCYTE®
(valganciclovir hydrochloride)
Powder for Oral Solution
50 mg/mL

Roche Palo Alto LLC
Nutley, NJ

Division of Antiviral Drug Products
HFD-530
FDA CDER

Ted Chang, Ph.D.
ONDQA Pre-Marketing Assessment and
Manufacturing Science Division III/Branch VI

Table of Contents

CMC Review Data Sheet

1. **NDA 22-257**

2. REVIEW #: 1

3. REVIEW DATE: 26-AUG-2008

4. REVIEWER: Ted Chang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA Meeting Response	03-SEP-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Subject Title
NDA 22-257	30-APR-2008	Original submission
NDA Amendment (N000-BC)	28-MAY-2008	Establishment Information and Cross References

7. NAME & ADDRESS OF APPLICANT:

Name	Roche Palo Alto LLC
Address	c/o Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110
Representative	Wendy L. Corbett, Ph.D.

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	VALCYTE® Powder for Oral Solution
Non-Proprietary Name (USAN)	Valganciclovir Hydrochloride, Ganciclovir Valinate Hydrochloride
Code Names	Ro 107-9070/F01
Chemistry Type	1
Submission Priority	P

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

10. PHARMACOL. CATEGORY: Anti-viral
INDICATION: Treatment of Cytomegalovirus (CMV) retinitis in patients with AIDS, and prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk.

11. DOSAGE FORM: Powder for Oral Solution

12. STRENGTH/POTENCY: 50 mg/mL (Re-Constituted solution)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product

__X__Not a SPOTS product

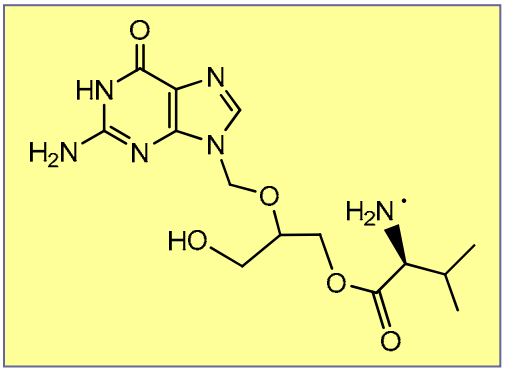
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: L-Valine, 2-[(amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride

9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]-guanine monoester with L-valine, monohydrochloride

US Adopted Name (USAN): VALCYTE® (valganciclovir hydrochloride)
International Non-proprietary Name (INN): valganciclovir
Laboratory Codes: RO1079070, Ro107-9070

Chemistry Review Data Sheet



Chemical Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$
Molecular Weight: 390.82
CAS Number: 175865-59-5 (for valganciclovir hydrochloride)
175865-60-8 (for valganciclovir free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
[redacted]			(b) (4)	1	Adequate	Review not required per policy
				1	Adequate	Review not required per policy
				1	Adequate	Review not required per policy
				1	Adequate	Review not required per policy

[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
CMC Review #1	NDA 21-304	Tablets—Valganciclovir HCl 450-mg

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	STATUS/ REVIEWER
EES	Pending	16-SEP-08	Office of Compliance
LNC	---	---	---
Methods Validation	To be initiated post-approval	---	---
OSE DMETS	VALCYTE®, ACCEPTABLE	---	---
EA	Category exclusion granted	15-AUG-2008	Ted Chang
Microbiology	ACCEPTABLE	---	Nilambar Biswal

The CMC Review for NDA 22-257

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Therefore this NDA is recommended for APPROVAL pending the "Acceptable" overall recommendation from Office of Compliance for all the facilities involved. As of 15-SEP-2008 this recommendation is still pending.

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

There are no Phase 4 commitments.

II. Summary of CMC Assessments

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

Valganciclovir hydrochloride is a pro-drug of the active pharmaceutical ingredient ganciclovir and consists of the valine monoester of ganciclovir. It exhibits improved oral bioavailability [redacted] (b) (4) over its parent compound ganciclovir [redacted] (b) (4) Valganciclovir hydrochloride is indicated for the treatment of cytomegalovirus (CMV) retinitis in immuno-compromised patients. It inhibits replication of herpes viruses in vitro and in vivo. The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and incorporation of ganciclovir triphosphate into viral DNA causing the termination of, or very limited, further viral DNA elongation."

The drug product—VALCYTE® Powder for Oral Solution—is a new formulation for the drug substance valganciclovir hydrochloride. This new formulation provides stability attribute (for pre-constitution dry powder) and dosing flexibility (for reconstituted oral solution). VALCYTE® Powder for Oral Solution fills the gaps of two approved drugs: 450-mg tablets (NDA 21-304 VALCYTE) and CYTOVENE-IV (NDA 19-661 for ganciclovir sodium for injection).

DRUG SUBSTANCE *Satisfactory*

Executive Summary Section

This section of Summary of CMC Assessment for the Drug Substance is excerpted from NDA 21-304 CMC Review #1, for the completeness of CMC review for NDA 22-257.

Valganciclovir is the valine monoester of ganciclovir, and consists of two diastereomers. Both diastereomers have the (S)-configuration at the valine chiral center and an approximately equimolar mixture of (R) and (S) configuration at the C-2 of the glyceryl side chain of the ganciclovir moiety. In vivo, both diastereomers are readily converted to ganciclovir, which is achiral. Two additional diastereomers having the R-configuration at the valine chiral center exist as impurities.

The drug substance is a hydrochloride salt and is freely soluble in aqueous solution, particular at low pH. The material exists as a white crystalline powder. Valganciclovir hydrochloride may contain up to (b) (4) It is reversibly hygroscopic and will either absorb or release moisture under ambient humidity conditions, depending on the water content of the compound and the relative humidity of the surrounding atmosphere.

(b) (4)

The structure of valganciclovir hydrochloride was confirmed by a combination of infrared, ultraviolet, 1H-NMR, 14C-NMR, mass spectra and elemental analysis. The information provided adequately supports the proposed structure of drug substance.

(b) (4)

The proposed specification of the drug substance includes appearance, identity (IR, UV, chloride), water, sulfated ash, heavy metals, residual solvents, organic impurities (identified, total and individual other identified impurities, total and individual other unidentified impurities and total of all impurities), diastereomer ratio, enantiomeric purity, assay and particle size. The methods and method validations are adequate to support the specifications.

Three early process development batches (b) (4) as well as ten pilot-scale (b) (4) (b) (4) batches and three full-scale (b) (4)) batches (the registration batches) of the commercial manufacturing process were produced. The early process development batches were manufactured at the (b) (4) research site, and pilot-scale batches and full-scale batches were manufactured at the Roche Colorado Corporation site. The batch analyses data comply with the proposed specifications.

Stress stability studies of the drug substance demonstrated that the material exhibits a good stability profile when exposed to extremes of heat, light, and humidity for periods up to eight weeks. No significant change in either the enantiomeric purity or the diastereomer ratio of the samples was observed. There was a slight but measurable increase in the levels of Ro 102-1592/000 (ganciclovir) in response to the heat and light stresses, but not under the high humidity conditions. The greatest effects were observed with the combination of heat and humidity.

At the time of approval, 24 months of primary stability data are available on the pilot-scale lots at 25°C/60%RH. The completed accelerated studies (40°C/75%RH) show that minor degradation is observable, although the assay and organic impurities of the DS remains within specification limits. [redacted] (b) (4) Long term stability studies (25°C/60%RH) have shown no time-dependent changes in the assay, purity profile, diastereomer ratio or the enantiomeric purity up to 24 months, other than to [redacted] (b) (4) [redacted] (b) (4) Based on the available stability test data, a [redacted] (b) (4) re-test period for the DS requested by the sponsor is justified.

DRUG PRODUCT *Satisfactory*

[redacted] (b) (4)

[redacted] (b) (4) After reconstitution with 91-mL of purified water, the resulting solution for oral administration is 100-mL in volume and 50-mg/mL valganciclovir free base in target strength.

The quality of manufactured drug products are ensured through in-process controls and release testing against specifications. [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

A battery of stability studies, long-term and stress, were conducted for the dry powder (up to 36 months), reconstituted solution (up to 3 months), antimicrobial preservative (i.e. (b) (4) user test (i.e. low level challenge tests), in-use solution, and leachables/extractables for the PIBA and plastic oral dispenser. Stability data are adequate to support the proposed shelf-life of 2 years for VALCYTE Powder stored at 25°C with excursion permitted to 15-30°C, and 49 days shelf-life for reconstituted solution stored at 5°C.

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

The drug product—VALCYTE Powder for Oral Solution—is packaged (b) (4) as dried powder/granulates (containing 5-gram drug substance) in a (b) (4) glass bottle. The powder is reconstituted with 91-mL purified water to make approximately 100-mL solution, and capped with a press-in bottle adaptor (PIBA). The strength of the solution is 50-gram/mL of valganciclovir free base. The appropriate amount of solution is withdrawn with a plastic syringe-like oral dispenser and administered directly into a patient's mouth. The PIBA and two oral dispensers are co-packaged with VALCYTE Powder for Oral Solution.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure system. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life. Labels have required information from the CMC perspective. Therefore this NDA is recommended for APPROVAL pending the "Acceptable" overall recommendation from Office of Compliance for all the facilities involved.

III. Administrative

A. Reviewer's Signature

/s/ H. Ted Chang, Ph.D.

/s/ Norman R. Schmuff, Ph.D.

B. Endorsement Block

CMC Reviewer:	H. Ted Chang, Ph.D.
Pharmaceutical Assessment Lead:	Stephen P. Miller, Ph.D.
Branch Chief:	Norman R. Schmuff, Ph.D.
Project Manager:	David Araojo

C. CC Block

Orig. NDA 22-257
HFD-530/Division File
Filename: Review-NDA 22257 Roche Valcyte Powder CMC#1.doc

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/s/

Ted Chang
9/18/2008 11:27:55 AM
CHEMIST

Norman Schmuff
9/18/2008 08:43:46 PM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 17, 2008

TO: NDA 22-257

FROM: Ted Chang
CMC Reviewer, ONDQA

SUBJECT: Update of EES Status for
NDA 22-257
VALCYTE® Powder for Oral Solution
Hoffmann-La Roche Inc.

The Executive Summary

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has provided—on October 16, 2008—an overall recommendation of "ACCEPTABLE" for all the manufacturing and testing sites. Therefore this NDA is recommended for APPROVAL from the CMC perspective.

EES Summary Report

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22257/000
Org Code : 530
Priority : 3P
Stamp Date : 01-MAY-2008
PDUFA Date : 01-NOV-2008
Action Goal :
District Goal: 02-SEP-2008

Sponsor: HOFFMONN LA ROCHE
NO CITY, , XX

Brand Name : VALCYTE
Estab. Name:
Generic Name: VALGANCICLOVIR HYDROCHLORIDE
Dosage Form: (FOR ORAL SOLUTION)
Strength : 50 MG/ML

FDA Contacts:			
	D. ARAOJO	Project Manager	301-796-0669
	H. CHANG	Review Chemist	301-796-1974
	S. MILLER	Team Leader	301-796-1418

Overall Recommendation: ACCEPTABLE on 16-OCT-2008by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN : 9690045 FEI : 3000264888
PATHEON INC TORONTO REGION OPERATIONS
2100 SYNTEX COURT
MISSISSAUGA, ONTARIO, CA
DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : POW OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-OCT-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9616748 FEI : 3002861690
PATHEON INC. - BURLINGTON CENTURY OPERATIONS
977 CENTURY DRIVE
BURLINGTON, ONTARIO, CA
DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JUN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1710165 FEI : 1710165
ROCHE COLORADO CORP
2075 NORTH 55TH ST
BOULDER, CO 80301
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 20-JUN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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/s/

Ted Chang
10/17/2008 03:01:36 PM
CHEMIST

Norman Schmuff
10/20/2008 01:34:02 PM
CHEMIST