CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-304

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-304 /SE_____ - _____

Drug VALCYTE™(valganciclovir HCl)Tablets Applicant Roche Pharmaceuticals

RPM Leslie Stephens Phone 301-827-2413

X☐505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ☐ S X☒P

Pivotal IND(s) _____

Application classifications:
Chem Class P2
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary March 29, 2001
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: X☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☒AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... ✓
  Original proposed labeling (package insert, patient package insert) ..... ✓
  Other labeling in class (most recent 3) or class labeling..... ✓
  Has DDMAC reviewed the labeling? ..... ☒ Yes (include review) ☐ No
  Immediate container and carton labels ..... ✓
  Nomenclature review ..... ✓

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Safety Update review(s) ..... √ ..... Contained in Ltr Review

- Pediatric Information
  - ☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
    Pediatric Page..... 3/21/01
  - ☒ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda ..... √ 3/21/01

- Biopharmaceutical review(s) and memoranda..... √ 3/21/01

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N A

- Microbiology (efficacy) review(s) and memoranda ..... √ 3/21/01

- DSI Audits ..... ✱
  - ☒ Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda ..... √ 3/21/01

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... √ 3

- DMF review(s) ..... NA

- Environmental Assessment review/FONSI/Categorical exemption ..... Exempt

- Micro (validation of sterilization) review(s) and memoranda ..... NA

- Facilities Inspection (include EES report)
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable

- Methods Validation ..... Pending ..... ☐ Completed ☒ Not Completed

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PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... √ 3/21/01

- Memo from DSI regarding GLP inspection (if any) ..... √ √ 3/21/01

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☒ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments ..... pending
  - Copy of Applicant's commitments ..... pending

- Was Press Office notified of action (for approval action only)? ..... ASAP 3/[illegible]/01 ☒ Yes ☐ No
  - Copy of Press Release or Talk Paper ..... N/A

- Patent
  - Information [505(b)(1)] ..... ✓ ..... ✓ 3/21/01
  - Patent Certification [505(b)(2)] ..... ✓ ..... ✓ 3/21/01
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ..... ✓ ..... ✓ 3/21/01

- Exclusivity Summary ..... ✓ ..... ✓ 3/21/01

- Debarment Statement ..... ✓ ..... ✓ 3/21/01

- Financial Disclosure
  - No disclosable information ..... ✓ ..... ✓ 3/21/01
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... ✓ 3/21/01

- Minutes of Meetings ..... ✓ 3/21/01
  - Date of EOP2 Meeting ✓ 12/16/98
  - Date of pre NDA Meeting ✓ 12/1/99
  - Date of pre-AP Safety Conference ✓ N/A
  - Date of pre-NDA CMC 6/5/2000

- Advisory Committee Meeting ..... ✓
  - Date of Meeting 2/27/2001
  - Questions considered by the committee ..... ✓
  - Minutes or 48-hour alert or pertinent section of transcript ..... ✓

- Federal Register Notices, DESI documents ..... ✓ 3/21/01

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....

- Clinical review(s) and memoranda ..... ✓ 3/21/01

Continued →

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

(Valganciclovir HCl)
Tablets 450mg

Roche

NDA 21-304 / Section 1
1. APPLICATION FORMS AND INDEX

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1 APPLICANT'S NAME AND ADDRESS

Synlex (U.S.A.) LLC
3401 Hillview Ave
Palo Alto, CA 94304

3 PRODUCT NAME
Valganciclovir hydrochloride

4 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT STOP HERE AND SIGN THIS FORM

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO CONTAINING THE DATA)

2 TELEPHONE NUMBER *(Include Area Code)*
(650) 496-3693

5 USER FEE I D NUMBER
4007

6 LICENSE NUMBER / NDA NUMBER
N021304

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7 reverse side before checking box)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food Drug and Cosmetic Act *(See item 7 reverse side before checking box)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug and Cosmetic Act *(See item 7 reverse side before checking box)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910 0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S W
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number

Please DO NOT RETURN this form to this address

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
H V Mante	Hermine Mante, PharmD Senior Regulatory Program Manager	09/18/2000

FORM FDA 3397 (5/98)

BEST POSSIBLE CO.

APPEARS THIS WAY ON ORIGINAL

Roche

Roche

Final Printed Labels

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA PO Box 360909)
Pittsburgh, Pennsylvania 15259-0001

Palo Alto, September 18, 2000
Re: NDA 21-304 - [redacted] (valganciclovir HCl) 450 mg Tablets
Human Drug Application Fee - [redacted]

Ladies and Gentlemen:

Enclosed please find a check in the amount of $285,740.00 made payable to the U.S. Food and Drug Administration. This payment represents the user fee required for our New Drug Application for [redacted] valganciclovir HCl) 450 mg Tablets, which is planned for submission on September 28, 2000.

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

Hermine Mante, PharmD.
Senior Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

Roche Global Development - Palo Alto a Division of Syntex (U.S.A.) LLC 3401 Hillview Ave
Palo Alto,
California 94304-1397

CERTIFICATION STATEMENT FOR GENERIC DRUG ENFORCEMENT ACT OF 1992

On behalf of Syntex (U.S.A.) LLC, Roche Global Development has made a diligent effort to insure that no person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act has provided any services in connection with this application. Relying on this effort, Roche certifies that it did not and will not use in capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

(Clinical Investigators)		
	See attached list of Investigators	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)), and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f))

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Bonnie Charpentier, Ph.D.	V.P. Regulatory Affairs
FIRM/ORGANIZATION	
Syntex (U.S.A.) LLC	
SIGNATURE	**DATE**
B. A. Charpentier	August 28, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane (Room 14C-03)
Rockville, MD 20857

FORM FDA 3454 (3/99)

ATTACHMENT 1 TO EXHIBIT A

First US Patent Number: 6,083,953

Expiration Date: July 28, 2014

Type of Patent-Indicate all that apply (check applicable boxes):

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent: Treatment of CMV retinitis.

Name of Patent Owner: Syntex (U.S.A.) LLC, successor by merger to Syntex (U.S.A.) Inc.

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **6,083,953** covers the composition, formulation and/or method of use of valganciclovir hydrochloride. This product is:

[ ] currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

[X] the subject of this application for which approval is being sought.

By: Nancy M Cohen
Name: Nancy Mahoney Cohen
Date: September 18, 2000
Title: Senior Vice President Legal Services
Telephone Number: 650-855-5217

EXHIBIT A2

PATENT INFORMATION FOR NDA NO. 21-304

1)	Active Ingredient(s)	Valganciclovir Hydrochloride
2)	Strength(s)	450 mg (as valganciclovir)
3)	Trade Name	[redacted]
4)	Dosage Form and Route of Administration	Tablets for oral administration
5)	Applicant (Firm) Name	Syntex (U.S.A.) LLC
6)	NDA Number	21-304
7)	First Approval Date	Not yet approved*
8)	Exclusivity: Date first ANDA could be approved	ANDA can not be approved for at least three (3) years from the date pending NDA is approved
9)	Patent Information	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application Supplement has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application Supplement has been approved.

Rev. 12/97

53264

EXCLUSIVITY SUMMARY for NDA # 21-304 SUPPL # _____

Trade Name VALCYTE™ Generic Name valganciclovir HCl

Applicant Name Roche Pharmaceuticals HFD- 530

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES / X / NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-661 CYTOVENE®-IV(ganciclovir sodium for injection)

NDA # 20-460 CYTOVENE®(ganciclovir capsules)

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # WV15376

Investigation #2, Study # WV15705

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # WV15376

Investigation #2_, Study # WV15705

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # 48,106 YES /X/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # 48,106 YES /X/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-304
HFD-530/Division File
HFD-530/RPM/L.Stephens
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 21-304 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD- 530 Trade and generic names/dosage form: Valcyte™ (valganciclovir hydrochloride) tablets

Action: AP AE **NA**

Applicant Roche Pharmaceuticals Therapeutic Class Antiviral

Indication(s) previously approved N/A
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application for the treatment of cytomegalovirus (CMV) in patients with acquired immunodeficiency syndrome (AIDS)

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

_x_ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply**, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

(See attached memo.)

/S/

Signature of Preparer and Title

3/22/01

Date

cc: Orig. NDA/PLA/PMA # N 21-304
HF D 530 /Div File 21-304
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **November 29, 2000**

NDA NUMBER: **21-304**

NAME OF DRUG: [redacted] (Primary) **and** [redacted] (Alternate)
(valganciclovir 450 mg capsules)

NDA HOLDER: **Syntex, Inc.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Drug Products, for assessment of the proposed proprietary drug name, [redacted] (Primary) and alternate name [redacted] regarding potential name confusion with other proprietary/generic drug names.

[redacted] IND 48-106, was the first proprietary name proposed. OPDRA had no objections to the use of the proprietary name, [redacted] on February 4, 2000 (consult # 99-039). The firm then responded with two additional proprietary names, [redacted] (primary) and [redacted] (alternate), under NDA 21-304 on July 20, 2000.

PRODUCT INFORMATION
The proposed product, [redacted] contains valganciclovir hydrochloride. Valganciclovir is an L-valyl ester salt (prodrug) of ganciclovir which, after oral administration, is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is an antiviral agent effective against cytomegalovirus (CMV) by inhibiting viral DNA synthesis. Valganciclovir is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Serious adverse reactions associated with valganciclovir include granulocytopenia, anemia, and thrombocytopenia. The recommended dose for patients with normal renal function is as follows:

- 900 mg twice daily for 21 days with food for patients with active CMV retinitis
- 900 mg once daily with food for patients with inactive CMV retinitis and following induction treatment

Dosage reductions according to creatinine clearance are required for valganciclovir. Valganciclovir will be supplied as 450 mg tablets and in bottles of 60 tablets.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to [redacted] and [redacted] to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted six prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names, [redacted] and [redacted]. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Several products were identified in the Expert Panel Discussion that was thought to have potential for confusion with [redacted] or [redacted] These products are listed in the table (see page 4), along with the dosage forms available and usual FDA-approved dosage.

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed). Martindale The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

1. Methodology

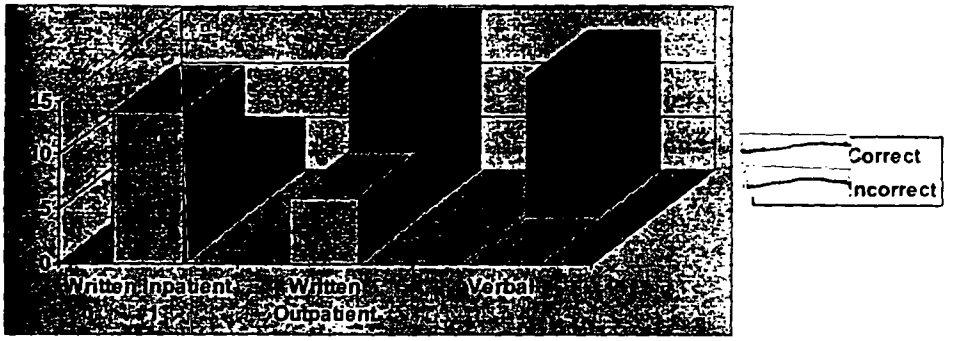
Six separate studies were conducted within FDA, to determine the degree of confusion of [redacted] and [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 90 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for [redacted] and [redacted] These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
[redacted]	
Outpatient: [redacted] i cap QD. #30 No refills	*Outpatient:* [redacted] one capsule daily. #30 No refills
Inpatient: Valcyt 1 po qd.	
[redacted]	
Outpatient [redacted] i cap QD. #30 No refills	*Outpatient:* [redacted] one capsule daily. #30 No refills
Inpatient. [redacted] 1 cap po QD.	

2. Results

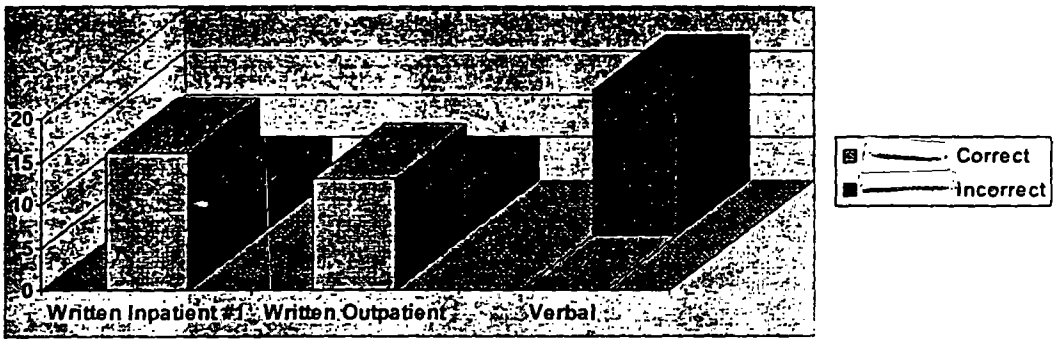
Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	[redacted] response	Other response
Written: Outpatient	30	21 (70 %)	6 (29 %)	15 (71 %)
Inpatient	29	19 (66 %)	14 (74 %)	5 (26 %)
Verbal: Outpatient	31	13 (42 %)	0 (0 %)	13 (100 %)
Total:	90	53 (59 %)	20 (38 %)	33 (62 %)
Study	No. of participants	# of responses (%)	[redacted] response	Other response
Written: Outpatient	31	18 (58 %)	13 (72 %)	5 (28 %)
Inpatient	30	21 (70 %)	16 (76 %)	5 (24%)
Verbal: Outpatient	29	17 (59 %)	0 (0 %)	17 (100 %)
Total:	90	56 (62 %)	29 (52 %)	27 (48 %)



Among the written prescription study participants for ——, 20 of 40 (50 %) participants interpreted the name incorrectly. *One respondent interpreted the name as "Valcef."* This response is important due to its close resemblance to a currently marketed product, *Velosef* (Cephradine). Five respondents interpreted the name as *Valcept* and five other respondents interpreted the name as *Valayt*. The remainder of the incorrect responses were *Valcipt, Volcyt, Valgf, Valoft, Valoyt, Valapt, Valgt, and Valopt.*

Among the verbal prescription study participants for ——13 of 13 (100 %) participants interpreted the name incorrectly. *Two respondents interpreted the name as "Valsed."* This response is important, since *Valsed* sounds very similar to a currently marketed drug product, *Versed* (Midazolam). Ten respondents interpreted the name as either *Valcet or Valset.* One other incorrect response to the verbal prescription study was *Valsec.*



Among the written prescription study participants for ——27 of 56 (48 %) participants interpreted the name incorrectly. Three respondents interpreted the name as *Aygance.* The majority of the incorrect name interpretations were misspelled variations of ——and the misinterpretations did not overlap with currently approved drug names.

Among the verbal prescription study participants for ——, all 17 of 17 (100 %) participants interpreted the name incorrectly. *One participant interpreted the name as "Tigan" (Trimethobenzamide), a currently marketed drug product.* It is also important to note that one participant interpreted the name to be *Zyben*, which differs from an approved drug product, *"Zyban,"* by one letter. Zyban (bupropion) is used for smoking cessation and it is available as tablets. Other incorrect responses were phonetic variations of the proposed name, ——

C. SAFETY EVALUATOR RISK ASSESSMENT

1. ———

In reviewing the proprietary name ———, the primary concerns raised were related to several sound-alike, look-alike names that already exist in the U.S. marketplace (*Versed, Velosef, and Valtrex*). In addition, there was concern that ——— closely resembles *Vercyte* and *Valacet*, which are no longer marketed but still appear in several references. (i.e. American Drug Index, Orange Book, and Micromedex)

We conducted prescription studies to simulate the prescription ordering process. *In this case, there was a suggestion that ——— could be confused with Versed and Velosef as discussed in the Expert Panel Discussion.* Two respondents from the verbal study provided *Valsed* as an interpretation. *Valsed* sounds like a currently marketed product, *Versed.* One respondent from an outpatient written study provided *Valcef* as an interpretation; *Valcef* sounds and looks very similar to a currently marketed drug product, *Velosef.* Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

We acknowledge that ——— and *Versed* do not share any overlapping strengths, dosing schedules, doses, and dosage forms and due to these differences it seems unlikely that these products would ever be confused. However, post-marketing experience has demonstrated that errors do occur between drugs that share no commonalties other than similar names. The study conducted by OPDRA just reinforces this concept. Also, in clinical settings, Celexa and Cerebyx have been confused for one another despite the fact that these drugs have different dosage forms, dosing schedule, doses, and strengths.

The proposed name, ——— and *Velosef* look similar when scripted, and could be easily be confused as demonstrated in the written prescription study and in the following written sample of prescription. ——— and Velosef also share overlapping dosing schedules; both drugs can be dosed twice daily.

If a prescription written for Velosef 500 mg BID is misinterpreted as ———900 mg BID, serious patient harm could occur due to the serious side effects associated with ———granulocytopenia, anemia, and thrombocytopenia.

The study did not confirm confusion between ——— and *Vercyte*, *Valacet*, or *Valtrex*. However, a negative finding in a study with a small sample size cannot be used to predict what may occur with broader use of the name in the general population. We also recognize that the products, *Valacet* and *Vercyte*, are no longer marketed in the United States, however until the names are removed from common drug references they could pose a problem.

Again, OPDRA believes there are numerous sound-alike/look-alike products currently on the market that have the potential for confusion with ——— *Given the above findings, we do not recommend the use of the proprietary name,* ———

2. [redacted]

In reviewing the proprietary name [redacted], the primary concerns raised were related to three sound-alike names that already exist in the U.S. marketplace, *Tigan, Zyban, and Ziagen*.

We conducted prescription studies to simulate the prescription ordering process. *In this case, there was confirmation that* [redacted] *could be confused with Tigan as discussed in the Expert Panel Discussion.* One respondent provided *Tigan* as an interpretation. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

[redacted] and *Tigan* do not share any overlapping strengths, dosing schedules, and dosage forms and due to these differences it seems unlikely that these products would ever be confused. However, we cannot ignore the fact that Tigan is phonetically very similar to [redacted]. Also, post-marketing experience has demonstrated that errors do occur between drugs that share no commonalties other than a similar name. The study conducted by OPDRA just reinforces this concept.

In addition, *Zyban*, which was not discussed in the expert panel, was uncovered in the verbal outpatient study as a potential sound-alike name. One participant from the verbal study interpreted the name as *Zyben. Zyben differs from Zyban, a currently marketed product in the United States, by one letter.* Zyban, bupropion, is indicated for smoking cessation. Not only do [redacted] and Zyban sound alike, they share overlapping dosing schedules and dosage forms. Zyban is available as 150 mg tablets and the maintenance dose is 150 mg twice daily. [redacted] is also supplied in tablets and it is dosed twice daily too. If these two drugs are confused for one another, serious patient harm could occur. Specifically, seizures could occur with Zyban and granulocytopenia, anemia, or thrombocytopenia could occur with [redacted]

During an independent search of several published drug product reference texts, *Ziagen* was discovered in the "Facts and Comparisions." The prescription study conducted by OPDRA did not confirm confusion between [redacted] and Ziagen. However, the potential for name confusion is possible, because not only do [redacted] and Ziagen sound alike, they share overlapping dosing schedules, dosage forms, and indication. Ziagen, abacavir, is available as 300 mg tablets and the recommended dose is 300 mg twice daily. [redacted] can also be dosed twice daily and it is available in tablets too. Furthermore, both drugs are used in the same patient population. Both Ziagen and [redacted] are used in patients with HIV infection, and the lack of either therapy could be detrimental. The omission of [redacted] could lead to permanent visual loss in patients with CMV retinitis. The omission of Ziagen could worsen HIV infection, since it is indicated for HIV infection in combination with other antiviral agents for the treatment of HIV-1 infection.

OPDRA believes that there are three sound-alike/look-alike products currently on the market that have the potential for confusion with [redacted]. *Given the above findings, we do not recommend the use of the proprietary name,* [redacted].

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container label and the package insert for [redacted] OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABEL

1. [redacted]

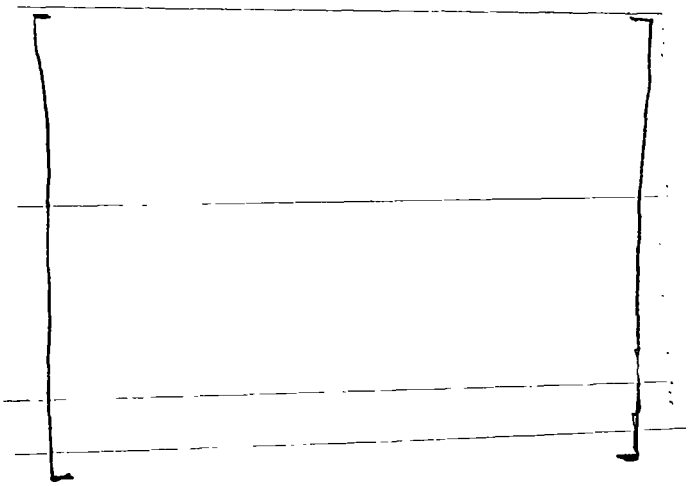
2. [redacted]

3. The current expression of the established name and strength is misleading and incorrect since each tablet contains 450 mg of valganciclovir [redacted]. This can be accomplished by expressing the established name and strength in one of the following three manners:

a.

b.

c.



OPDRA prefers the first example as an option because this nomenclature is consistent with USP recommendations on "labeling of salts of drugs" (General Notices, pg. 12).

B. PACKAGE INSERT LABEL

1. See 3 under CONTAINER LABEL.

IV. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary names [redacted] and "[redacted]".

B. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim at 301-827-3242.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

NDA: 21-304 **Submission Dates**: 09/28/2000, 03/15/2001
Product: Valganciclovir HCl or VGAN (Valcyte®)
Applicant: Roche Global Development
Formulation: Film-coated Tablets
Strength: 450 mg valganciclovir
Reviewer: Robert O. Kumi, Ph.D.
Team Leader: Kellie Reynolds, Pharm.D.
Draft Review Dates: 01/25/2001, 03/14/2001

Executive Summary

Ganciclovir (GAN) is a synthetic guanine derivative active against cytomegalovirus (CMV). CMV treatment requires induction and maintenance therapy. Intravenous GAN (Cytovene®-IV) is indicated for the treatment of CMV retinitis in immunocompromised patients and for the prevention of CMV disease in transplant patients at risk for CMV disease. Oral GAN (Cytovene®) capsules are indicated for prevention of CMV disease in patients with advanced HIV infection at risk for CMV disease, for maintenance treatment of CMV retinitis in immunocompromised patients, and for prevention of CMV disease in solid organ transplant recipients. Oral GAN administration provides adequate GAN serum levels, but the poor oral bioavailability (BA = 6- 9 % under fed conditions) of this formulation necessitates the use of high doses (3000 mg/day). Valganciclovir or ganciclovir valinate hydrochloride (VGAN), is a prodrug of GAN that is rapidly and extensively converted to GAN after oral administration. The absolute BA of GAN is approximately 60 % following oral VGAN administration. According to the applicant, increasing the BA of GAN may increase its efficacy and simplify dosing, while retaining GAN's safety profile. VGAN is being proposed for induction and maintenance treatment of CMV disease in AIDS patients.

Pharmacokinetic (PK), safety and efficacy (one pivotal study) studies with VGAN and an exposure response (PK/PD) analysis with GAN (maintenance therapy) were conducted in support of the VGAN application. In all PK studies, VGAN systemic exposure was low compared to GAN systemic exposure. Administration of the proposed 900 mg oral VGAN dose and the approved 5 mg/kg IV GAN dose in induction (twice-daily) and maintenance (once-daily) regimens produced comparable GAN AUC. On the other hand, GAN C_{max} following VGAN administration was 40 % lower than following IV GAN administration, but was 30-fold higher than the C_{max} produced by oral GAN administration. An exposure-response relationship for GAN during maintenance therapy could not be validated, because GAN pharmacokinetic measures could not be determined accurately. Consequently, comparisons between oral VGAN and GAN (IV and oral) plasma concentration-time profiles and PK measures were made to support VGAN use in maintenance therapy. The comparisons indicate that GAN plasma concentrations following VGAN administration are approximately bracketed by the GAN plasma concentrations following administration of approved GAN products. Thus, the comparison supports the use of VGAN during maintenance therapy.

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II. Major Questions/Issues

1. Has an adequate exposure-response relationship for GAN been developed? If so, what is its utility with respect to VGAN dose selection? *(Page 4)*

2. In the absence of an adequate exposure-response relationship, what additional evidence is available to support the use of VGAN? *(Page 5)*

3. Are VGAN dosing adjustments required for patients in special populations, particularly patients with impaired renal function? *(Page 11)*

III. Introduction and Background

CMV Retinitis

Human cytomegalovirus (CMV) is a herpes virus that is an important pathogen in immunocompromised patients, particularly patients with advanced HIV infection and organ transplant recipients receiving immunosuppressant agents. CMV retinitis (CMVR) is an ocular manifestation of systemic viral infection and appears as lesions in the retina that destroy retinal tissue, ultimately leading to a permanent loss of vision in the involved area. The goal of CMVR therapy is to prevent or delay progression into healthy retinal tissue. Treatment of CMV disease is divided into a 3-week induction phase followed by a maintenance phase of indefinite length. Presently available induction treatments for CMVR are IV ganciclovir, IV foscarnet, or IV cidofovir. Additionally, two local intraocular treatments are available, fomivirsen and a ganciclovir implant.

Successful induction is achieved when no further lesion enlargement (progression) is observed. However, if therapy is stopped and the patient is still immunocompromised, progression occurs. Induction may be repeated in a cyclic manner to stop the progression, but with each progression, additional retinal tissue is destroyed. Maintenance therapy may prevent or delay progression following a satisfactory response to induction treatment. The success of maintenance therapy is measured by the time from the start of therapy to the next progression of retinitis (time to progression). Time to progression may be assessed by retinal photography or by an ophthalmologist.

Dosing Regimens and Difficulties with Current GAN Treatments

Ganciclovir (GAN) is a synthetic guanine derivative that is active against CMV. During induction, intravenous GAN is given twice daily (BID) as a 5 mg/kg 1 hour infusion for 3 weeks. In the maintenance phase, GAN is given as an IV infusion 5 mg/kg once daily (QD), or orally as GAN 1000 mg capsules three-times daily (TID) or 500 mg six-times daily. Due to the low absolute BA of oral GAN (6-9 % in the fed state), a large oral GAN dose is required for effective maintenance treatment, and oral GAN can not be used for induction treatment. The highest strength of GAN capsules available is 500 mg; thus, patients have a relatively high pill burden.

Clinical Considerations in VGAN Development

The applicant developed valganciclovir (VGAN), an oral prodrug of GAN, with the following potential advantages over current GAN therapy in mind:

- orally administered therapeutic alternative to IV GAN for induction and maintenance treatment of CMV retinitis
- avoidance of morbidity associated with long term venous access required for IV GAN
- a simple oral regimen with reduced tablet count that could improve adherence to long term maintenance treatment

The VGAN development program relies heavily on the assumption that the activity of VGAN is due solely to the activity of its metabolite, GAN. Consequently, the applicant indicates that the VGAN

development program is abbreviated and builds on the extensive efficacy and safety experience with GAN. The major toxicities of GAN are granulocytopenia, neutropenia, anemia and thrombocytopenia.

Clinically, CMV induction therapy is considered a bigger therapeutic hurdle to overcome than maintenance therapy. Hence, the applicant hypothesizes that if VGAN induction efficacy is comparable to IV GAN, one can reasonably infer that VGAN will be efficacious during maintenance therapy. The applicant also indicates that the exposure-response relationship for GAN (Study2226) supports the use of VGAN for maintenance therapy.

Studies Reviewed
The clinical division reviewed controlled safety and efficacy data (Study 15376) for VGAN induction treatment. Bioavailability, bioequivalence, food effect and dissolution studies were submitted and reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The dissolution study results have been previously reviewed (Re: IND 48106 SN 089, June 1999). A pharmacometrics consult was obtained for Study 2226, which was submitted in support of the use of VGAN during the maintenance phase. The pharmacometrics review is included in the Appendix to this review.

IV. Physico-Chemical Characteristics for VGAN and Bioanalytical Methods

Physico-Chemical Characteristics

1. Chemical Name: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxyl]-3-hydroxypropyl ester, monohydrochloride
2. VGAN is a valine monoester prodrug of the active moiety GAN. *In vitro* VGAN is hydrolyzed ($t_{1/2}$ = 11 hr) to GAN and valine at neutral pH, but hydrolysis is slower at lower pH
3. Molecular Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$
4. VGAN Molecular Weight: 390.83 (free base 354.3); GAN Molecular Weight: 255.23
5. Stereochemistry- two diastereomers exist as a racemic, almost equal mixture of R and S stereoisomers in the **solid state** (52:48)
6. Interconversion (epimerization) of diastereomers in **solution**- process is fairly rapid at neutral pH, $t_{1/2}$ = 1 hr but is much slower at lower pH (at pH = 3.8 $t_{1/2} \approx$ 500 hr)
7. Absorption and epimerization of isomers ***in vivo***- rates of interconversion, and hydrolysis to GAN are the same for both isomers
8. Solubility at pH 6.8 = 68 mg/mL and solubility > 200 mg/mL at pH < 6
9. Appearance: white to off-white crystalline powder; two polymorphic forms, but only one form manufactured

Bioanalytical Methods

Validated bioanalytical methods for the analysis of VGAN and GAN from plasma were provided and considered acceptable. Plasma concentrations of GAN and VGAN were measured by [redacted] respectively. Features of the assays included:

- **For GAN**

Excitation λ = [redacted] Emission λ = [redacted]
Linear Range: [redacted]
Interassay precision: [redacted]
Interassay Accuracy: [redacted]
LLOQ: [redacted]
Specificity: [redacted]

APPEARS THIS WAY ON ORIGINAL

- **For VGAN**

UV λ = [redacted]
Linear Range: [redacted]
Precision: [redacted]
Accuracy: [redacted]
Specificity: [redacted]

V. Efficacy Study and its Pharmacokinetic Implications

Evaluation of Safety and Efficacy (Study 15376)

Induction efficacy of VGAN was evaluated in one controlled pivotal clinical efficacy study, WV 15376, in which oral VGAN and IV GAN were administered to HIV+ patients with CMV retinitis. The study was underpowered, but considered acceptable by DAVDP (see Medical Reviewer's review for details).

In the maintenance phase of Study 15376 all patients received VGAN, therefore a comparison to IV GAN can not be made. Due to the lack of a suitable control for VGAN during maintenance therapy, the applicant proposes that the use of VGAN in maintenance therapy can be supported by exposure-response analyses using oral GAN and IV GAN data obtained during maintenance therapy (Study 2226). Findings from the exposure-response analyses are presented in Section on Exposure-Response Relationship for GAN. The applicant indicates that the range of exposure ($AUC_{0\text{-}24\ hr}$) provided by IV ($AUC_{0\text{-}24\ hr}$ = 25 μg hr/mL) and oral GAN ($AUC_{0\text{-}24\ hr}$ ≈ 15 μg hr/mL) administration during maintenance therapy, represent the highest safe and minimum effective concentrations for GAN efficacy and tolerability, respectively.

VI. Review

Has an adequate exposure-response relationship for GAN been developed? If so, what is its utility with respect to VGAN dose selection?

Exposure-Response (PK/PD) Relationship for GAN

The applicant did not conduct exposure-response studies using VGAN; however, the applicant concluded that an exposure-response relationship existed between GAN AUC_{ssavg} (exposure or PK measure) and time to first photographic progression (response or PD measure) during GAN maintenance therapy. For this study, PK data were collected at weeks 2 and 6 from HIV+ patients with newly diagnosed CMV retinitis receiving oral GAN (1000, 1500 and 2000 mg TID) or IV GAN (5 mg/kg QD). PK samples were also collected when an adverse event or CMVR progression occurred. In addition, the time to first photographic progression (FPP) was determined.

According to the applicant's analyses, C_{min} had no significant correlation with the time to FPP; alternatively, C_{max} and AUC_{ssavg} both correlated with time to FPP. The applicant notes that when AUC and C_{max} were tested in the same model, C_{max} no longer correlated with time to FPP. Consequently, the applicant concluded that neither C_{max} nor C_{min} add any predictive value over AUC to the exposure-response relationship and can be omitted. The OCPB pharmacometrics reviewer, Dr. Sue-Chi Lee, could not validate the applicant's exposure-response analyses (see Appendix for Pharmacometrics review).

Dr. Lee concluded that the dosing time records were not sufficient enough to perform the population pharmacokinetic analysis needed for further exposure-response assessment. Specifically, the dosing time was recorded only for the one dose administered prior to blood sample collection. The scheme used in determining dosing times for the two doses before the recorded dose event appears to be clinically

reasonable; however, it relies heavily on assumptions that are not supported by any data. Since errors in dosing times will result in errors in PK parameter estimates, the exposure-response analysis is not acceptable. Another point of concern is that only one blood sample per dose was collected, with most patients having a total of two samples for analysis. Under this circumstance, the accuracy of individual PK parameter estimates obtained from the population PK analysis is unknown.

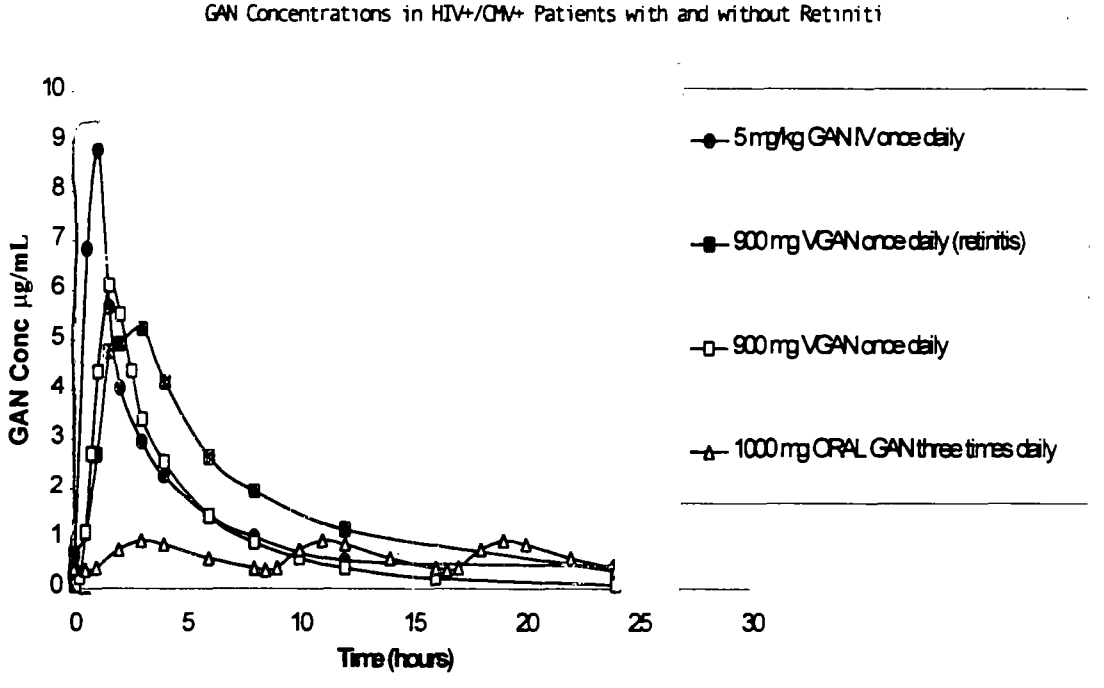
In the absence of an adequate exposure-response relationship, what additional evidence is available to support the use of VGAN during maintenance therapy?

Pharmacokinetic Profile Comparisons

Due to the concerns with the exposure-response analysis (see Exposure-Response Relationship for GAN), alternative methods were explored to support VGAN use during maintenance therapy. Ultimately, pharmacokinetic comparisons (VGAN vs. IV and oral GAN) were considered to be a more appropriate predictor of VGAN safety and efficacy in maintenance therapy than the submitted exposure-response analysis. Consequently, these pharmacokinetic comparisons were used during the review.

GAN concentration vs. time profiles obtained following administration of VGAN and the two approved GAN regimens, IV GAN and oral GAN, are presented in figure 1.

Figure 1: Delivery of GAN to HIV+/CMV+ Patients



Data Sources: Study WV15376 for HIV+/CMV+/Retinitis (IV ganciclovir and valganciclovir), Study WP15347 for HIV+/CMV+ (valganciclovir), and Study GANS2638 for HIV+/CMV+ (oral ganciclovir).

At the proposed maintenance dose of 900 mg VGAN once daily, GAN AUC was comparable to the AUC produced by the approved 5 mg/kg IV GAN dose ($AUC_{0-24} \approx 28$ µg hr/mL). The main difference in GAN exposure between VGAN and IV GAN is the higher C_{max} value following IV GAN. However, beginning one to two hours after dosing, GAN plasma concentrations following VGAN administration exceeded GAN concentrations following IV GAN administration. Although C_{max} following VGAN is lower than following IV GAN, it is much higher than the C_{max} observed following oral GAN. Empirically, it appears

that the C_{max} value may not contribute significantly to GAN efficacy during maintenance therapy, because the C_{max} of IV GAN (5 mg/kg once daily) is almost 10-fold higher than the C_{max} of oral GAN (1000 mg q 8 hr), yet oral GAN efficacy is acceptable. Thus, the above plasma concentration-time profile comparisons suggest that VGAN efficacy for CMV maintenance treatment should be comparable to the efficacy of the approved IV and oral GAN regimens. Using this line of reasoning, the exposure-response model is not needed to support VGAN use during maintenance therapy.

Theoretical Considerations

The applicant contends that the short duration of high (C_{max}) and low (C_{min}) GAN concentrations (peak to trough fluctuations) does not appear to have significant impact on GAN efficacy. This observation supports the theory that GAN is converted intracellulary to an active triphosphate form that has a longer intracellular $t_{1/2}$ than GAN plasma $t_{1/2}$. If GAN activity is driven by the formation of an active intracellular triphosphate, systemic exposure, expressed as AUC, would be a more important determinant of active triphosphate concentration than C_{max}. However, it must be noted that none of the above observations regarding the active intracellular triphosphate form have been confirmed experimentally. Consequently, the active triphosphate theory is not acceptable from a regulatory standpoint.

How was the VGAN Dose selected?

According to the applicant, the proposed exposure-response relationship served as a guide in determining VGAN dose selection. Target $AUC_{0\text{-}24\ hr}$ was ≈ 25 μg·hr/mL, because that was the AUC value obtained following IV administration (5 mg/kg) of GAN. Results from studies GAN 2661 and WV 15347 were used to select the VGAN dose.

Table II: Pharmacokinetic Data Used in Selecting VGAN Dose

Study #	Formulation and Dose	GAN $AUC_{0\text{-}24\ hr}$* in μg·hr/mL	Bioavailability
2661	Oral VGAN solution, 360 mg	10.8 ± 1.92	60.9
	IV GAN, 5 mg/kg	25.1 ± 3.8	NA
15347	Oral VGAN tablet, 875 mg	24.8 (15)	ND

NA- not applicable; ND- not determined, * values reported as mean ± SD or mean (% CV)

Are the VGAN clinical trial and proposed market formulations bioequivalent/equivalent?

Bioequivalence (BE) between the VGAN clinical trial and proposed market formulations could not be established in the pivotal BE study. However, the nature of the formulation differences between the clinical and proposed market formulations did not require that a bioequivalence study be conducted; thus, equivalence between the formulations was established on the basis of *in vitro* dissolution studies.

Bioequivalence

The *in vivo* bioequivalency study was conducted in HIV positive volunteers (Study No.: W-144111; Protocol WP 15509). Subjects received VGAN after a meal, which is contrary to the current regulatory recommendation that BE studies be conducted in the fasted state. Because the study was conducted in the fed state, it is possible that potential formulation differences may not have been adequately identified.

Table III: Geometric Mean Ratio (GMR, Market: Clinical) and 90 % Confidence Interval (CI) for GAN

Relative GAN Exposure Measure	GMR	90 % CI
$AUC_{0\text{-}24\ hr}$ (μg·hr/mL)	101	97 – 105
C_{max} (μg/mL)	114	101 - 128

The GMR and 90 % confidence intervals for AUC were within the required range to establish BE, but the C_{max} slightly exceeded the upper limit. The increase in C_{max} with the to-be-marketed formulation is unlikely to pose additional safety concerns, because GAN concentrations following IV administration are

almost two-fold higher than concentrations produced by VGAN and are tolerated in the target population. Thus, the study results do not preclude approval of the market formulation.
Prior to submission of the NDA, internal (within FDA) and external discussions (FDA and applicant) were held to discuss possible ways to establish equivalence between the formulations. Based on these discussions it was determined that *in vitro* dissolution data may be sufficient to demonstrate equivalence of the two formulations, without conducting an *in vivo* bioequivalence study in the fasted state.

Dissolution Studies
The nature of the changes (similar to level 2, SUPAC IR Solid Oral Dosage Form Guidance) in the VGAN formulation indicated that *in vitro* dissolution data comparing the two formulations in three media (12 tablets each) should be submitted. The two formulations can be declared equivalent because dissolution profiles for the two formulations in a given medium were similar:

- both formulations exhibit —% dissolution in — minutes
- differences in mean percent dissolved between the two formulations were — at all time points in all media,
- percentage of VGAN dissolved reached plateau within —minutes for both formulations.

Therefore, results from the dissolution study, coupled with the BE study in the fed state, were sufficient to establish equivalence between the clinical trial and proposed market formulations.

What are the Clinical Pharmacology and Pharmacokinetic Characteristics of VGAN and GAN?
The VGAN clinical pharmacology program enrolled healthy subjects and subjects from 5 different patient groups. PK data were obtained from all of the subject groups. Subsequent discussion of VGAN and GAN PK will encompass data from all of these groups, unless otherwise indicated.

Table IV: Study Populations- Number of Subjects Enrolled in VGAN Clinical Pharmacology Studies

	Healthy Volunteers	HIV +	HIV +/ CMV +	HIV +/CMV + retinitis	Renally Impaired	Liver Transplant Recipients
Study ID	WP 15511	WP 15509	GANS 2661 and WP 15511	WV 15376	WP 15511	WV 15711
Randomized	12	18	65	160	24	28
PK evaluable	12	18	58	51	23	28

Values for GAN and VGAN pharmacokinetic measures obtained in the efficacy study are presented in Table V as a point of reference for the subsequent PK discussion. Data in Table V are from HIV +, CMV retinitis patients, who tended to have higher GAN plasma concentrations than other populations (see GAN Pharmacokinetics in the Target Patient Population Compared to Other Populations, page 11)

Table V: Arithmetic Mean ± SD (CV %) VGAN and GAN PK Parameters at Week 4 during Efficacy trial

Pharmacokinetic Measure	900 mg VGAN Administered QD in Week 4	
	GAN	VGAN
T_{max} (hr)	2.49 ± 0.98 (39.4); n = 25	1.46 (43.8); n = 20
C_{max} (µg/mL)	5.87 ± 1.46 (24.9); n = 25	0.162 (42.5); n = 20
$AUC_{0\text{-}24\ hr}$ (µg hr/mL)	34.9 ± 13.3 (38.1); n = 25	0.347 (57.3); n = 20
$T_{1/2}$ (h)	4.12 ± 0.86 (20.9); n = 25	2.33 (91.5); n = 9

Absolute Bioavailability of GAN

- **Oral VGAN**

The absolute BA of GAN following oral VGAN administration was approximately 60 % in all populations studied. BA was assessed in subjects with different disease states, but normal renal function.

Each subject received single oral doses of 900 mg VGAN and 5 mg/kg IV GAN in a crossover fashion. Results from selected studies in which absolute BA was assessed are presented in Table VI.

Table VI: Absolute BA of GAN (fed state) when administered as VGAN CT Formulation

GMR	Population	Dose (mg)	F (%)	95 % CI
WP 15509	HIV +, CMV +	900	59	56 – 62
	HIV +, CMV +	900*	59	56 – 62
WP 15511	Healthy volunteers	900	59	54 – 64
	HIV +, CMV +	900	61	55 – 67
WV 15711	Liver Transplant Recipients	450	60	56 – 64
	Liver Transplant Recipients	900	59	55 – 63

* given as to-be-marketed formulation

What are the Absorption, Food Effect, Accumulation, and Dose Proportionality Characteristics of VGAN and GAN following VGAN Administration?

Absorption

VGAN

VGAN is well absorbed from the GI tract, and undergoes the following reaction in the GI tract

Oral VGAN ----------> GAN + valine
(intestinal and hepatic esterases)

The reaction is rapid and extensive, with VGAN AUC < 4 % relative to GAN AUC. For all studies and study populations, formulations and doses, VGAN T_{max} < 2 hours.

GAN

Following VGAN administration, GAN T_{max} occurred between 2 and 3 hours and GAN C_{max} was more than 30 times greater than VGAN C_{max}. The rate of appearance of GAN following oral VGAN administration was more rapid than following oral GAN administration. Approximately 60 % of the administered VGAN dose reaches the systemic circulation as GAN when corrected for the differences in molecular weight. The relatively high bioavailability (BA) and low systemic VGAN exposure indicate that VGAN is highly effective in delivering GAN to the systemic circulation.

Food Effect (Study WP15347)

A food effect was observed on GAN BA when different VGAN doses were administered to fasted and fed HIV +/CMV + subjects.

Table VII: Relative GAN Exposure Following Oral Administration of VGAN to fed and fasted individuals

Relative Exposure Measure	Dose (mg)	Point Estimate	95 % Confidence Interval
AUC_{24}	450	1.24	1.07 – 1.44
	875	1.30	1.12 – 1.51
(μg hr/mL)	1750	1.37	1.18 – 1.59
	2625	1.56	1.35 – 1.81
C_{max}	450	1.06	0.89 – 1.26
	875	1.14	0.95 – 1.36
(μg/mL)	1750	1.15	0.96 – 1.37
	2625	1.26	1.05 – 1.50

A statistically significant increase in GAN AUC (20 – 56 %) was observed following administration of a high fat meal (total calories = 569; fat 31.1 g) relative to the fasted state, but the increase in mean GAN C_{max} was statistically significant only at the highest studied dose. Median T_{max} and $t_{1/2}$ appeared to increase

with increasing dose, but no difference between the fasted state and fed state were observed with these pharmacokinetic measures. The study design employed by the applicant was not ideal because:

- A parallel study design was used in the comparison, which might not account for intraindividual variability
- Study drug was administered only one hour after a meal in the fasted treatment. This may not represent a true fasted state as food may still be present in the GI tract and affect drug absorption.

Because the drug will be administered in the fed state and was administered in the fed state in clinical trials, determination of the absolute magnitude of the food effect is not critical.

At the recommended dose, GAN AUC following oral GAN administration resulted in a 20 % increase in AUC, slight increase in C_{max}, and longer T_{max}. VGAN administration at the proposed dose resulted in a similar trend in food effect as with oral GAN (GAN AUC increased 30 %).

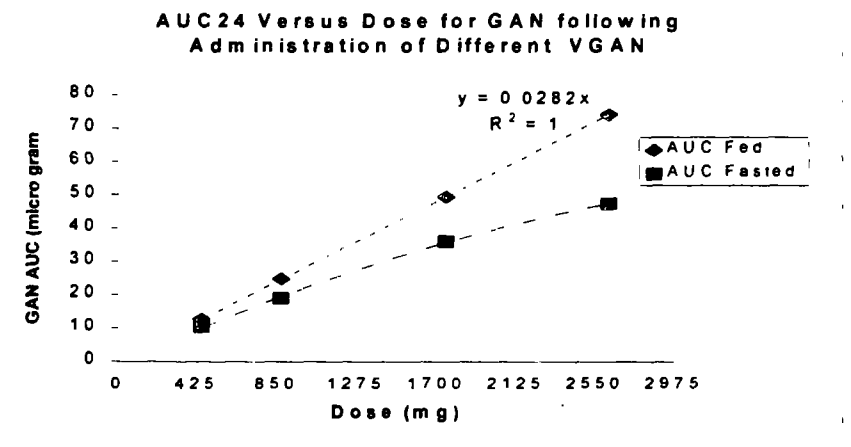
Accumulation

A multiple dose pharmacokinetics study (WP 15347) indicated that VGAN does not accumulate following once daily dosing over the dose range 450 – 2625 mg. VGAN levels could not be quantified beyond 6 hours, even at the highest dose levels. Accumulation is not expected for GAN following VGAN administration, based on the short GAN half-life (< 4 hr) and the proposed BID and QD dosing regimens.

Dose Proportionality of GAN and VGAN

Following multiple dose administration of oral VGAN, GAN PK were dose proportional in the fed state but non-dose proportional in the fasted state, as shown in Figure 2.

Figure 2: Dose Proportionality of GAN Following VGAN Administration



In the fed group, no significant deviation from dose proportionality was found ($p = 0.997$) whereas, in the fasted group, significant deviation from dose proportionality was observed ($p \leq 0.001$). Less than dose proportional increases in AUC and C_{max} were observed with increasing dose for the fasted group. Based on these study results, the applicant recommends that VGAN be given with food. Considering the results from this study, the applicant's proposal is acceptable.

What are the Distribution, Metabolism, and Elimination Characteristics of VGAN and GAN following VGAN Administration?

Distribution

No studies were conducted with VGAN to assess VGAN distribution. GAN volume of distribution at steady-state ($V_{ss} \approx 50$ L) following IV administration in the VGAN program were comparable to volume

Table IX: Mean ± SD GAN Pharmacokinetic Measures in Target Population during Efficacy Trial

	IV GAN		Oral VGAN	
	GAN (week 1)	GAN (week 4)	GAN (week 1)	GAN (week 4)
Pharmacokinetic Measure	N = 18	N = 18	N = 25	N = 25
$AUC_{0\text{-}12 \text{ or } 24}$* (μg hr/mL)	28.6 ± 9.02	30.7 ± 7.69	32.8 ± 10.1	34.9 ± 13.3
$AUC_{0\text{-}\infty}$ (μg hr/mL)	31.9 ± 10.7	31.3 ± 7.95	38.1 ± 13.1	35.9 ± 14.0
C_{max} (μg/mL)	10.4 ± 4.9	9.86 ± 3.14	6.71 ± 2.12	5.87 ± 1.46
C_{ss} (μg/mL)	2.4 ± 0.75	1.28 ± 0.32	2.74 ± 0.84	1.46 ± 0.56
T_{max} (hr)	0.89 ± 0.26	0.98 ± 0.21	2.31 ± 0.93	2.49 ± 0.98
$T_{1/2}$ (hr)	3.99 ± 0.85	4.32 ± 0.69	3.94 ± 1.10	4.12 ± 0.86

C_{ss} = $AUC_{0\text{-}12}$/Dosing Interval or C_{ssavg}; * $AUC_{0\text{-}12}$ for week 1, and $AUC_{0\text{-}24}$ for week 4

Analyses of the PK data indicated that VGAN systemic exposure was low in HIV+ patients with CMV retinitis, as was seen in other studies for different patient populations. Neither 4-week nor 1-week PK data were available for other study populations; therefore the comparisons with other populations are not direct comparisons (non-steady state data). However, numerically GAN AUC, and plasma concentrations (see figure 1, page 5) appeared to be higher in these patients compared to other patient populations. The reason for the apparently increased GAN exposure may be attributed to the apparently lower renal clearance in these subjects. The applicant indicates that the CL_R values obtained in the efficacy trial may not be accurate because the experimental conditions, such as accurate urine collection, were not as controlled as in other studies (see Tables VIII and X for comparisons).

Were any drug-drug interactions between VGAN and other drugs observed?

Drug-drug Interactions

No pharmacokinetic drug-drug interaction studies were submitted for the VGAN NDA. The applicant indicates that drug interactions observed with GAN are likely to occur with VGAN. This assumption is reasonable, because of the following two observations

- VGAN levels are low systemically and are unlikely to be affected by or affect other drugs
- VGAN produces only GAN; GAN produced by VGAN administration is present in a sufficiently large quantity to be involved in drug-drug interactions

Potential Transporter-based Drug-Drug Interactions

VGAN is a substrate for the human hpepT1 transporter with a K_m of approximately 4 mM in Caco-2 cells overexpressing the hpepT1 transporter. The K_m falls within the range of VGAN clinical concentrations in the gut ($C_{max,intestine}$ 10 mM) following administration of 900 mg VGAN; consequently, this transport system may partially contribute to the mechanism of absorption.

Are VGAN dosing adjustments required for patients in special populations, particularly patients with impaired renal function?

Meta Analyses

The applicant conducted meta analyses to determine which demographic factors may affect GAN PK following VGAN administration. Demographic factors studied included disease state, gender, age, and race. No definitive conclusions could be made from the analyses regarding age, gender and race, because patient numbers in each category were insufficient. However, the applicant's analyses indicated that AIDS patients with CMV retinitis and normal renal function (CL_{CR} > 70 mL/min) had approximately 30 % higher GAN AUC compared to HIV +/CMV+ patients. In this reviewer's analysis, the mean AUC values were approximately 25 % higher in CMVR patients than in HIV+/CMV+ patients, but the difference did not appear to be statistically significant.

Special Populations

Pediatric Development

VGAN has not been tested in pediatric patients.

Elderly

VGAN has not been studied in adults over the age of 65.

Renal Impairment

A decrease in GAN renal clearance and apparent oral CL was observed with decreasing renal function. VGAN and GAN PK were evaluated in healthy volunteers with normal renal function, HIV+/CMV patients with normal renal function, and otherwise healthy patients with varying renal function. Based on the study results a dosing algorithm for VGAN in patients with varying renal function was proposed by the applicant.

Pharmacokinetics of GAN in Renal Impairment Study

All subjects received a single 900 mg dose of oral VGAN. In addition, 8 out of 12 healthy subjects (Group 2) and 8 HIV+/CMV+ subjects (Group 1) received a single dose of 5 mg/kg IV GAN. PK results from groups 3-6 were compared to the PK of healthy individuals with normal renal function, excluding subjects who received IV GAN before oral VGAN.

Table X: Effect of Renal Impairment on Mean (% CV) GAN PK Measures following oral VGAN Administration (900 mg)

		Mean Ganciclovir Pharmacokinetic Parameters (% CV)					
Group	CL_{CR} (mL/min)	$AUC_{0-\infty}$ ^ (μg hr/mL)	C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	CL_{po} (mL/min)	CL_R
1	> 70	27.1 (13)	5.68 (19)	2.0	3.83 (13)	404 (13)	ND
2^G	> 70	27.8 (25)	5.56 (29)	2.0	3.46 (19)	413 (28)	209 (21)
3	51 – 70	50.5 (46)	6.88 (37)	2.0	4.85 (28)	249 (40)	145 (41)
4	21 – 50	99.7 (55)	7.08 (23)	3.0	10.2 (43)	136 (48)	67.1 (40)
5	11 – 20	252 (25)	8.54 (14)	3.0	21.8 (24)	45 (25)	21.4 (38)
6^D	< 10	407 (20)	10.5 (18)	6.0	67.5 (50)	12.8 (62)	nc

Where: Treatment A = 900 mg VGAN PO; Treatment B = 5 mg/kg IV GAN; * = median values

^ AUC_{0-x} was not more than 11 % greater than AUC_{last}

2^G – healthy subjects who received VGAN before IV GAN or received only VGAN

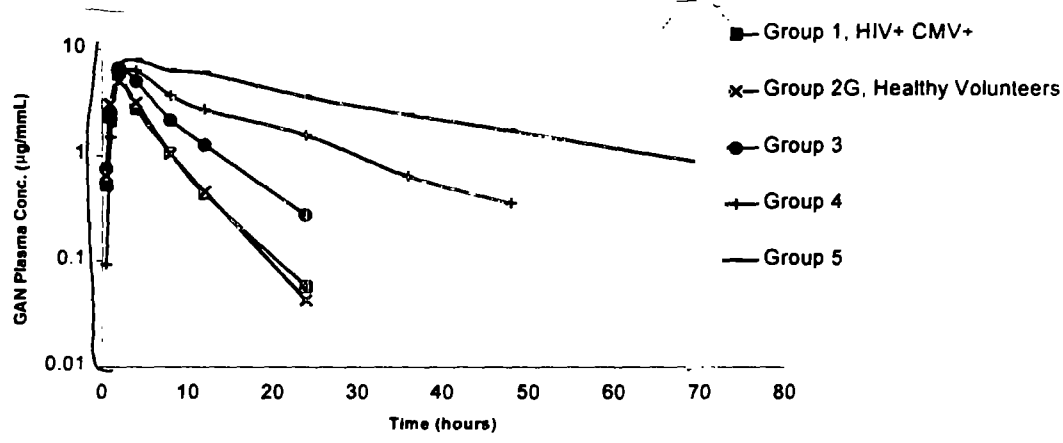
6^D- subjects received dialysis during VGAN dosing

Overall, renal impairment had no clinically significant effect on exposure to VGAN. VGAN PK parameters were comparable between healthy volunteers and HIV+/CMV+ patients. GAN PK parameters were also comparable between these two patient groups following administration of oral VGAN and IV GAN, respectively. The similarity in PK between these two patient groups was also reflected in their similar absolute GAN BA (healthy BA = 59 % and HIV+/CMV+ BA = 61 %).

Subjects with decreasing renal function (Groups 3-6), assessed by calculated creatinine CL, had longer GAN half-life and higher AUC than healthy volunteers. The higher AUC was attributed to the decreased renal CL in these study groups. C_{max} increases were not as profound as the AUC increases. Dialysis removed approximately 50 % of the GAN amount present at the onset of dialysis, as was observed in previous studies with GAN; however, this value was obtained from only 3 out of 6 patients and did not account for the rebound in plasma concentration at the end of dialysis. Consequently, interpretation of the dialysis results is not considered reliable. The sponsor indicates that VGAN will not be administered to patients requiring hemodialysis due to lack of an appropriate tablet strength. However, if VGAN will

ultimately be administered to these patients, an additional PK study will be required to provide more accurate GAN PK estimates in this patient population.

Figure 4: Mean GAN Plasma Disposition Following Administration of oral VGAN to patients with varying renal function



VGAN Dosing Algorithm in Patients with Impaired Renal Function, but Not Requiring Hemodialysis

The applicant proposed a dosing algorithm for VGAN based on the observed approximately linear relationship between CL_{CR} and CL_{po} of GAN, and predicted steady state AUCs for a given CL_{CR} after VGAN administration.

The relationship between CL_{CR} and GAN CL_{po} was based on data from groups 2- 5, which comprised healthy subjects receiving oral VGAN with varying degrees of renal function. The applicant's model is shown in equation 1

$$CL_{po} = 2.33 \times CL_{cr}^{1.13} \exp(\varepsilon),\ \varepsilon \sim N(0, 0.078) \qquad \text{equation 1}$$

Where, ε is the random deviation in CL_{CR} value and N is the number of subjects. CL_{po} is apparent renal clearance and CL_{CR} creatinine clearance This model was derived by using a logarithmic regression model, which is equivalent to a multiplicative model.

A simpler linear relationship, equation 2, without an error component was developed by this reviewer

$$CL_{po} = 4.58 \times CL_{CR} - 23.37 \qquad \text{equation 2}$$

However, the multiplicative model has a greater ability to predict apparent oral clearance from CL_{CR} than the linear model (see Individual Study Review for more details).

Using the multiplicative model, the applicant generated simulated data for GAN AUC_{ss}. Relevant selected sections of the simulated data are in the appendix to this review. In the clinical trial, the average GAN AUC achieved in the target population (CL_{CR} > 75 mL/min; mean $CL_{CR} \cong$ 130 mL/min) was ≈ 32 µg hr/mL following multiple dosing of IV GAN (5 mg/kg) or VGAN (900 mg) at week 4. The applicant indicated that the target $AUC_{0\text{-}24\ hr}$ was 26 µg hr/mL.

The proposed dosing algorithm (Table XI) is unacceptable for groups 1 and 2 because mean AUC values will exceed the mean target AUC by almost two fold.

Table XI: Applicants Proposed Oral VGAN Dose Modifications for patients with Impaired Renal Function

CL_{CR} (mL/min)	Daily AUC During Maintenance Dosing		Dose	
	Mean AUC * (μg hr/mL)	AUC Range* (μg hr/mL)	Induction	Maintenance
60 – group 1 100	46 26	41 – 52 22 - 31	900 mg BID	900 mg QD
40 – group 2 59	36 23	32 – 41 20 – 26	450 mg BID	450 mg QD
25 – group 3 39	31 18	27 – 36 16 – 20	450 mg QD	450 mg every 2 days
10 – group 4 24	50 18	39 – 63 15 - 20	450 mg every 2 days	450 mg twice weekly

* AUC was obtained by using mean 95 % CI values for CL_{po} (applicant's model) and back-calculating for AUC. The mean AUC and AUC range represent the AUC value and 95 % CI associated with the mean AUC for the CL_{CR} value

This reviewer proposes the following dosing algorithm.

Table XII: Oral VGAN Dose Modifications for patients with Impaired Renal Function

CL_{CR} (mL/min)	Daily AUC During Maintenance Dosing		Dose	
	Mean AUC * (μg hr/mL)	AUC Range* (μg hr/mL)	Induction	Maintenance
70 – group 1 100	39 26	34 – 44 22 - 31	900 mg BID	900 mg QD
50 – group 2 69	28 19	25 – 32 17 - 22	450 mg BID	450 mg QD
25 – group 3 49	31 15	27 - 36 13 – 16	450 mg QD	450 mg every 2 days
10 – group 4 24	50 18	39 – 63 15 - 20	450 mg every 2 days	450 mg twice weekly

* AUC was obtained by using mean 95 % CI values for CL_{po} and back-calculating for AUC. The mean AUC and AUC range represent the AUC value and 95 % CI associated with the mean AUC for the CL_{CR} value

The modifications proposed in this review will be more in line with the current recommendations for oral and IV GAN dosing in patients with impaired renal function and provide AUCs close to the target AUC.

Patients on Hemodialysis

The applicant recommends that patients on hemodialysis not take oral VGAN, but should take IV GAN in accordance with the labeled dose-reduction algorithm for Cytovene-IV®. This recommendation is based on the fact that administration of the available oral VGAN tablet, 450 mg strength, will result in unacceptably high exposures in these patients (exposure level 20 fold greater than in other patients given a similar dose). The applicant's recommendation is acceptable, but should be revised in the label to indicate that VGAN should not be administered in these patients.

Discussion: Applicability of Dosing Algorithm to other Patient Populations

The renal impairment study was conducted in subjects who had varied renal function, but were otherwise healthy (HIV seronegative and CMV seronegative). Because HIV+/CMV+ patients had comparable GAN PK to healthy volunteers with CL_{CR} > 70 mL/min it may be reasonable to assume that the same relationship between GAN PK in these two populations may hold true as renal function decreases. Therefore the proposed dosing algorithm may be applied to HIV+/CMV+ patients. However, extrapolation of this algorithm to other patient groups such as AIDS patients with CMV retinitis may not be straightforward because of the observed differences in CL_R of GAN in these two patient groups. In general, the GAN CL_R in these patients (HIV +, CMV retinitis) was lower than the GAN CL_R in other populations (e.g. HIV+/CMV+ and healthy subjects), who had similar (normal) renal function (CL_{CR} > 70

mL/min) measured by CL_{CR}. The effect of increased exposure (AUC) in these patients may pose a significant safety concern.

In general the mean AUC in HIV+ patients with CMV retinitis with normal renal function was approximately 25 % higher than those of other populations. If one assumes that the 25 % relative increase in GAN AUC will remain constant as renal function decreases, the dosing regimen proposed in this review is acceptable in this population. Currently, VGAN is available in only one strength, 450 mg tablet; therefore arriving at a suitable dose in these patients may be problematic if further dosage adjustments are required.

VGAN Formulations

The clinical trial and commercial formulations are similar except for minor changes in the amount of excipients and the addition of a film coat. The film coat was introduced in light of potential safety concerns for people coming into contact with VGAN tablets, because VGAN is a potent antiviral agent that may be teratogenic and carcinogenic.

Table IV: Commercial and Clinical Formulations for VGAN Film-Coated Tablets, 450 mg

Tablet Core Ingredients	Commercial Formulation		Clinical Formulation	
	Weight per tablet (mg)	% (w/w)	Weight per tablet (mg)	% (w/w)
Valganciclovir Hydrochloride				
Povidone K-30.				
Intragranular Crospovidone				
Extragranular Crospovidone				
Microcrystalline Cellulose				
Stearic Acid Powder				
Total Theoretical Weight				
Purified Water				
Coating Ingredients				
Opadry Pink YS				
Purified Water				

Dissolution

All clinical trial dosage formulations had similar *in vitro* dissolution characteristics. The proposed dissolution methodology is acceptable.

Apparatus: USP Apparatus 2 at 50 rpm
Medium: 900 mL 0.1 N HCl, pH =1 at 37°C
Assay:
Specifications: Q = in 30 minutes

APPEARS THIS WAY
ON ORIGINAL

Recommendations

Data submitted to the Human pharmacokinetics and Biopharmaceutics Section of NDA 21-304 for valganciclovir satisfy the requirements for the Office of Clinical Pharmacology and Biopharmaceutics

The dissolution data indicate that the 450 mg valganciclovir capsules manufactured at Patheon are similar to those manufactured at ——— consequently, *in vivo* bioavailability studies are not required for capsules manufactured at Patheon.

Labeling

In general, the applicant's proposed label is acceptable. ———

Proposed Phase IV Commitment or Traditional Approval Requirement

Evaluation of the effect of gender and race on ganciclovir pharmacokinetics following valganciclovir administration.

/S/

Robert O. Kumi, Ph.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III

Concurrence: /S/

Kellie Schoolar Reynolds, Pharm.D.
Pharmacokinetics Team Leader
Antiviral Drug Products Section

cc:

HFD-530	/NDA ———
	/MO/Toerner
	/PM/Stephens
HFD-880	/Kumi, R.
	/TL/Reynolds
HFD-340	/Viswanathan

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: March 21, 2001

TO: NDA 21-304

FROM: Leslie Stephens

SUBJECT: **Pediatric Indication**
NDA 21-304, Valcyte (valganciclovir) tablets

The sponsor's proposed indication for this drug is the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. At this time, there is an insufficient number of pediatric AIDS patients with CMV retinitis to perform an adequate study to establish safety and efficacy in the pediatric population.

/S/

Leslie Stephens, RN, MSN,
Regulatory Project Manager, HFD-530

/S/

Joseph Toerner, MD
Medical Reviewer, HFD-530

APPEARS THIS WAY
ON ORIGINAL

Group Leader Memorandum

NDA:	**21-304**
Drug:	**valganciclovir (Valcyte™) 450 mg. Capsules**
Indication:	**Treatment of CMV retinitis in AIDS patients**
Dose:	**Induction therapy 900 mg BID** **Maintenance therapy 900mg QD**
Application:	**Syntex LLC**
Submission received:	**September 29, 2000**
Date of memorandum:	**March 23, 2001**

In this NDA submission the applicant requests approval of valganciclovir, a valine ester of ganciclovir that provides improved bioavailability compared to oral ganciclovir. Ganciclovir is a synthetic guanosine nucleoside analogue, available as intravenous and oral formulations that is approved for the prophylaxis, induction, and maintenance therapy of CMV disease. Most therapy for CMV infections require long-term administration, which magnifies the limitations of the currently available formulations of ganciclovir (the need for long-term IV access when using the IV formulation, and the very limited bioavailability of the oral formulation). Valganciclovir provides serum levels of ganciclovir that are similar to those achieved with IV ganciclovir, with the exception of a lower Cmax. The pharmacokinetic parameters that correlate with clinical efficacy are not known. Therefore, clinical data were required to support the applicant's contention that that the lower Cmax achieved with valganciclovir dosing would not negatively impact efficacy.

In support of this request for approval of valganciclovir for the treatment of CMV retinitis in AIDS patients, the applicant has submitted the results of a single, active-controlled, equivalence designed, phase 3 study of the efficacy and safety of oral valganciclovir vs. IV ganciclovir for the induction therapy of newly diagnosed CMV retinitis in patients with AIDS. Safety data from two open-label, single arm studies of patients treated with valganciclovir as maintenance therapy of CMV retinitis, along with pharmacokinetic data supportive of maintenance treatment was also provided.

Study WV 15376 was conducted in 160 AIDS patients with newly diagnosed CMV retinitis. The impact of changing antiretroviral therapy (as is recommended with development of a new AIDS-defining disease) was minimized by the

for HIV infection have resulted in decreased incidence of CMV in AIDS patients. Active-controlled trials require much larger numbers of subjects than the placebo-controlled studies that supported older applications. Use of the four week endpoint to evaluate the efficacy of induction therapy is controversial, but at this time it appears to be the only viable option for evaluation of efficacy. The optimal time to evaluate the efficacy of induction therapy is not known, and studies that would seek to define this would present similar challenges to those outlined here. Furthermore, because most patients who develop retinitis cannot be expected to delay a change in their antiretroviral therapy much beyond four weeks, studies of maintenance therapy will need to demonstrate efficacy over and above that associated with the improvement of immunologic parameters that may occur with potent antiretroviral regimens.

2. Need for a patient package insert

Approval of valganciclovir will introduce a product to the market that has the potential for overdose of ganciclovir should precautions against substituting valganciclovir for oral ganciclovir not be heeded. Ganciclovir is dialyzable and therapy for granulocytopenia and anemia are available, thereby somewhat diminishing the potential for severe outcomes should overdose occur. However, because we believed that this was information important for the patient to have we requested that the applicant submit their proposal for wording of a PPI; we also sought advice from OPDRA on the applicability of the Medication Guide regulations to this product. Evaluation of a patient package insert (PPI) for valganciclovir was undertaken only during the last month of the review. An agreed-upon PPI for valganciclovir will be approved along with the application.

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3. Implications of wording in approved valganciclovir label for the current valganciclovir label.

Much of the wording for the valganciclovir label was derived from the existing ganciclovir label. Based upon current approaches to labeling, much of this wording was either deleted or revised in the valganciclovir label. It will therefore, be necessary to revise the ganciclovir label so that there will not be inconsistancies in the ganciclovir label with the wording approved in the valganciclovir label. The applicant is aware that approval of valganciclovir will necessitate revisions to the ganciclovir label.

4. Studies in other populations.

It would be useful to have more information on the use of valganciclovir in other populations. At this time, the applicant has a large phase 3 study in transplant patients ongoing. These results will be submitted in an efficacy supplement in the fourth quarter of 2002. Because of the difficulty in conducting studies, it is unlikely that efficacy data will be available in the following groups: those with sight-threatening CMV retinitis, patients requiring retreatment (induction therapy), those receiving maintenance therapy of retinitis, other immunocompromised patients with retinitis, pediatric patients with retinitis, and infants with neonatal CMV infection. Because there are so few pediatric patients who develop CMV retinitis, the requirement for a pediatric assessment under the 1998 Pediatric Rule was waived.

[redacted]

/S/

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