MEMORANDUM

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

DATE: March 7, 2001

FROM: Antoine El-Hage, Ph.D., Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations

SUBJECT: Clinical Inspection Summary - **NDA 21-304**

TO: Leslie Stephens, PM
Joseph Toerner, M.D.
Division of Antiviral Drug Products (HFD-530)

APPLICANT: Syntex US, LLC

DRUG: ——— (valganciclovir HCl tablets)

CHEMICAL CLASSIFICATION: 2

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of Cytomegalovirus (CMV) Retinitis in patients with AIDS

CONSULTATION DATE: October 6, 2000

DIVISION ACTION GOAL DATE: March 22, 2001

ACTION GOAL DATE: March 29, 2001

I. BACKGROUND

Human cytomegalovirus (CMV) is a herpes virus recognized as a pathogen in individuals with AIDS and in organ transplant recipients. In immunocompromised patients, CMV retinitis is an ocular manifestation of systemic CMV infection.

Valganciclovir is a valyl ester prodrug of ganciclovir which is rapidly converted to ganciclovir, and provides ganciclovir systemic exposures comparable to I.V. ganciclovir which is currently approved for this indication. Despite the benefits of standard treatment regimens, intravenous treatment is time-consuming, expensive, inconvenient and associated with catheter-related morbidity. The development of valganciclovir was targeted to address the unmet medical need

for a simple oral regimen which could be used for both induction and maintenance treatment of CMV retinitis.

The two sites selected for inspection were essential to approval, had high enrollment, and covered protocol WV15376.

II. RESULTS

		City	State	IN	Assigned	Action	Reviewer	Class
*	Martin	Atlanta	GA	DA	17-Oct-00	PEND	AEH	NAI
	Wolitz	San Francisco	CA	DA	17-Oct-00	01-Mar-01	AEH	VAI

A. **Dr. Wolitz**:

This site screened 12 subjects; enrolled 10; and 6 subjects' records were reviewed. Informed consent for all subjects were reviewed and found them adequately documented. Deficiencies were noted which included protocol deviations in that screening tests for one subject were performed prior to signing the informed consent and another subject was enrolled in another investigational study while in protocol WV15376. The doctor acknowledged the oversight and promised corrections in the future. Data appear acceptable from this site.

B. **Dr. Martin**:

* The summary for Dr. Martin's site is based solely on email communication with the field inspector. No Form FDA 483 was issued. Should the EIR contain information that would change the acceptability of the data, we will inform you.

This site enrolled 18 subjects; 9 subjects received the IV ganciclovir treatment and 9 subjects received the valganciclovir treatment during the 4-week study phase. All 18 subjects completed the 4-week study phase and entered the extension phase. All 18 subjects received the valganciclovir treatment during the extension phase of the study. Only two subjects were active on the extension phase of the study at the time of the inspection. 11 subjects discontinued due to disease progression of end stage AIDS/Death. One subject discontinued due to immune recovery reasons. One subject was considered treatment failure, one subject was incarcerated and subsequently discontinued and two subjects were lost followup.

All subjects' charts were reviewed to verify 100% informed consent compliance. There was a complete audit of five subjects' records and the only item discussed was the inability to determine who completed different portions of the source document/case report form.

At the time of the inspection, 8 subjects had expired; 2 subjects expired approximately 2 months after study discontinuation; the other 6 subjects received study medication until their deaths. All SAEs were reported appropriately. Data appear acceptable from this site.

Limitation of the inspections – none

No follow-up actions are planned.

III. OVERALL ASSESSMENT OF FINDINGS/GENERAL RECOMMENDATIONS

The two requested inspections have been completed. No objectionable conditions were found which would preclude use of the data submitted in support of the pending application

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47

cc:
NDA #21-036
HFD-45
HFD-47/KMS
HFD-47/AEH
HFD-47/rf/cf
HFD-45/rf

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

PM

Richard A. Wolitz, M.D.
Kaiser Permanente Medical Center
1635 Divisadero Street, Suite 360
San Francisco, California 94115-3000

MAR - 1 2001

Dear Dr. Wolitz:

Between January 24 and February 9, 2001, Dr. Gerald N. McGirl, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol #WV15376) of the investigational drug, ——— valganciclovir) tablets, performed for Syntex LLC. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find some departures from federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Dr. McGirl presented and discussed with you the items listed on the Form FDA 483. The discussion included the performance of screening assessments prior to signing the informed consent for one subject, and the simultaneous enrollment of one subject into two clinical trials.

We note your agreement to the findings, and accept your explanations and intent as stated in your letter dated February 13, 2001. This letter has been made part of your official file.

We appreciate the cooperation shown Investigator McGirl during the inspection. Should you have questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place

CFN: [redacted] FEI: 3003234081
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__x__2)VAI-response received
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
__x__inadequate informed consent
_____inadequate drug accountability
__x__failure to adhere to protocol
_____inadequate records
_____failure to report ADRS _____
_____other

cc:
HFA-224
HFD-530 Review Div. Dir.
HFD-530 MO
HFD-530 PM
HFD-530 Doc. Rm. NDA #21-034
HFD- 45 r/f
HFD- 47 c/r/s GCP file#10291
HFD- 47 (AEH/KMS)
HFR-PA150 DIB (Moss)
HFR-PA150 BIMO/Investigator(McGirl)

APPEARS THIS WAY
ON ORIGINAL

r/d:**(AEH):(2/16/01)**
reviewed:AEH:**(2/22/01)**
f/t:mrb:**(2/26/01)**
O:\AEH\[redacted].doc

Reviewer's Note to Rev. Div. M.O.

This site screened 12 subjects; enrolled 10; and reviewed 6 subjects' records. Informed consent for all subjects were reviewed and found them adequately documented. Deficiencies were noted which included protocol deviations in that screening tests for one subject were performed prior to signing the informed consent and another subject was enrolled in another investigational study while in protocol WV15376. The doctor acknowledged the oversight and promised corrections in the future.

The data from this site are acceptable.

NDA 21-304

Syntex (U.S.A.) LLC
Attention: Hermine Mante, Pharm.D.
Senior Regulatory Program Manager
3401 Hillview Avenue
Palo Alto, CA 94304

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Mante:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ——(valganciclovir) tablet

Review Priority Classification: Priority (P)

Date of Application: September 28, 2000

Date of Receipt: September 29, 2000

Our Reference Number: NDA 21-304

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 29, 2001.

We have determined that this application will be reviewed under 21 CFR 314 Subpart H (accelerated approval). We remind you that as required under 21 CFR 314.550, unless otherwise informed by the Agency, you must submit for Agency review before approval of this application copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days after marketing approval.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

APPEARS THIS WAY
ON ORIGINAL

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products,
HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Leslie Stephens, RN, MSN, at 301-827-2335.

Sincerely,

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Antiviral Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Antiviral Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA regulatory issues.

Date and Time: The meeting will be held on February 27, 2001, 9 a.m. to 5:30 p.m.

Location: Holiday Inn, The Ballrooms, 2 Montgomery Avenue, Gaithersburg, MD.

Contact Person: Tara P. Turner, Pharm.D., Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane (for express delivery 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301-827-7001, e-mail: TurnerT@cder.fda.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12531. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss new drug application (NDA) 21-304, valganciclovir hydrochloride tablets, 450mg, Syntex (U.S.A.) LLC, proposed for treatment of cytomegalovirus

(CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by February 20, 2001. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before February 20, 2001, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated 1-8-01

/S/

Tara P. Turner, Pharm.D.
Executive Secretary

APPEARS THIS WAY
ON ORIGINAL

Stephens, Leslie

From: Sammie Beam 301-827-3161 FAX 301-480-8173 [BEAMS@cder.fda.gov]
Sent: Tuesday, March 27, 2001 3:47 PM
To: stephensl
Subject: [redacted] to Valcyte

Sensitivity: Confidential

Hi,

I just presented the name to our Panel Discussion group this afternoon to see if there would be any additional names that might be a potential for confusion with the different spelling and pronunciation.
The panel did NOT find any additional names that might present potential problems for confusion.
Hope this helps.

Thanks,
Sammie Beam

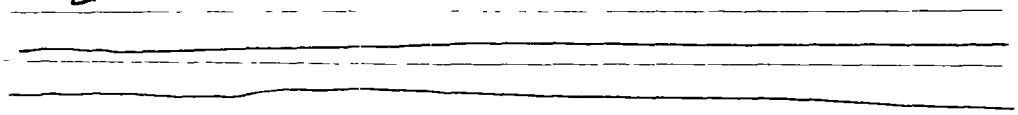
APPEARS THIS WAY
ON ORIGINAL

dispensing of either Valcyte or Valtrex in patients with Acquired Immune Deficiency Syndrome.

We would also like to provide feedback to your Office on issues related to the container labels. The following comments have been sent to the applicant as part of the CMC recommendations:

1. We recommend that the bottle label be revised to read:

2.



3. Please indicate if any physicians' samples are planned, and if so, please submit copies of the container label(s).

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 7/20/2000	DUE DATE: 1/05/2001	OPDRA CONSULT #: 00-0204

TO: Heidi M. Jolson, M.D.
Director, Division of Anti-Viral Drug Products
HFD-530

Received 12/21/00

THROUGH: Leslie Stephens
Project Manager
HFD-530

PRODUCT NAME:	MANUFACTURER: Patheon Inc.
[redacted] (Primary) - and [redacted] Alternate) (valganciclovir 450mg capsules) NDA #: 21-304	DISTRIBUTOR: Roche Laboratories Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), OPDRA conducted a review of the proposed proprietary names [redacted] and [redacted] to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary names [redacted] or [redacted]

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the Name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Antiviral Drugs Advisory Committee

February 27, 2001

Revised Questions to the Committee

1. Do the data submitted in this NDA support the efficacy of valganciclovir for induction therapy of CMV retinitis? If the answer to this question is yes, in your discussion please consider the limited sample size in a study with an equivalence design and the clinical significance of the lower bound of the 95% Confidence Interval of –13%. If the answer to this question is no, in addition to the above considerations please comment on what further clinical data should be required.

2. Do the data submitted in this NDA support the use of valganciclovir for the maintenance therapy of CMV retinitis? If the answer to this question is no, please comment on what further clinical data should be required.

3. Do the data submitted in this NDA support the safety of valganciclovir for the treatment of CMV retinitis? If the answer to this question is no, please comment on additional safety studies that should be required.

4. If the answers to the above questions are yes, are there additional clinical trials that you would recommend the applicant conduct as phase IV studies?

Antiviral Drugs Advisory Committee
February 27, 2001

The following is an internal report which has not been reviewed by the Agency or the Antiviral Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. A verbatim transcript will be available in about 3 weeks and will be sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/acmenu.htm
All external requests should be submitted to the Freedom of Information office.

The Antiviral Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 27, 2001 at the Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland. There were approximately 150 people in attendance. The meeting was chaired by Roger J. Pomerantz, M.D.

The Committee discussed NDA 21-304, valganciclovir hydrochloride tablets, 450mg, Syntex (USA) LLC, proposed for treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). The Committee had received a briefing document from both Syntex (USA) LLC and the FDA Division of Antiviral Drug Products.

The meeting was called to order at 9:00am by Roger J. Pomerantz, M.D., Acting Chair. The Committee members, consultants, guests, and FDA participants introduced themselves. The Conflict of Interest Statement was read by Tara P. Turner, Pharm.D., Executive Secretary of the Antiviral Drugs Advisory Committee.

Opening remarks were given by Debra Birnkrant, M.D., Acting Director, Division of Antiviral Drug Products. The regulatory background of current CMV treatment options was presented by William Boyd, M.D., Medical Officer, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products.

Syntex (USA) LLC made the following presentation:

Introduction: Mary Jean Stempien, M.D., M.S.
Clinical Background: Daniel F. Martin, M.D.
Development Program & Study Results: Mary Jean Stempien, M.D., M.S.

The FDA presentation consisted of:

Medical: Joseph Toerner, M.D.
Pharmacokinetics: Robert Kumi, Ph.D.

The only speaker for the Open Public Hearing was Michael Marco of Treatment Action Group (TAG).

The Committee was asked to address a revised list of questions, different from the list that was distributed as part of the agenda packet.

Revised Questions to the Committee

1. Do the data submitted in this NDA support the efficacy of valganciclovir for induction therapy of CMV retinitis? If the answer to this question is yes, in your discussion please consider the limited sample size in a study with an equivalence design and the clinical significance of the lower bound of the 95% Confidence Interval of –13%. If the answer to this question is no, in addition to the above considerations please comment on what further clinical data should be required.

   YES- 12 NO- 1

The majority of the Committee agreed that the 4 week study results clearly support efficacy for induction therapy. One member questioned the appropriateness of the premises on which the studies were based.

2. *(Reworded)* Do the data submitted in this NDA support the *use* of valganciclovir for the maintenance therapy of CMV retinitis? If the answer to this question is no, please comment on what further clinical data should be required.

   YES- 13 NO- 0

The Committee agreed that direct comparative data are needed to support efficacy for maintenance therapy. No such data are available. Therefore, "use" was substituted for "efficacy".

3. Do the data submitted in this NDA support the safety of valganciclovir for the treatment of CMV retinitis? If the answer to this question is no, please comment on additional safety studies that should be required.

   YES- 11 NO- 0 ABSTAIN- 2

4. If the answers to the above questions are yes, are there additional clinical trials that you would recommend the applicant conduct as phase IV studies?

The Committee had the following recommendations for further study: longer follow-up for the purpose of evaluating safety and toxicity; population pharmacokinetic/pharmacodynamic studies (including investigations of age and sex differences); studies of drug interactions; studies to determine optimal dose and frequency of administration; study the use of valganciclovir in the setting of immune recovery; define the standard of care for CMV retinitis and then conduct studies to directly compare valganciclovir to that standard.

The meeting adjourned at 3:15 pm.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21304/000**
Stamp: **29-SEP-2000** Regulatory Due: **29-MAR-2001**
Applicant: **SYNTEX (USA) LLC**
3401 HILLVIEW AVE
PALO ALTO, CA 94304

Priority: **P** Org Code: **530**
Action Goal: District Goal: **30-MAY-2001**
Brand Name: **VALCYT(VALGANCICLOVIR HYDROCHLORIDE)450M**
Established Name:
Generic Name: **VALGANCICLOVIR HYDROCHLORIDE**
Dosage Form: **TAB (TABLET)**
Strength: **450 MG**

FDA Contacts:			
	L. STEPHENS	**(HFD-530)**	**301-827-2335 , Project Manager**
	Z. GU	**(HFD-530)**	**301-827-2391 , Review Chemist**
	S. MILLER	**(HFD-530)**	**301-827-2392 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 29-MAR-2001 by P. ALCOCK (HFD-324) 301-827-0062

Establishment:
DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities:

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

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF TELECON

Date: **July 7, 1999**

IND: **48,106**

Drug: **Valganciclovir Hydrochloride**

APPEARS THIS WAY
ON ORIGINAL

Sponsor: **Roche Global Development**

BETWEEN: **Representatives of Roche**
Stella Andrews, Global Regulatory Leader
Francis Brown, Ph.D., Clinical Pharmacologist
William Buhles, D.V.M., Ph.D., Clinical Scientist
Zoe Conway, M.D., Clinical Team Leader
Nick Coppard, Ph.D., Global Project Leader
Hermine Mante, Pharm.D., US Regulatory Program Manager
Charles Robinson, M.D., clinical Science Leader
Rebecca Sudlow, M.S., Project Statistician

AND: **Representatives of DAVDP**
Heidi Jolson, M.D., M.P.H., Division Director
Therese Cvetkovich, M.D., Medical Team Leader
John Martin, M.D., Medical Reviewer
Mike Elashoff, Ph.D., Statistical Reviewer
Girish Aras, Ph.D., Statistical Reviewer
Andrei Breazna, Ph.D., Statistical Reviewer
Prabhu Rajagopalan, Ph.D., Acting Biopharmaceutical Team Leader
Robert Kumi, Ph.D., Biopharmaceutical Reviewer
Leslie Stevens, RN, MS, Regulatory Management Officer
Christine Kelly, RN, MS, MBA, Project Manager

SUBJECT: Submission number 087, NDA for a CMV indication

Background: This telecon was requested by the Roche to discuss the sponsor's outline for filing an NDA in December 1999 for a CMV indication (IND 48,106 sn. 087, 4/19/99). In addition, the sponsor faxed in a copy of what they will be submitting as sn. 094, which contained additional information for the NDA submission, and well as three questions for discussion with the review team. Please see below.

Discussion: Sponsor's questions are in bold. DAVDP responses follow them.

1. **In principle, is the CMV retinitis application as described in the April 16, 1999 background package acceptable as a stand-alone submission? (Please note: this question is in addition to the 2 questions below from the original April 16, 1999 submission).**

   There are several important concerns in our consideration of your question:

   - We understand that you intend to submit a single clinical efficacy study on induction therapy of CMV retinitis, as well as non-comparative safety data
   - As we discussed previously, we understand that this study is likely to be under-powered to demonstrate equivalence of valganciclovir to the IV formulation
   - Valganciclovir is considered as an new molecular entity
   - On the other hand, there is a need for an oral alternative to the IV formulation for treatment of CMV retinitis.

Although we do not make decisions about filing applications until we receive them, it is likely that we would file your CMV retinitis application despite its limitations.

Whether the application is sufficiently persuasive regarding the efficacy and safety of valganciclovir would then be a focus of the review. It is likely that this application would be presented to the advisory committee.

[redacted]

2. In light of the information supplied in the April 16, 1999 submission, are there further concerns for discussion with the Division, that the current development program is acceptable to support an indication for the treatment of CMV retinitis in immunocompromised patients?

See question number three.

3. Is the proposed safety database at time of filing (December 1999) acceptable?

The anticipated safety database at the time of filing (183-244 patients with at least 6 months exposure to valganciclovir) is marginal. This could be strengthened by providing safety information from an ongoing study in transplant recipients both at the time of filing and at the time of a safety update.

Action/Conclusions:

1. It was suggested to the sponsor that if they wish to consider an application under the accelerated approval regulations, they submit a letter to DAVDP requesting accelerated approval for a CMV indication. This should include rationale explaining the clinical benefit for CMV disease.

2. The sponsor will request a pre-NDA meeting with the Division in a few months when the data is available from the studies that will be included in the application.

3. It was suggested to the sponsor that they submit available safety information from the transplant study as a study update during the NDA review for the CMV indication.

Concurrence:
HFD-530/MTL/Cvetkovich
HFD-530/MO/Martin 7/13/99

cc:
Original IND 48,106
Division File
HFD-530/Martin

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and drug Administration
Rockville MD 20857

Memorandum of 45 day Filing Meeting

Date: November 1, 2000

Drug: valganciclovir tablets

NDA: 21-304

Sponsor: Roche Global Development

FDA Participants: Heidi Jolson, Debra Birnkrant, Therese Cvetkovich, Walla Dempsey, Kellie Reynolds, Tony DeCicco, Jim Farrelly, Joseph Toerner, Rebecca Sheets, Stephen Miller, Zi Qiang Gu, Robert Kumi, Kendall Marcus, Leslie Stephens, Karen Young, Sean Byrd

Background: The purpose of this meeting is to discuss filability of NDA 21-304, valganciclovir tablets for the treatment of CMV retinitis in immunocompromised patients. This application has been given a Priority review with a 6-month review date. **PDUFA date is March 29, 2001**. The Division has previously discussed whether this study could support an approval utilizing subpart H (accelerated approval regulations) with the study on [redacted] Notably, this NDA was not submitted under the subpart H regulations.

Discussions:

1. **Pharmacology/Toxicology**: Dr. Farrelly concluded that the NDA is **filable**. There were no pharmacotoxicologic issues.

2. **Microbiology**: Dr. Sheets concluded that the NDA is **filable**. The NDA contains PCR data obtained with an unapproved assay but which contributes little to the analysis of the efficacy data. Assay validation may be needed when the solid organ transplant study is submitted.

3. **Clinical Pharmacology/Biopharmaceutics:** Dr. Kumi determined that this NDA is **filable.** The PK/PD data will provide important information. There will be a Pharmacometrics consultation for this review.

4. **Chemistry:** Dr. Gu concluded that the NDA is **filable**. The manufacturing site inspection is scheduled for September 29, 2000. There is 18-month stability data and the company is requesting a [redacted] month expiry date.

5. **Statistical:** Dr. Breazna concluded that the NDA is **filable**. This NDA has one principal trial, which is underpowered. There are sufficient safety data from the open-label and expanded access portions of the trial. There is concern about whether patients had any changes in their HIV regime during the 4-week induction phase.

6. **Clinical:** Dr. Toerner concluded that the NDA is **filable**. He will need to see HIV RNA baseline data with date of specimen as well as information on any changes in HIV treatment during the trial. He also stated that it would be helpful to see CD4 data with date of specimen during the 4-week induction period.

7. **DSI**: Consult request sent to Dr. El Hage on October 11, 2000.

8. **OPDRA:** A request for review of the tradename [redacted] was submitted to OPDRA on July 17, 2000. As of October 31, 2000, their review was not completed.

9. **Advisory Committee:** The AC date is pending but will be in late February 2001. The due date for the sponsors backgrounder is 60 days prior to the AC if redaction is required. The Division's backgrounder has to be completed and submitted to the FOI office by the end of January 01. It was decided that the Advisory Committee should consist of the DAVDP committee, the ophthalmologic subcommittee, and others with expertise in CMV retinitis and in pharmacology.

10. **Pediatric exclusivity:** The Written Request has been reviewed by the PDIT committee and is being presented to the GC due to issues regarding addressing requests for ganciclovir and valganciclovir in one written request.

Conclusion:
The review team concluded that NDA 21-304 is filable. The sponsor will be notified of our decision to file this NDA.

Action Items:

The following requests will be communicated to the sponsor:

1. Please submit HIV RNA data with dates of specimen.
2. Please submit CD4 counts with dates of specimen collection if available
3. Please indicate what HIV medications patients were taking during the 4-week induction phase.

23 Pages have been redacted in full from this document

Reason:

_____ b(2) 'low'
__✓__ b(4) CCI
__✓__ b(4) TS
_____ b(5) Deliberative Process: Attorney Client and Attorney Work Product Privilege
_____ b(6) Personal Privacy
_____ b(7) Law Enforcement Records

B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 8, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: Robert Kumi, Ph.D., Clinical Pharmacokinetics Reviewer, DAVDP
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-304

Subject: Biopharmaceutical comments

The following comments are being conveyed on behalf of Dr. Kumi with regard to NDA 21-304, Report W-144128, Protocol WP 15511, volume 43.

Title: The effect of renal impairment on the pharmacokinetics of valganciclovir and ganciclovir following oral administration of valganciclovir

Comments to sponsor

1. What target ganciclovir AUC (in μg•hr/mL) values were used in determining the valganciclovir dosing algorithm for patients with impaired renal function?

2. Please indicate why the dosing algorithms for patients with renal impairment differ for intravenous ganciclovir and oral valganciclovir.

3. Please indicate what you consider to be the maximum and minimum ganciclovir AUC values that provide acceptable ganciclovir efficacy and safety following administration of valganciclovir or ganciclovir (oral or intravenous) in the target patient population.

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Public Health Service
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Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 6, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: William Boyd, M.D., Ophthalmologic Consultant, DAAODP,eso: 02/06/01
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP, eso: 02/06/01

NDA: 21-304

Subject: Ophthalmologic consult comments

The following comments are being conveyed on behalf of Dr. Boyd and are in reference to NDA 21-304:

In volume 123, page 74, Section 3.1.5, the study report for WV15376 states,

> "Three of the four patients who withdrew due to insufficient response to therapy withdrew as a result of CMV retinitis progression diagnosed by the study ophthalmologist."

Please identify the three subjects who were withdrawn as a result of CMV retinitis progression diagnosed by the study ophthalmologist.

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Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 2, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: Robert Kumi, Ph.D., Clinical Pharmacokinetics Reviewer, DAVDP
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-304

Subject: Biopharmaceutical comments

The following comments are being conveyed on behalf of Dr. Kumi with regard to the PK/PD Analyses Conducted in support of valganciclovir use during CMV maintenance treatment.

We conclude that that there were insufficient dosing time records to perform the population pharmacokinetic analysis needed for further pharmacokinetics/pharmacodynamics (PK/PD) 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 PK/PD 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.

Due to these concerns, we consider pharmacokinetic comparisons (valganciclovir vs. IV and oral ganciclovir) to be a more appropriate predictor of valganciclovir

use in maintenance therapy than the submitted PK/PD analyses. Consequently, these pharmacokinetic comparisons will be used during the review.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 26, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: Joseph Toerner, M.D., Medical Officer, DAVDP, eso: 1/26/01
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP, eso: 1/26/01

NDA: 21-304

Subject: Comments regarding Advisory Committee Background Package

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The following comments are being conveyed on behalf of Dr. Toerner and are in reference to the Advisory Committee background package submitted to NDA 21-304.

Comments to sponsor:

1. The background materials that you recently submitted state that an analysis of the disproportionate withdrawals between weeks 4 and 12 in study WV 15376 demonstrated that the time to failure was similar between the groups. Please provide the results of your analysis of these withdrawals.

2. In addition, please provide your interpretation of the significance of these withdrawals, and why these withdrawals should not be considered as failures of induction therapy. In doing so, please provide your analysis of any differences in initiation or response to HAART therapy during the maintenance phase.

3. [redacted]

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 23, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: William Boyd, M.D., Ophthamalogic Consultant, DAAODP, eso: 1/23/01
Joseph Toerner, M.D., Medical Officer, DAVDP, eso: 1/23/01
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP, eso: 1/23/01

NDA: 21-304

Subject: Ophthamalogic consult comments

The following comments are being conveyed on behalf of Dr. Boyd and are in reference to the photographic slides of the eye submitted to NDA 21-304.

Comments to sponsor:

1. Subject 18675/2102 did not have retinal images (photos) submitted. Were any photos taken of this subject, even at baseline?

Presumably this subject received study therapy because he/she was not excluded from the safety population according to Appendix 3, volume 123, page 181 of the NDA..

2. Subject 21484/5802 is included in the standard population and is listed as unevaluable at week 4 (in an email from the applicant received 1/22/01).

This subject has only baseline photos submitted. Why was this subject included in the standard population and not the intent-to-treat population?

3. No baseline photos were submitted of the left eye for subject 21485/5902. Were photos taken of the left eye at baseline in this subject?

4. Subject 17838/404 is considered a progressor by the applicant at week 4 (in an email from the applicant received 1/22/01).

There are no retinal photos for this subject at week 4. How was this subject classified as a progressor at week 4?

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Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 22, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: Sue-Chih Lee, Ph.D., Pharmacometrics Consultant, DPE 3
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, DPE 3
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP(eso 1/22/01)

NDA: 21-304

Subject: Pharmacometric comments

The following comments are being conveyed on behalf of Dr. Lee with regard to study GANS2226: Population PK/PD.

Comments to sponsor:

1. Which (electronic) data file was used in the final PK/PD analysis? Is it TRUNC?

2. PK samples that were designated NQ or NR were excluded from analysis. It is unclear what NQ and NR refer to.

3. Dosing times for the dose prior to blood collection were available, but not for the two doses before that. Are there patient diaries that may have dosing times for these two doses?

4. Please provide a scatter plot showing dosing times (in terms of time of the day) for the dose prior to blood collection.

5. Were missed doses recorded for individual patients during the study?

6. How was the average Cmax and AUC calculated when the dosing time records were scanty? Were dosing times assumed to be the same everyday in the same patient?

7. What were the major concomitant medications in the study? Please indicate how many patients were on them and explain why they were not included in covariate analysis.

8. What assumptions (e.g. re: dosing times and CL_{CR} etc.) made in the previous PK/PD analysis were different from those in the current analysis?

9. The population PK model was developed based on stepwise addition/deletion. The Objective function values for each step should be provided.

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Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 10, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: Robert Kumi, Ph.D., Clinical Biopharmaceutical Reviewer, DAVDP
Kellie Reynolds, Ph.D., BiopharmaceuticalTeam Leader, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-304

Subject: Biopharmaceutical comments

The following comments are being conveyed on behalf of Dr. Kumi with regard to the pharmacokinetic-pharmacodynamic analysis for ganciclovir in Study GANS2226 (Volumes 80 and 81 of NDA 21-304)

1. Please provide an explanation for how the dosing history in the table on page 80-23 of Volume 1.80 (NDA 21-304) was developed and please provide a clarification of the underlying assumptions and how they are justified. The effect of error in dosing time on Bayesian estimates of pharmacokinetic parameters (AUC, C_{max} and C_{min}) needs to be evaluated. Simulation may be used for this purpose.

2. Please provide additional clarification of the clinical reasoning behind the categories listed under the Rule column in Table 8 on page 80-68 of Volume 1.80 (NDA 21-304).

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Public Health Service
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Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 18, 2001

To: Dr. Hermine Mante

Address: Roche Global Development
Drug Regulatory Affairs
3401 Hillview Avenue, MS-11100
Palo Alto, CA 94304
Fax- 650-852-1861

From: Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, DAVDP

Through: Robert Kumi, Ph.D., Clinical Biopharmaceutical Reviewer, DAVDP
Kellie Reynolds, Pharm.D., Biopharmaceutical Team Leader, DAVDP
Andrei Breazna, Ph.D., Statistical Reviewer, DAVDP
Greg Soon, Ph.D., Statistical Team Leader, DAVDP
Joseph Toerner, M.D., Medical Reviewer, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-304

Subject: Comments on the draft Advisory Committee Background Package

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The following comments are being conveyed on behalf of the review team in response to your draft backgrounder submitted on 9 January 2001.

General:

The draft background document as written is overly long and complex. The content should be edited to provide the Advisory Committee with information adequate to allow discussion of this NDA submission. We recommend that you revise the document with the intent of simplifying and condensing the information provided. For most of the studies, you should provide the most important outcomes along with your conclusions. Tables should be uncomplicated. Supportive data should be placed in appendices.

Specific:

- Sections 2-4.1: The majority of these data should be moved into an appendix. Sections 2.2 and 2.3 should be retained.

- Section 5.4: The description of study PV16000 is overly detailed and should be revised. Throughout the document, description of this study as supporting the efficacy of valganciclovir for CMV retinitis is confusing and should be clarified.

- Section 6: Only the overall results and conclusions for these studies should be provided. Supportive data should be placed in an appendix.

- Section 7: The description of and conclusions from study W15376 should be emphasized. Inclusion of the analysis proposed on page 10 would be appropriate in this section. You should discuss the implications of the imbalance and reasons for early withdrawal for the evaluation of valganciclovir's efficacy. Most of the tables can be placed in an appendix. Each of the studies included in the NDA should be discussed separately.

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_____ b(6) Personal Privacy
_____ b(7) Law Enforcement Records

C

Roche

CYTOVENE®-IV (ganciclovir sodium for injection)

FOR INTRAVENOUS INFUSION ONLY

CYTOVENE® (ganciclovir capsules)

FOR ORAL ADMINISTRATION

WARNING THE CLINICAL TOXICITY OF CYTOVENE AND CYTOVENE-IV INCLUDES GRANULOCYTOPENIA ANEMIA AND THROMBOCYTOPENIA IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC TERATOGENIC AND CAUSED ASPERMATOGENESIS

CYTOVENE-IV IS INDICATED FOR USE *ONLY* IN THE TREATMENT OF CYTOMEGALOVIRUS (CMV) RETINITIS IN IMMUNOCOMPROMISED PATIENTS AND FOR THE PREVENTION OF CMV DISEASE IN TRANSPLANT PATIENTS AT RISK FOR CMV DISEASE

CYTOVENE CAPSULES ARE INDICATED *ONLY* 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 (see INDICATIONS AND USAGE)

BECAUSE CYTOVENE CAPSULES ARE ASSOCIATED WITH A RISK OF MORE RAPID RATE OF CMV RETINITIS PROGRESSION THEY SHOULD BE USED AS MAINTENANCE TREATMENT ONLY IN THOSE PATIENTS FOR WHOM THIS RISK IS BALANCED BY THE BENEFIT ASSOCIATED WITH AVOIDING DAILY INTRAVENOUS INFUSIONS

DESCRIPTION Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV) CYTOVENE-IV and CYTOVENE are the brand names for ganciclovir sodium for injection and ganciclovir capsules respectively

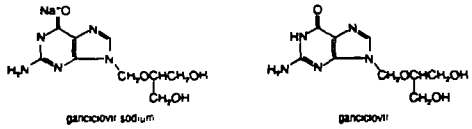
CYTOVENE IV is available as sterile lyophilized powder in strength of 500 mg per vial for intravenous administration only Each vial of CYTOVENE IV contains the equivalent of 500 mg ganciclovir as the sodium salt (46 mg sodium) Reconstitution with 10 mL of Sterile Water for Injection USP yields a solution with pH 11 and a ganciclovir concentration of approximately 50 mg/mL Further dilution in an appropriate intravenous solution must be performed before infusion (see DOSAGE AND ADMINISTRATION)

CYTOVENE is available as 250 mg and 500 mg capsules Each capsule contains 250 mg or 500 mg ganciclovir respectively and inactive ingredients croscarmellose sodium, magnesium stearate and povidone Both hard gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide and FD&C Blue No 2

Ganciclovir is a white to off white crystalline powder with a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255 23 The chemical name for ganciclovir is 9-[(2-hydroxy-1-(hydroxymethyl)-ethoxy)methyl]guanine Ganciclovir is a polar hydrophilic compound with a solubility of 2 6 mg/mL in water at 25°C and an n-octanol/water partition coefficient of 0 022 The pK_as for ganciclovir are 2 2 and 9 4

Ganciclovir when formulated as monosodium salt in the IV dosage form is a white to off-white lyophilized powder with a molecular formula of $C_9H_{12}N_5NaO_4$ and a molecular weight of 277 22 The chemical name for ganciclovir sodium is 9-[(2-hydroxy-1-(hydroxymethyl)-ethoxy)methyl]guanine monosodium salt The lyophilized powder has an aqueous solubility of greater than 50 mg mL at 25°C At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C

The chemical structures of ganciclovir sodium and ganciclovir are



ganciclovir sodium ganciclovir

All doses in this insert are specified in terms of ganciclovir

VIROLOGY *Mechanism of Action* Ganciclovir is an acyclic nucleoside analogue of 2 -deoxyguanosine that inhibits replication of herpes viruses Ganciclovir has been shown to be active against cytomegalovirus (CMV) and herpes simplex virus (HSV) in human clinical studies

To achieve anti-CMV activity, ganciclovir is phosphorylated first to the monophosphate form by a CMV-encoded (UL97 gene) protein kinase homologue then to the di- and triphosphate forms by cellular enzymes Ganciclovir triphosphate concentrations may be 100-fold greater in CMV-infected than in uninfected cells indicating preferential phosphorylation in infected cells Ganciclovir triphosphate once formed persists for days in the CMV-infected cell Ganciclovir triphosphate is believed to inhibit viral DNA synthesis by (1) competitive inhibition of viral DNA polymerases, and (2) incorporation into viral DNA resulting in eventual termination of viral DNA elongation

Antiviral Activity The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) in vitro (laboratory strains or clinical isolates) has ranged from 0 02 to 3 48 µg/mL Ganciclovir inhibits mammalian cell proliferation (IC_{50}) in vitro at higher concentrations ranging from 30 to 725 µg/mL Bone marrow-derived colony-forming cells are more sensitive (IC_{50} 0 028 to 0 7 µg/mL) The reasonableness of in vitro sensitivity of CMV to ganciclovir and clinical response has not been established

Clinical Antiviral Effect of CYTOVENE-IV and CYTOVENE Capsules *CYTOVENE-IV* In a study of CYTOVENE-IV treatment of life- or sight threatening CMV disease in immunocompromised patients 121 of 314 patients had CMV cultured within 7 days prior to treatment and sequential posttreatment viral cultures of urine blood and/or semen As judged by conversion to culture negativity or a greater than 100-fold decrease in in vitro CMV titer at least 83% of patients had a virologic response with a median response time of 7 to 15 days

Antiviral activity of CYTOVENE-IV was demonstrated in two randomized studies for the prevention of CMV disease in transplant recipients (see table below)

	Patients With Positive CMV Cultures			
	Heart Allograft* (n=147)		Bone Marrow Allograft (n=72)	
Time	CYTOVENE IV†	Placebo	CYTOVENE IV†	Placebo
Pretreatment	147 (72%)	5/64 (8%)	37/37 (100%)	35/35 (100%)
Week 2	27/57 (13%)	11/67 (16%)	2/31 (6%)	19/28 (68%)
Week 4	3/66 (5%)	28/66 (43%)	0/24 (0%)	16/20 (80%)

*CMV seropositive or receiving graft from seropositive donor
†5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days
‡5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 posttransplant

CYTOVENE Capsules In trials comparing CYTOVENE-IV with CYTOVENE capsules for the maintenance treatment of CMV retinitis in patients with AIDS serial urine cultures and other available cultures (semen, biopsy specimens blood and others) showed that a small proportion of patients remained culture-positive during maintenance therapy with no statistically significant differences in CMV isolation rates between treatment groups

A study of CYTOVENE capsules (1000 mg q8h) for prevention of CMV disease in individuals with advanced HIV infection (ICM 1654) evaluated antiviral activity as measured by CMV isolation in culture. most cultures were from urine At baseline 40% (176/436) and 44% (92/210) of ganciclovir and placebo recipients respectively had positive cultures (urine or blood) After 2 months on treatment, 10% vs 44% of ganciclovir vs placebo recipients had positive cultures

Viral Resistance The current working definition of CMV resistance to ganciclovir in in vitro assays is IC_{50} >3.0 µg/mL (12 0 µM) CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with CYTOVENE-IV In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment Of these, 113 had at least one positive culture The first available isolate from each subject was tested for reduced sensitivity and 2 of 40 were found to be resistant to ganciclovir These resistant isolates were associated with subsequent treatment failure for retinitis

The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety Resistant viruses have been described that contain mutations in the UL97 gene of CMV that controls phosphorylation of ganciclovir Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir

CLINICAL PHARMACOLOGY: ***Pharmacokinetics***

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR CYTOVENE-IV AND SHOULD BE CONSIDERED FOR CYTOVENE CAPSULES. FOR DOSAGE INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

Absorption. The absolute bioavailability of oral ganciclovir under fasting conditions was approximately 5% (n=6) and following food was 6% to 9% (n=32) When ganciclovir was administered orally with food at a total daily dosage of 3 g/day (500 mg q3h 6 times daily and 1000 mg bid), the steady-state absorption as measured by area under the serum concentration vs time curve (AUC) over 24 hours and maximum serum concentrations (C_{max}) were similar following both regimens with an AUC_{0-24} of 15 9 ± 4 2 (mean ± SD) and 15 4 ± 4 3 µg·hr/mL and C_{max} of 1 02 ± 0 24 and 1 18 ± 0.36 µg/mL, respectively (n=16)

At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir total AUC ranged between 22 1 ± 3.2 (n=16) and 26 8 ± 6 1 µg·hr/mL (n=16) and C_{max} ranged between 8.27 ± 1 02 (n=16) and 9 0 ± 1 4 µg/mL (n=16)

Food Effects When CYTOVENE capsules were given with a meal containing 602 calories and 46 5% fat at a dosage of 1000 mg every 8 hours to 20 HIV-positive subjects the steady-state AUC increased by 22 ± 22% (range -6% to 66%) and there was a significant prolongation of time to peak serum concentrations (T_{max}) from 1 8 ± 0 8 to 3 0 ± 0 6 hours and a higher C_{max} (0 85 ± 0.25 vs 0 86 ± 0 27 µg/mL) (n=20)

Distribution. The steady-state volume of distribution of ganciclovir after intravenous administration was 0 74 ± 0 15 L/kg (n=68) For CYTOVENE capsules no correlation was observed between AUC and bioptical weight (range 55 to 128 kg) since dosing according to weight is not required Cerebrospinal fluid concentrations obtained 0.25 to 5 67 hours postdose in 3 patients who received 2 5 mg/kg ganciclovir intravenously q8h or q12h ranged from 0.31 to 0 68 µg/mL representing 24% to 70% of the respective plasma concentrations Binding to plasma proteins was 1% to 2% over ganciclovir concentrations of 0 5 and 51 µg/mL

Metabolism. Following oral administration of a single 1000 mg dose of ^{14}C-labeled ganciclovir 86 ± 3% of the administered dose was recovered in the feces and 5 ± 1% was recovered in the urine (n=4) No metabolite accounted for more than 1% to 2% of the radioactivity recovered in urine or feces

Elimination When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1 6 to 5 0 mg/kg and when administered orally it exhibits linear kinetics up to a total daily dose of 4 g/day Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir In patients with normal renal function 91 3 ± 5 0% (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine Systemic clearance of intravenously administered ganciclovir was 3 52 ± 0 80 mL/min/kg (n=98) while renal clearance was 3 20 ± 0 80 mL/min/kg (n=47) accounting for 91 ± 11% of the systemic clearance (n=47) After oral administration of ganciclovir, steady-state is achieved within 24 hours Renal clearance following oral administration was 3 1 ± 1.2 mL/min/kg (n=22) Half-life was 3 5 ± 0 9 hours (n=98) following IV administration and 4 8 ± 0 9 hours (n=39) following oral administration

Special Populations: Renal Impairment The pharmacokinetics following intravenous administration of CYTOVENE-IV solution were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1 25 to 5 0 mg/kg

Estimated Creatinine Clearance (mL/min)	n	Dose	Clearance (mL/min/kg) Mean ± SD	Half-life (hours) Mean ± SD
50-79	4	3.2-5 mg/kg	128 ± 63	4 6 ± 1 4
25-49	3	3-5 mg/kg	57 ± 8	4 4 ± 0 4
<25	3	1.25-5 mg/kg	30 ± 13	10 7 ± 5 7

The pharmacokinetics of ganciclovir following oral administration of CYTOVENE capsules were evaluated in 44 patients who were either solid organ transplant recipients or HIV positive Apparent oral clearance of ganciclovir decreased and AUC_{0-tau} increased with diminishing renal function (as expressed by creatinine clearance) Based on these observations it is necessary to modify the dosage of ganciclovir in patients with renal impairment (see DOSAGE AND ADMINISTRATION)

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both intravenous and oral administration

Race/Ethnicity and Gender The effects of race/ethnicity and gender were studied in subjects receiving a dose regimen of 1000 mg every 8 hours Although the numbers of blacks (18%) and Hispanics (20%) were small there appeared to be a trend towards a lower steady-state C_{min} and AUC_{0-8} in these subpopulations as compared to Caucasians No definitive conclusions regarding gender differences could be made because of the small number of females (12%) however no differences between males and females were observed

Pediatrics Ganciclovir pharmacokinetics were studied in 27 neonates aged 2 to 49 days At an intravenous dose of 4 mg/kg (n=14) or 6 mg/kg (n=13) the pharmacokinetic parameters were respectively C_{max} of 5 5 ± 1 6 and 7 0 ± 1 6 µg/mL, systemic clearance of 3 14 ± 1 75 and 3 56 ± 1,27 mL/min/kg and $t_{1/2}$ of 2 4 hours (harmonic mean) for both

Ganciclovir pharmacokinetics were also studied in 10 pediatric patients, aged 9 months to 12 years The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) intravenous doses (5 mg/kg) The steady-state volume of distribution was 0 64 ± 0 22 L/kg (C_{max} was 7 9 ± 3 9 µg/mL, systemic clearance was 4 7 ± 2 2 mL/min/kg and $t_{1/2}$ was 2 4 ± 0 7 hours The pharmacokinetics of intravenous ganciclovir in pediatric patients are similar to those observed in adults

Elderly No studies have been conducted in adults older than 65 years of age

INDICATIONS AND USAGE CYTOVENE-IV is indicated for the treatment of CMV retinitis in immunocompromised patients including patients with acquired immunodeficiency syndrome (AIDS) CYTOVENE-IV is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease (see CLINICAL TRIALS)

CYTOVENE capsules are indicated for the prevention of CMV disease in solid organ transplant recipients and in individuals with advanced HIV infection at risk for developing CMV disease CYTOVENE capsules are also indicated as an alternative to the intravenous formulation for maintenance treatment of CMV retinitis in immunocompromised patients including patients with AIDS in whom retinitis is stable following appropriate induction therapy and for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily IV infusions (see CLINICAL TRIALS)

SAFETY AND EFFICACY OF CYTOVENE-IV AND CYTOVENE HAVE NOT BEEN ESTABLISHED F CONGENITAL OR NEONATAL CMV DISEASE NOR FOR THE TREATMENT OF ESTABLISHED C DISEASE OTHER THAN RETINITIS NOR FOR USE IN NON-IMMUNOCOMPROMISED INDIVIDUA THE SAFETY AND EFFICACY OF CYTOVENE CAPSULES HAVE NOT BEEN ESTABLISHED F TREATING ANY MANIFESTATION OF CMV DISEASE OTHER THAN MAINTENANCE TREATMEN CMV RETINITIS

CLINICAL TRIALS

1 Treatment of CMV Retinitis

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy Other conditions in differential diagnosis of CMV retinitis include candidiasis toxoplasmosis histoplasmosis ret scars and cotton wool spots any of which may produce a retinal appearance similar to CMV For reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar w the retinal presentation of these conditions The diagnosis of CMV retinitis may be supported culture of CMV from urine, blood throat or other sites but a negative CMV culture does not rule CMV retinitis

Studies With CYTOVENE-IV In a retrospective non-randomized single-center analysis of 41 patie with AIDS and CMV retinitis diagnosed by ophthalmologic examination between August 1983 a April 1988 treatment with CYTOVENE IV solution resulted in a significant delay in mean time to first retinitis progression compared to untreated controls (105 (71) days from diagnc vs 35 (29) days from diagnosis) Patients in this series received induction treatment of CYTOVENE 5 mg/kg bid for 14 to 21 days followed by maintenance treatment with either 5 mg/kg once da 7 days per week or 6 mg/kg once daily, 5 days per week (see DOSAGE AND ADMINISTRATION)

In a controlled, randomized study conducted between February 1989 and December 199 immediate treatment with CYTOVENE-IV was compared to delayed treatment in 42 patients w AIDS and peripheral CMV retinitis 35 of 42 patients (13 in the immediate-treatment group and 22 the delayed-treatment group) were included in the analysis of time to retinitis progression Based masked assessment of fundus photographs the mean [95% CI] and median [95% CI] times progression of retinitis were 66 days [39 94] and 50 days [40 84] respectively in the immedia treatment group compared to 19 days [11 27] and 13 5 days [8 18] respectively in the delaye treatment group

Studies Comparing CYTOVENE Capsules to CYTOVENE-IV

Population Characteristics in Studies ICM 1653, ICM 1774 and AVI 034

		ICM 1653 (n=121)	ICM 1774 (n=225)	AVI 034 (n=159)
Median age (years) Range		38 24-62	37 22 56	39 23-62
Sex	Males	116 (96%)	222 (99%)	148 (93%)
	Females	5 (4%)	3 (1%)	10 (6%)
Ethnicity	Asian	3 (3%)	5 (2%)	7 (4%)
	Black	11 (9%)	9 (4%)	3 (2%)
	Caucasian	98 (81%)	186 (83%)	140 (88%)
	Other	9 (7%)	25 (11%)	8 (5%)
Median CD4 Count Range		9 5 0-141	7 0 0-80	10 0 0-320
Mean (SD) Observation Time (days)		107 9 (43 0)	97 6 (42 5)	80 9 (47 0)

ICM 1653 In this randomized, open-label, parallel group trial conducted between March 1993 a November 1992 patients with AIDS and newly diagnosed CMV retinitis received a 3-week induc course of CYTOVENE-IV solution 5 mg/kg bid for 14 days followed by 5 mg/kg once daily fo 1 additional week Following the 21-day intravenous induction course patients with stable CM retinitis were randomized to receive 20 weeks of maintenance treatment with either CYTOVENE-I solution 5 mg/kg once daily, or CYTOVENE capsules 500 mg 6 times daily (3000 mg/day) Th study showed that the mean [95% CI] and median [95% CI] times to progression of CMV retinitis a assessed by masked reading of fundus photographs were 57 days [44 70] and 29 days [28 43 respectively for patients on oral therapy compared to 62 days [50 73] and 49 days [29 61 respectively for patients on intravenous therapy The difference [95% CI] in the mean time t progression between the oral and intravenous therapies (oral - IV) was -5 days [22 12] See Figure for comparison of the proportion of patients remaining free of progression over time

ICM 1774 In this three-arm randomized open-label parallel group trial conducted between Jun 1991 and August 1993 patients with AIDS and stable CMV retinitis following from 4 weeks to months of treatment with CYTOVENE-IV solution were randomized to receive maintenance treatmer with CYTOVENE-IV solution 5 mg/kg once daily CYTOVENE capsules 500 mg 6 times daily o CYTOVENE capsules 1000 mg bid for 20 weeks The study showed that the mean [95% CI] an median [95% CI] times to progression of CMV retinitis as assessed by masked reading of fundu photographs were 54 days [48 60] and 42 days [31 54] respectively for patients on oral therap compared to 66 days [56 76] and 54 days [41 69] respectively for patients on intravenous therapy The difference [95% CI] in the mean time to progression between the oral and intravenous therapies (oral - IV) was -12 days [-24 0] See Figure 2 for comparison of the proportion of patients remaining free of progression over time

AVI 034 In this randomized, open-label, parallel group trial conducted between June 1991 and February 1993 patients with AIDS and newly diagnosed (81%) or previously treated (19%) CMV retinitis who had tolerated 10 to 21 days of induction treatment with CYTOVENE IV 5 mg/kg twice daily were randomized to receive 20 weeks of maintenance treatment with either CYTOVENE capsules 500 mg 6 times daily or CYTOVENE-IV solution 5 mg/kg/day The mean [95% CI] and median [95% CI] times to progression of CMV retinitis as assessed by masked reading of fundus photographs were 51 days [44, 57] and 41 days [31 45] respectively for patients on oral therapy compared to 62 days [52 72] and 60 days [42, 83] respectively for patients on intravenous therapy The difference [95% CI] in the mean time to progression between the oral and intravenous therapies (oral - IV) was -11 days [-24, 1] See Figure 3 for comparison of the proportion of patients remaining free of progression over time

Comparison of other CMV retinitis outcomes between oral and IV formulations (development of bilateral retinitis progression into Zone 1 and deterioration of visual acuity) while not definitive showed no marked differences between treatment groups in these studies Because of low event rates among these endpoints these studies are underpowered to rule out significant differences in these endpoints

Figure 1 - ICM 1653

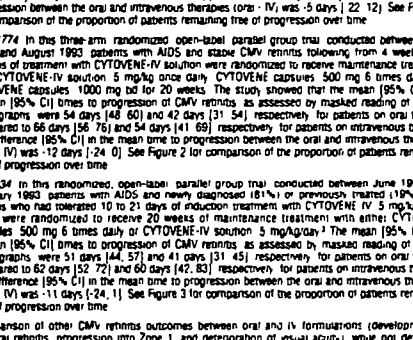


Figure 2 - ICM 1774

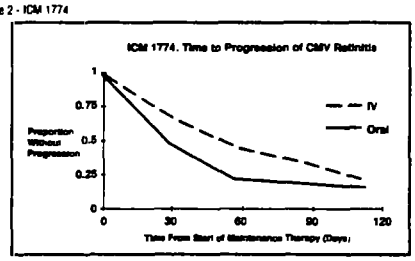
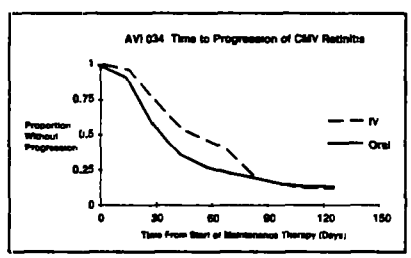


Figure 3 - AVI 034



2 Prevention of CMV Disease in Subjects With AIDS

ICM 1654 In a double-blind study conducted between November 1992 and July 1994, 725 subjects with AIDS who were CMV seropositive and/or culture positive were randomized to receive CYTOVENE capsules 1000 mg every 8 hours or placebo.* The study population had a median age of 38 years (range 21 to 69); were 99% male; were 82% Caucasian, 10% Hispanic, 7% African-American, and 1% Asian; and had a median CD_4 count of 21 (range 0 to 100). The mean observation time was 351 days (range 5 to 621). As shown in the following table, significantly more placebo recipients developed CMV disease.

Incidence of CMV Disease at 6, 12 and 18 Months After Enrollment (Kaplan-Meier Estimates)

	Incidence (Number Still at Risk)	
	CMV Disease	
	Ganciclovir	Placebo
6 months	8% (397)	11% (190)
12 months	14% (225)	26% (92)
18 months	20% (27)	39% (9)

3 Prevention of CMV Disease in Transplant Recipients

CYTOVENE-IV CYTOVENE-IV was evaluated in three randomized, controlled trials of prevention of CMV disease in organ transplant recipients.

ICM 1416 In a randomized, double-blind, placebo-controlled study of 149 heart transplant recipients† at risk for CMV infection (CMV seropositive or a seronegative recipient of an organ from a CMV seropositive donor), there was a statistically significant reduction in the overall incidence of CMV disease in patients treated with CYTOVENE-IV. Immediately posttransplant, patients received CYTOVENE IV solution 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for an additional 14 days. Twelve of the 76 (16%) patients treated with CYTOVENE IV vs 31 of the 73 (43%) placebo-treated patients developed CMV disease during the 120-day posttransplant observation period. No significant differences in hematologic toxicities were seen between the two treatment groups (refer to table in ADVERSE EVENTS).

ICM 1689 In a randomized, double-blind, placebo-controlled study of 72 bone marrow transplant recipients‡ with asymptomatic CMV infection (CMV positive culture of urine, throat or blood), there was a statistically significant reduction in the incidence of CMV disease in patients treated with CYTOVENE-IV following successful hematopoietic engraftment. Patients with virologic evidence of CMV infection received CYTOVENE-IV solution 5 mg/kg bid for 7 days followed by 5 mg/kg qd through day 100 posttransplant. One of the 37 (3%) patients treated with CYTOVENE-IV vs 15 of the 35 (43%) placebo-treated patients developed CMV disease during the study. At 6 months posttransplant, there continued to be a statistically significant reduction in the incidence of CMV disease in patients treated with CYTOVENE IV. Six of 37 (16%) patients treated with CYTOVENE-IV vs 15 of the 35 (43%) placebo-treated patients developed disease through 6 months posttransplant. The overall rate of survival was statistically significantly higher in the group treated with CYTOVENE-IV both at day 100 and day 180 posttransplant. Although the differences in hematologic toxicities were not statistically significant, the incidence of neutropenia was higher in the group treated with CYTOVENE-IV (refer to table in ADVERSE EVENTS).

ICM 1571 A second randomized, unblinded study evaluated 40 allogeneic bone marrow transplant recipients at risk for CMV disease.† Patients underwent bronchoscopy and bronchoalveolar lavage (BAL) on day 35 posttransplant. Patients with histologic, immunologic or virologic evidence of CMV infection in the lung were then randomized to observation or treatment with CYTOVENE-IV solution (5 mg/kg bid for 14 days followed by 5 mg/kg qd 5 days/week until day 120). Four of 20 (20%) patients treated with CYTOVENE-IV and 14 of 20 (70%) control patients developed interstitial pneumonia. The incidence of CMV disease was significantly lower in the group treated with CYTOVENE-IV, consistent with the results observed in ICM 1689.

CYTOVENE Capsules: GAM040 CYTOVENE capsules were evaluated in a randomized, double-blind, placebo-controlled study of 304 orthotopic liver transplant recipients who were CMV seropositive or recipients of an organ from a seropositive donor. Administration of CYTOVENE capsules (1000 mg three times daily) or matching placebo commenced as soon as patients were able to take medication by mouth, but no later than 10 days following transplantation, and continued through 14 weeks after transplantation. Dosing was adjusted for patients with an estimated creatinine clearance <50 mL/min. The incidence of CMV disease at 6 months is summarized in the table below.

Incidence of CMV Disease at 6 Months (Kaplan-Meier Estimates)

CMV Disease at 6 months			
	Ganciclovir (n=150)	Placebo (n=154)	Relative Risk (95% CI)
CMV Disease,* N (%)	7 (4.8%)	29 (18.9%)	0.22 (0.10, 0.51)
CMV syndrome†	6 (4.1%)	19 (12.4%)	
CMV hepatitis	1 (0.7%)	9 (5.9%)	
CMV GI disease	0 (0.0%)	3 (2.0%)	
CMV lung disease	0 (0.0%)	4 (2.6%)	

* One or more CMV endpoints.
† CMV syndrome: CMV viremia and unexplained fever accompanied by malaise and/or neutropenia.

CYTOVENE capsules significantly reduced the 6-month incidence of CMV disease in patients at increased risk of CMV disease, including seronegative recipients of organs from seropositive donors (15% [3/21] with CYTOVENE capsules vs 44% [11/25] with placebo), and patients receiving antilymphocyte antibodies (5% [2/44] with CYTOVENE capsules vs 33% [12/37] with placebo). The incidence of HSV infection at 6 months was 4% (5/150) on ganciclovir vs 24% (36/154) on placebo (relative risk: 0.13; 95% CI: 0.05, 0.32).

CONTRAINDICATIONS CYTOVENE-IV and CYTOVENE are contraindicated in patients with hypersensitivity to ganciclovir or acyclovir.

WARNINGS ***Hematologic*** **CYTOVENE-IV and CYTOVENE should not be administered if the absolute neutrophil count is less than 500 cells/µL or the platelet count is less than 25,000 cells/µL.** Granulocytopenia (neutropenia), anemia and thrombocytopenia have been observed in patients treated with CYTOVENE-IV and CYTOVENE. The frequency and severity of these events vary widely in different patient populations (see ADVERSE EVENTS).

CYTOVENE-IV and CYTOVENE should therefore be used with caution in patients with pre-existing cytopenias or with a history of cytopenic reactions to other drugs, chemicals or irradiation. Granulocytopenia usually occurs during the first or second week of treatment but may occur at any time during treatment. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving CYTOVENE-IV solution for treatment of CMV retinitis.

Impairment of Fertility Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS, *Carcinogenesis, Mutagenesis* and *Impairment of Fertility*). Although data in humans have not been obtained regarding this effect, it is considered probable that ganciclovir at the recommended doses causes temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYTOVENE-IV or CYTOVENE (see *Pregnancy*, Category C).

PRECAUTIONS. ***General*** In clinical studies with CYTOVENE-IV, the maximum single dose administered was 6 mg/kg by intravenous infusion over 1 hour. Larger doses have resulted in increased toxicity. It is likely that more rapid infusions would also result in increased toxicity (see OVERDOSAGE). Administration of CYTOVENE-IV solution should be accompanied by adequate hydration.

Initially reconstituted solutions of CYTOVENE-IV have a high pH (pH 11). Despite further dilution in intravenous fluids, phlebitis and/or pain may occur at the site of intravenous infusion. Care must be taken to infuse solutions containing CYTOVENE-IV only into veins with adequate blood flow to permit rapid dilution and distribution (see DOSAGE AND ADMINISTRATION).

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR CYTOVENE IV AND SHOULD BE CONSIDERED FOR CYTOVENE CAPSULES. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION).

Information for Patients All patients should be informed that the major toxicities of ganciclovir are granulocytopenia (neutropenia), anemia and thrombocytopenia, and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take CYTOVENE capsules with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause infertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with CYTOVENE IV or CYTOVENE. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYTOVENE IV or CYTOVENE.

Patients should be advised that ganciclovir causes tumors in animals. Although there is no information from human studies, ganciclovir should be considered a potential carcinogen.

All HIV+ Patients These patients may be receiving zidovudine (Retrovir®). Patients should be counseled that treatment with both ganciclovir and zidovudine simultaneously may not be tolerated by some patients and may result in severe granulocytopenia (neutropenia). Patients with AIDS may be receiving didanosine (Videx®). Patients should be counseled that concomitant treatment with both ganciclovir and didanosine can cause didanosine serum concentrations to be significantly increased.

HIV+ Patients With CMV Retinitis Ganciclovir is not a cure for CMV retinitis, and immunocompromised patients may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with CYTOVENE-IV or CYTOVENE. Some patients will require more frequent follow-up.

Transplant Recipients Transplant recipients should be counseled regarding the high frequency of impaired renal function in transplant recipients who received CYTOVENE IV solution in controlled clinical trials, particularly in patients receiving concomitant administration of nephrotoxic agents such as cyclosporine and amphotericin B. Although the specific mechanism of this toxicity, which in most cases was reversible, has not been determined, the higher rate of renal impairment in patients receiving CYTOVENE IV solution compared with those who received placebo in the same trials may indicate that CYTOVENE-IV played a significant role.

Laboratory Testing Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving CYTOVENE-IV and CYTOVENE (see ADVERSE EVENTS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µL at the beginning of treatment. Increased serum creatinine levels have been observed in trials evaluating both CYTOVENE-IV and CYTOVENE. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION).

Drug Interactions ***Didanosine*** At an oral dose of 1000 mg of CYTOVENE every 8 hours and didanosine, 200 mg every 12 hours, the steady-state didanosine AUC_{0-12} increased 111 ± 114% (range: 10% to 493%) when didanosine was administered either 2 hours prior to or concurrent with administration of CYTOVENE (n=12 patients, 23 observations). A decrease in steady-state ganciclovir AUC of 21 ± 17% (range: -44% to 5%) was observed when didanosine was administered 2 hours prior to administration of CYTOVENE, but ganciclovir AUC was not affected by the presence of didanosine when the two drugs were administered simultaneously (n=12). There were no significant changes in renal clearance for either drug.

When the standard intravenous ganciclovir induction dose (5 mg/kg infused over 1 hour every 12 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours, the steady-state didanosine AUC_{0-12} increased 70 ± 40% (range: 3% to 121%, n=11) and C_{max} increased 49 ± 48% (range: -28% to 125%). In a separate study, when the standard intravenous ganciclovir maintenance dose (5 mg/kg infused over 1 hour every 24 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours, didanosine AUC_{0-12} increased 50 ± 26% (range: 22% to 110%, n=11) and C_{max} increased 36 ± 36% (range: -27% to 94%) over the first didanosine dosing interval. Didanosine plasma concentrations (AUC_{12-24}) were unchanged during the dosing interval when ganciclovir was not coadministered. Ganciclovir pharmacokinetics were not affected by didanosine in neither study were there significant changes in the renal clearance of either drug.

Zidovudine At an oral dose of 1000 mg of CYTOVENE every 8 hours, mean steady state ganciclovir AUC_{0-8} decreased 17 ± 25% (range: 52% to 23%) in the presence of zidovudine 100 mg every 4 hours (n=12). Steady-state zidovudine AUC_{0-4} increased 19 ± 27% (range: -11% to 74%) in the presence of ganciclovir.

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy with these drugs at full dosage.

Probenecid At an oral dose of 1000 mg of CYTOVENE every 8 hours (n=10), ganciclovir AUC_{0-8} increased 53 ± 91% (range: -14% to 299%) in the presence of probenecid 500 mg every 6 hours. Renal clearance of ganciclovir decreased 22 ± 20% (range: -54% to -4%), which is consistent with an interaction involving competition for renal tubular secretion.

Imipenem-cilastatin Generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Other Medications It is possible that drugs that inhibit replication of rapidly dividing cell populations, such as bone marrow, spermatogonia and germinal layers of skin and gastrointestinal mucosa, may have additive toxicity when administered concomitantly with ganciclovir. Therefore, drugs such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B

trimethoprim/sulfamethoxazole combinations or other nucleoside analogues should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks

No formal drug interaction studies of CYTOVENE-IV or CYTOVENE and drugs commonly used in transplant recipients have been conducted. Increases in serum creatinine were observed in patients treated with CYTOVENE-IV plus either cyclosporine or amphotericin B, drugs with known potential for nephrotoxicity (see ADVERSE EVENTS). In a retrospective analysis of 93 liver allograft recipients receiving ganciclovir (5 mg/kg infused over 1 hour every 12 hours) and oral cyclosporine (at therapeutic doses), there was no evidence of an effect on cyclosporine whole blood concentrations.

Carcinogenesis, Mutagenesis Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1x and 3.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day, there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vaginal and liver in females). At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach, and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans.

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2000 µg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (1x) (2.8 to 10x human exposure based on AUC) but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 µg/mL.

Impairment of Fertility Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg based on AUC comparisons). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose.

Pregnancy Category C Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia in mice; effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see *Carcinogenesis, Mutagenesis*). The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Ganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. CYTOVENE-IV or CYTOVENE should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Footnote All dose comparisons presented in the *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy* subsections are based on the human AUC following administration of a single 5 mg/kg intravenous infusion of CYTOVENE-IV as used during the maintenance phase of treatment. Compared with the single 5 mg/kg intravenous infusion, human exposure is doubled during the intravenous induction phase (5 mg/kg bid) and approximately halved during maintenance treatment with CYTOVENE capsules (1000 mg tid). The cross-species dose comparisons should be divided by 2 for intravenous induction treatment with CYTOVENE IV and multiplied by 2 for CYTOVENE capsules.

Nursing Mothers It is not known whether ganciclovir is excreted in human milk. However, many drugs are excreted in human milk and because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely. Therefore, **Category C** mothers should be instructed to discontinue nursing if they are receiving CYTOVENE-IV or CYTOVENE. The minimum interval before nursing can safely be resumed after the last dose of CYTOVENE IV or CYTOVENE is unknown.

Pediatric Use. **SAFETY AND EFFICACY OF CYTOVENE-IV AND CYTOVENE IN PEDIATRIC PATIENTS HAVE NOT BEEN ESTABLISHED. THE USE OF CYTOVENE-IV OR CYTOVENE IN THE PEDIATRIC POPULATION WARRANTS EXTREME CAUTION DUE TO THE PROBABILITY OF LONG-TERM CARCINOGENICITY AND REPRODUCTIVE TOXICITY. ADMINISTRATION TO PEDIATRIC PATIENTS SHOULD BE UNDERTAKEN ONLY AFTER CAREFUL EVALUATION AND ONLY IF THE POTENTIAL BENEFITS OF TREATMENT OUTWEIGH THE RISKS.**

The spectrum of adverse events reported in 120 immunocompromised pediatric clinical trial participants with serious CMV infections receiving CYTOVENE IV solution were similar to those reported in adults. Granulocytopenia (17%) and thrombocytopenia (10%) were the most common adverse events reported.

Sixteen pediatric patients (8 months to 15 years of age) with life- or sight-threatening CMV infections were evaluated in an open-label CYTOVENE-IV solution pharmacokinetics study. Adverse events reported for more than one pediatric patient were as follows: hypokalemia (4/16, 25%), abnormal kidney function (3/16, 19%), sepsis (3/16, 19%), thrombocytopenia (3/16, 19%), leukopenia (2/16, 13%), coagulation disorder (2/16, 13%), hypertension (2/16, 13%), pneumonia (2/16, 13%), and immune system disorder (2/16, 13%).

There has been very limited clinical experience using CYTOVENE IV for the treatment of CMV retinitis in patients under the age of 12 years. Two pediatric patients (ages 9 and 5 years) showed improvement or stabilization of retinitis for 23 and 9 months, respectively. These pediatric patients received induction treatment with 2.5 mg/kg IV infused every 8 hours for 14 to 21 days, followed by maintenance therapy with 6 mg/kg once per day, 5 to 7 days per week. When retinitis progressed during once-daily maintenance therapy, both pediatric patients were treated with the 5 mg/kg bid regimen. Two other pediatric patients (ages 2.5 and 4 years) who received similar induction regimens showed only partial or no response to treatment. Another pediatric patient, a 6-year-old with T-cell dysfunction, showed stabilization of retinitis for 3 months while receiving continuous infusions of CYTOVENE-IV at doses of 2 to 5 mg/kg/24 hours. Continuous infusion treatment was discontinued due to granulocytopenia.

Eleven of the 72 patients in the placebo-controlled trial in bone marrow transplant recipients were pediatric patients, ranging in age from 3 to 10 years (5 treated with CYTOVENE IV and 6 with placebo). Five of the pediatric patients treated with CYTOVENE-IV received 5 mg/kg intravenously bid for up to 7 days; 4 patients went on to receive 5 mg/kg qd up to day 100 posttransplant. Results were similar to those observed in adult transplant recipients treated with CYTOVENE IV. Two of the 6 placebo-treated pediatric patients developed CMV pneumonia vs none of the 5 patients treated with CYTOVENE-IV. The spectrum of adverse events in the pediatric group was similar to that observed in the adult patients.

CYTOVENE capsules have not been studied in pediatric patients under age 13.

Geriatric Use The pharmacokinetic profiles of CYTOVENE-IV and CYTOVENE in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of CYTOVENE-IV or CYTOVENE (see DOSAGE AND ADMINISTRATION).

Clinical studies of CYTOVENE-IV and CYTOVENE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. CYTOVENE IV and CYTOVENE are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, in addition, renal function should be monitored and dosage adjustments should be made accordingly (see *Use in Patients With Renal Impairment* and DOSAGE AND ADMINISTRATION).

Use in Patients With Renal Impairment CYTOVENE IV and CYTOVENE should be used with caution in patients with impaired renal function because the half-life and plasma/serum concentrations of ganciclovir will be increased due to reduced renal clearance (see DOSAGE AND ADMINISTRATION and ADVERSE EVENTS, *Renal Toxicity*).

Hemodialysis has been shown to reduce plasma levels of ganciclovir by approximately 50%.

ADVERSE EVENTS Adverse events that occurred during clinical trials of CYTOVENE IV solution and CYTOVENE capsules are summarized below, according to the particular study subject population.

Subjects With AIDS Three controlled, randomized, phase 3 trials comparing CYTOVENE-IV and CYTOVENE capsules for maintenance treatment of CMV retinitis have been completed. During these trials CYTOVENE-IV or CYTOVENE capsules were prematurely discontinued in 9% of subjects because of adverse events. In a placebo-controlled, randomized, phase 3 trial of CYTOVENE capsules for prevention of CMV disease in AIDS, treatment was prematurely discontinued because of adverse events, new or worsening intercurrent illness, or laboratory abnormalities in 19.5% of subjects treated with CYTOVENE capsules and 16% of subjects receiving placebo. Laboratory data and adverse events reported during the conduct of these controlled trials are summarized below.

Laboratory Data

Selected Laboratory Abnormalities in Trials for Treatment of CMV Retinitis and Prevention of CMV Disease

	CMV Retinitis Treatment*		CMV Disease Prevention	
Treatment	CYTOVENE Capsules† 3000 mg/day	CYTOVENE-IV‡ 5 mg/kg/day	CYTOVENE Capsules§ 3000 mg/day	Placebo¶
Subjects, number	320	175	478	234
Neutropenia				
<500 ANC/µL	18%	25%	10%	6%
500 – <749	17%	14%	16%	7%
750 – <1000	19%	26%	22%	16%
Anemia				
Hemoglobin				
<6.5 g/dL	2%	5%	1%	<1%
6.5 – <8.0	10%	16%	5%	3%
8.0 – <9.5	25%	26%	15%	16%
Maximum Serum Creatinine				
≥2.5 mg/dL	1%	2%	1%	2%
≥1.5 – <2.5	12%	14%	19%	11%

* Pooled data from Treatment Studies ICM 1653, Study ICM 1774 and Study AVI 034.
† Mean time on therapy = 91 days, including allowed reinduction treatment periods.
‡ Mean time on therapy = 103 days, including allowed reinduction treatment periods.
§ Data from Prevention Study, ICM 1654.
¶ Mean time on ganciclovir = 269 days.
# Mean time on placebo = 240 days.
(See discussion of clinical trials under INDICATIONS AND USAGE.)

Adverse Events The following table shows selected adverse events reported in 5% or more of the subjects in three controlled clinical trials during treatment with either CYTOVENE-IV solution (5 mg/kg/day) or CYTOVENE capsules (3000 mg/day), and in one controlled clinical trial in which CYTOVENE capsules (3000 mg/day) were compared to placebo for the prevention of CMV disease.

Selected Adverse Events Reported in ≥ 5% of Subjects in Three Randomized Phase 3 Studies Comparing CYTOVENE Capsules to CYTOVENE-IV Solution for Maintenance Treatment of CMV Retinitis and in One Phase 3 Randomized Study Comparing CYTOVENE Capsules to Placebo for Prevention of CMV Disease

		Maintenance Treatment Studies		Prevention Study	
Body System	Adverse Event	Capsules (n=326)	IV (n=179)	Capsules (n=478)	Placebo (n=234)
Body as a Whole	Fever	38%	48%	35%	33%
	Infection	9%	13%	8%	4%
	Chills	7%	10%	7%	4%
	Sepsis	4%	15%	3%	2%
Digestive System	Diarrhea	41%	44%	48%	42%
	Anorexia	15%	14%	19%	16%
	Vomiting	13%	13%	14%	11%
Hemic and Lymphatic System	Leukopenia	29%	41%	17%	9%
	Anemia	18%	25%	9%	7%
	Thrombocytopenia	6%	6%	3%	1%
Nervous System	Neuropathy	8%	9%	21%	15%
Other	Sweating	11%	12%	14%	12%
	Pruritus	6%	5%	10%	9%
Catheter Related*	Total Catheter Events	6%	22%	–	–
	Catheter Infection	4%	9%	–	–
	Catheter Sepsis	1%	8%	–	–

* Some of these events also appear under other body systems.

The following events were frequently observed in clinical trials but occurred with equal or greater frequency in placebo-treated subjects: abdominal pain, nausea, flatulence, pneumonia, paresthesia, rash.

Retinal Detachment Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with ganciclovir. Its relationship to therapy with ganciclovir is unknown. Retinal detachment occurred in 11% of patients treated with CYTOVENE IV solution and in 8% of patients treated with CYTOVENE capsules. Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retina(s) and to detect any other retinal pathology.

Transplant Recipients: There have been three controlled clinical trials of CYTOVENE-IV solution and one controlled clinical trial of CYTOVENE capsules for the prevention of CMV disease in transplant recipients. Laboratory data and adverse events reported during these trials are summarized below.

Laboratory Data The following table shows the frequency of granulocytopenia (neutropenia) and thrombocytopenia observed.

Controlled Trials – Transplant Recipients

	CYTOVENE IV				CYTOVENE Capsules	
	Heart Allograft*		Bone Marrow Allograft*		Liver Allograft#	
	CYTOVENE IV (n=76)	Placebo (n=73)	CYTOVENE-IV (n=57)	Control (n=55)	CYTOVENE Capsules (n=150)	Placebo (n=154)
Neutropenia						
Minimum ANC < 500/µL	4%	3%	12%	6%	3%	1%
Minimum ANC 500-1000/µL	3%	8%	29%	17%	3%	2%
TOTAL ANC ≤1000/µL	7%	11%	41%	23%	6%	3%
Thrombocytopenia						
Platelet count < 25 000/µL	3%	1%	32%	28%	0%	3%
Platelet count 25 000-50 000/µL	5%	3%	25%	37%	5%	3%
TOTAL Platelet ≤50 000/µL	8%	4%	57%	65%	5%	6%

* Study ICM 1496: Mean duration of treatment = 28 days.
† Study ICM 1570 and ICM 1689: Mean duration of treatment = 45 days.
‡ Study GANC40: Mean duration of ganciclovir treatment = 82 days.
(See discussion of clinical trials under INDICATIONS AND USAGE.)

The following table shows the frequency of elevated serum creatinine values in these controlled clinical trials.

Controlled Trials – Transplant Recipients

	CYTOVENE-IV						CYTOVENE Capsules	
	Heart Allograft*		Bone Marrow Allograft*		Bone Marrow Allograft†		Liver Allograft‡	
Maximum Serum Creatinine Level	CYTOVENE-IV (n=76)	Placebo (n=73)	CYTOVENE-IV (n=20)	Control (n=20)	CYTOVENE-IV (n=37)	Placebo (n=35)	CYTOVENE Capsules (n=150)	Placebo (n=154)
Serum Creatinine ≥ 2.5 mg/dL	18%	4%	20%	0%	0%	0%	16%	10%
Serum Creatinine ≥1.5 – <2.5 mg/dL	56%	68%	50%	35%	43%	44%	39%	47%

In 3 out of 4 trials, patients receiving either CYTOVENE-IV solution or CYTOVENE capsules had elevated serum creatinine levels when compared to those receiving placebo. Most patients in these studies also received cyclosporine. The mechanism of impairment of renal function is not known. However, careful monitoring of renal function during therapy with CYTOVENE IV solution or CYTOVENE capsules is essential, especially for those patients receiving concomitant agents that may cause nephrotoxicity.

General Other adverse events that were thought to be "probably" or "possibly" related to CYTOVENE-IV solution or CYTOVENE capsules in controlled clinical studies in either subjects with AIDS or transplant recipients are listed below. These events all occurred in at least 3 subjects.

Body as a Whole abdomen enlarged, asthenia, chest pain, edema, headache, injection site inflammation, malaise, pain

Digestive System abnormal liver function test, aphthous stomatitis, constipation, dyspepsia, eructation

Hemic and Lymphatic System pancytopenia

Respiratory System cough increased, dyspnea

Nervous System abnormal dreams, anxiety, confusion, depression, dizziness, dry mouth, insomnia, seizures, somnolence, thinking abnormal, tremor

Skin and Appendages alopecia, dry skin

Special Senses abnormal vision, taste perversion, tinnitus, vitreous disorder

Metabolic and Nutritional Disorders creatinine increased, SGOT increased, SGPT increased, weight loss

Cardiovascular System hypertension, phlebitis, vasodilatation

Urogenital System creatinine clearance decreased, kidney failure, kidney function abnormal, urinary frequency

Musculoskeletal System arthralgia, leg cramps, myalgia, myasthenia

The following adverse events reported in patients receiving ganciclovir may be potentially fatal: gastrointestinal perforation, multiple organ failure, pancreatitis, and sepsis.

Adverse Events Reported During Postmarketing Experience With CYTOVENE-IV and CYTOVENE Capsules. The following events have been identified during postapproval use of the drug. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness, frequency of reporting, the apparent causal connection or a combination of these factors:

acidosis, allergic reaction, anaphylactic reaction, arthritis, bronchospasm, cardiac arrest, cardiac conduction abnormality, cataracts, cholelithiasis, cholestasis, congenital anomaly, dry eyes, dysesthesia, dysphasia, elevated triglyceride levels, encephalopathy, exfoliative dermatitis, extrapyramidal reaction, facial pain, hallucinations, hemolytic anemia, hemolytic uremic syndrome, hepatic failure, hepatitis, hypercalcemia, hyponatremia, inappropriate serum ADH, infertility, intestinal ulceration, intracranial hypertension, irritability, loss of memory, loss of sense of smell, myelopathy, oculomotor nerve paralysis, peripheral ischemia, pulmonary fibrosis, renal tubular disorder, rhabdomyolysis, Stevens-Johnson syndrome, stroke, testicular hypotrophy, Torsades de Pointes, vasculitis, ventricular tachycardia.

OVERDOSAGE. *CYTOVENE IV* Overdosage with CYTOVENE IV has been reported in 17 patients (13 adults and 4 children under 2 years of age). Five patients experienced no adverse events following overdosage at the following doses: 7 doses of 11 mg/kg over a 3-day period (adult); single dose of 3500 mg (adult); single dose of 500 mg (72.5 mg/kg) followed by 48 hours of peritoneal dialysis (4-month-old); single dose of approximately 60 mg/kg followed by exchange transfusion (18-month-old); 2 doses of 500 mg instead of 31 mg (21-month-old).

Irreversible pancytopenia developed in 1 adult with AIDS and CMV colitis after receiving 3000 mg of CYTOVENE-IV solution on each of 2 consecutive days. He experienced worsening GI symptoms and acute renal failure that required short-term dialysis. Pancytopenia developed and persisted until his death from a malignancy several months later. Other adverse events reported following overdosage included: persistent bone marrow suppression (1 adult with neutropenia and thrombocytopenia after a single dose of 6000 mg); reversible neutropenia or granulocytopenia (4 adults; overdoses ranging from 8 mg/kg daily for 4 days to a single dose of 25 mg/kg); hepatitis (1 adult receiving 10 mg/kg daily and one 2 kg infant after a single 40 mg dose); renal toxicity (1 adult with transient worsening of hematuria after a single 500 mg dose and 1 adult with elevated creatinine (5.2 mg/dL) after a single 5000 to 7000 mg dose); and seizure (1 adult with known seizure disorder after 3 days of 9 mg/kg). In addition, 1 adult received 0.4 mL (instead of 0.1 mL) CYTOVENE IV solution by intravitreal injection and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

CYTOVENE Capsules There have been no reports of overdosage with CYTOVENE capsules. Doses as high as 6000 mg/day given either as 1000 mg 6 times daily or as 2000 mg tid did not result in overt toxicity other than transient neutropenia. Daily doses of more than 6000 mg have not been studied.

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered.

DOSAGE AND ADMINISTRATION CAUTION – DO NOT ADMINISTER CYTOVENE IV SOLUTION BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF CYTOVENE-IV MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

CAUTION – INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF RECONSTITUTED CYTOVENE-IV SOLUTION MAY RESULT IN SEVERE TISSUE IRRITATION DUE TO HIGH pH (11).

Dosage THE RECOMMENDED DOSE FOR CYTOVENE-IV SOLUTION AND CYTOVENE CAPSULES SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR CYTOVENE IV SOLUTION SHOULD NOT BE EXCEEDED.

For Treatment of CMV Retinitis in Patients With Normal Renal Function

1 Induction Treatment

The recommended initial dosage for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days. CYTOVENE capsules should not be used for induction treatment.

2 Maintenance Treatment

CYTOVENE IV Following induction treatment, the recommended maintenance dosage of CYTOVENE IV solution is 5 mg/kg given as a constant-rate intravenous infusion over 1 hour once daily, 7 days per week or 6 mg/kg once daily, 5 days per week.

CYTOVENE Capsules Following induction treatment, the recommended maintenance dosage of CYTOVENE capsules is 1000 mg tid with food. Alternatively, the dosing regimen of 500 mg 6 times daily every 3 hours with food during waking hours may be used.

For patients who experience progression of CMV retinitis while receiving maintenance treatment with either formulation of ganciclovir, re-induction treatment is recommended.

For the Prevention of CMV Disease in Patients With Advanced HIV Infection and Normal Renal Function

CYTOVENE Capsules The recommended prophylactic dose of CYTOVENE capsules is 1000 mg tid with food.

For the Prevention of CMV Disease in Transplant Recipients With Normal Renal Function

CYTOVENE-IV The recommended initial dosage of CYTOVENE IV solution for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days, followed by 5 mg/kg once daily, 7 days per week or 6 mg/kg once daily, 5 days per week.

CYTOVENE Capsules The recommended prophylactic dosage of CYTOVENE capsules is 1000 mg tid with food

The duration of treatment with CYTOVENE-IV solution and CYTOVENE capsules in transplant recipients is dependent upon the duration and degree of immunosuppression In controlled clinical trials in bone marrow allograft recipients, treatment with CYTOVENE-IV was continued until day 100 to 120 posttransplantation CMV disease occurred in several patients who discontinued treatment with CYTOVENE-IV solution prematurely In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with CYTOVENE-IV was stopped at day 28 posttransplant, suggesting that continued dosing may be necessary to prevent late occurrence of CMV disease in this patient population In a controlled clinical trial of liver allograft recipients, treatment with CYTOVENE capsules was continued through week 14 posttransplantation (see INDICATIONS AND USAGE section for a more detailed discussion)

Renal Impairment:

CYTOVENE-IV For patients with impairment of renal function, refer to the table below for recommended doses of CYTOVENE-IV solution and adjust the dosing interval as indicated

Creatinine Clearance* (mL/min)	CYTOVENE-IV Induction Dose (mg/kg)	Dosing Interval (hours)	CYTOVENE-IV Maintenance Dose (mg/kg)	Dosing Interval (hours)
≥70	5.0	12	5.0	24
50-69	2.5	12	2.5	24
25-49	2.5	24	1.25	24
10-24	1.25	24	0.625	24
<10	1.25	3 times per week, following hemodialysis	0.625	3 times per week, following hemodialysis

*Creatinine clearance can be related to serum creatinine by the formulas given below

Dosing for patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week, following each hemodialysis session CYTOVENE-IV should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%

CYTOVENE Capsules In patients with renal impairment, the dose of CYTOVENE capsules should be modified as shown below

Creatinine Clearance* mL/min	CYTOVENE Capsule Dosages
≥70	1000 mg tid or 500 mg q3h, 6x/day
50-69	1500 mg qd or 500 mg tid
25-49	1000 mg qd or 500 mg bid
10-24	500 mg qd
<10	500 mg 3 times per week, following hemodialysis

*Creatinine clearance can be related to serum creatinine by the following formulas

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0 85 x male value

Patient Monitoring: Due to the frequency of granulocytopenia, anemia and thrombocytopenia in patients receiving ganciclovir (see ADVERSE EVENTS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in cytopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment Patients should have serum creatinine or creatinine clearance values followed carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION)

Reduction of Dose: Dosage reductions in renally impaired patients are required for CYTOVENE-IV and should be considered for CYTOVENE capsules (see *Renal Impairment*) Dosage reductions should also be considered for those with neutropenia, anemia and/or thrombocytopenia (see ADVERSE EVENTS) Ganciclovir should not be administered in patients with severe neutropenia (ANC less than 500/μL) or severe thrombocytopenia (platelets less than 25,000/μL)

Method of Preparation of CYTOVENE-IV Solution: Each 10 mL clear glass vial contains ganciclovir sodium equivalent to 500 mg of ganciclovir and 46 mg of sodium The contents of the vial should be prepared for administration in the following manner

1 *Reconstituted Solution*

a Reconstitute lyophilized CYTOVENE-IV by injecting 10 mL of Sterile Water for Injection, USP, into the vial

DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING PARABENS IT IS INCOMPATIBLE WITH CYTOVENE-IV AND MAY CAUSE PRECIPITATION

b. Shake the vial to dissolve the drug

c. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion solution Discard the vial if particulate matter or discoloration is observed

d Reconstituted solution in the vial is stable at room temperature for 12 hours It should not be refrigerated

2 *Infusion Solution*

Based on patient weight the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable (see below) infusion fluid (typically 100 mL) for delivery over the course of 1 hour Infusion concentrations greater than 10 mg/mL are not recommended The following infusion fluids have been determined to be chemically and physically compatible with CYTOVENE-IV solution 0.9% Sodium Chloride, 5% Dextrose Ringer's Injection and Lactated Ringer's Injection, USP

CYTOVENE-IV, when reconstituted with sterile water for injection, further diluted with 0 9% sodium chloride injection, and stored refrigerated at 5°C in polyvinyl chloride (PVC) bags, remains physically and chemically stable for 14 days

However because CYTOVENE-IV is reconstituted with nonbacteriostatic sterile water, it is recommended that the infusion solution be used within 24 hours of dilution to reduce the risk of bacterial contamination The infusion should be refrigerated Freezing is not recommended

Handling and Disposal: Caution should be exercised in the handling and preparation of solutions of CYTOVENE-IV and in the handling of CYTOVENE capsules Solutions of CYTOVENE-IV are alkaline (pH 11) Avoid direct contact with the skin or mucous membranes of the powder contained in CYTOVENE capsules or of CYTOVENE-IV solutions If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water CYTOVENE capsules should not be opened or crushed

Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity and mutagenicity) consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs Several guidelines on this subject have been published [9-10]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

HOW SUPPLIED: CYTOVENE®-IV (ganciclovir sodium for injection) is supplied in 10 mL sterile vials each containing ganciclovir sodium equivalent to 500 mg of ganciclovir, in cartons of 25 (NDC 0004-6940-03)

Store vials at temperatures below 40°C (104°F)

CYTOVENE® (ganciclovir capsules) 250 mg are two-pieced, size No 1, opaque green hard gelatin capsules with ROCHE and CYTOVENE 250 mg imprinted on the capsules in dark blue ink and with two blue lines partially encircling the capsule body Each capsule contains 250 mg of ganciclovir as a white to off-white powder CYTOVENE capsules are supplied as follows. Bottles of 180 capsules (NDC 0004-0269-48)

CYTOVENE® (ganciclovir capsules) 500 mg are two-pieced, size No 0 elongated opaque yellow/opaque green hard gelatin capsules with ROCHE and CYTOVENE 500 mg imprinted on the capsules in dark blue ink and with two blue lines partially encircling the capsule body Each capsule contains 500 mg of ganciclovir as a white to off-white powder CYTOVENE capsules are supplied as follows Bottles of 180 capsules (NDC 0004-0278-48)

Store between 5° and 25°C (41° and 77°F)

* Retrovir is a registered trademark of Glaxo Wellcome

† Videx is a registered trademark of Bristol-Myers Squibb

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VISTIDE® (cidofovir injection)

FOR INTRAVENOUS INFUSION ONLY.
NOT FOR INTRAOCULAR INJECTION.

WARNING:

RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF VISTIDE. CASES OF ACUTE RENAL FAILURE RESULTING IN DIALYSIS AND/OR CONTRIBUTING TO DEATH HAVE OCCURRED WITH AS FEW AS ONE OR TWO DOSES OF VISTIDE. TO REDUCE POSSIBLE NEPHROTOXICITY, INTRAVENOUS PREHYDRATION WITH NORMAL SALINE AND ADMINISTRATION OF PROBENECID MUST BE USED WITH EACH VISTIDE INFUSION. RENAL FUNCTION (SERUM CREATININE AND URINE PROTEIN) MUST BE MONITORED WITHIN 48 HOURS PRIOR TO EACH DOSE OF VISTIDE AND THE DOSE OF VISTIDE MODIFIED FOR CHANGES IN RENAL FUNCTION AS APPROPRIATE (SEE DOSAGE AND ADMINISTRATION). VISTIDE IS CONTRAINDICATED IN PATIENTS WHO ARE RECEIVING OTHER NEPHROTOXIC AGENTS.

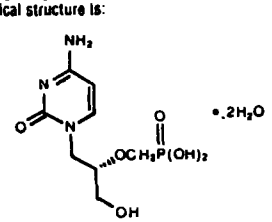
NEUTROPENIA HAS BEEN OBSERVED IN ASSOCIATION WITH VISTIDE TREATMENT. THEREFORE, NEUTROPHIL COUNTS SHOULD BE MONITORED DURING VISTIDE THERAPY.

VISTIDE IS INDICATED ONLY FOR THE TREATMENT OF CMV RETINITIS IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME.

IN ANIMAL STUDIES CIDOFOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED HYPOSPERMIA (SEE CARCINOGENESIS, MUTAGENESIS, & IMPAIRMENT OF FERTILITY).

DESCRIPTION

VISTIDE® is the brand name for cidofovir injection. The chemical name of cidofovir is 1-[(*S*)-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine dihydrate (HPMPC), with the molecular formula of $C_8H_{14}N_3O_6P \cdot 2H_2O$ and a molecular weight of 315.22 (279.19 for anhydrous). The chemical structure is:



Cidofovir is a white crystalline powder with an aqueous solubility of ≥ 170 mg/mL at pH 6-8 and a log P (octanol/aqueous buffer, pH 7.1) value of -3.3.

VISTIDE is a sterile, hypertonic aqueous solution for intravenous infusion only. The solution is clear and colorless. It is supplied in clear glass vials, each containing 375 mg of anhydrous cidofovir in 5 mL aqueous solution at a concentration of 75 mg/mL. The formulation is pH-adjusted to 7.4 with sodium hydroxide and/or hydrochloric acid and contains no preservatives. The appropriate volume of VISTIDE must be removed from the single-use vial and diluted prior to administration (see DOSAGE AND ADMINISTRATION).

MICROBIOLOGY

Mechanism of Action. Cidofovir suppresses cytomegalovirus (CMV) replication by selective inhibition of viral DNA synthesis. Biochemical data support selective inhibition of CMV DNA polymerase by cidofovir diphosphate, the active intracellular metabolite of cidofovir. Cidofovir diphosphate inhibits herpesvirus polymerases at concentrations that are 8- to 600-fold lower than those needed to inhibit human cellular DNA polymerases alpha, beta, and gamma[1, 2, 3]. Incorporation of cidofovir into the growing viral DNA chain results in reductions in the rate of viral DNA synthesis.

In Vitro Susceptibility. Cidofovir is active *in vitro* against a variety of laboratory and clinical isolates of CMV and other herpesviruses (Table 1). Controlled clinical studies of efficacy have been limited to patients with AIDS and CMV retinitis.

Table 1. Cidofovir Inhibition of Virus Multiplication in Cell Culture

Virus	IC_{50} (μM)
Wild-type CMV Isolates	0.5 - 2.8
HSV-1, HSV-2	12.7 - 31.7

Resistance. CMV isolates with reduced susceptibility to cidofovir have been selected *in vitro* in the presence of high concentrations of cidofovir[4]. IC_{50} values for selected resistant isolates ranged from 7-15 μM.

There are insufficient data at this time to assess the frequency or the clinical significance of the development of resistant isolates following VISTIDE administration to patients.

The possibility of viral resistance should be considered for patients who show a poor clinical response or experience recurrent retinitis progression during therapy.

Cross Resistance. Cidofovir-resistant isolates selected *in vitro* following exposure to increasing concentrations of cidofovir were assessed for susceptibility to ganciclovir and foscarnet[4]. All were cross resistant to ganciclovir, but remained susceptible to foscarnet. Ganciclovir- or ganciclovir/foscarnet-resistant isolates that are cross resistant to cidofovir have been obtained from drug naive patients and from patients following ganciclovir or ganciclovir/ foscarnet therapy. To date, the majority of ganciclovir-resistant isolates are UL97 gene product (phosphokinase) mutants and remain susceptible to cidofovir[5]. Reduced susceptibility to cidofovir, however, has been reported for DNA polymerase mutants of CMV which are resistant to ganciclovir[6-9]. To date, all clinical isolates which exhibit high level resistance to ganciclovir, due to mutations in both the DNA polymerase and UL97 genes, have been shown to be cross resistant to cidofovir. Cidofovir is active against some, but not all, CMV isolates which are resistant to foscarnet[10-12]. The incidence of foscarnet-resistant isolates that are resistant to cidofovir is not known.

A few triple-drug resistant isolates have been described. Genotypic analysis of two of these triple-resistant isolates revealed several point mutations in the CMV DNA polymerase gene. The clinical significance of the development of these cross-resistant isolates is not known.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

VISTIDE must be administered with probenecid. The pharmacokinetics of cidofovir, administered both without and with probenecid, are described below.

The pharmacokinetics of cidofovir without probenecid were evaluated in 27 HIV-infected patients with or without asymptomatic CMV infection. Dose-independent pharmacokinetics were demonstrated after one hr infusions of 1.0 (n = 5), 3.0 (n = 10), 5.0 (n = 2) and 10.0 (n = 8) mg/kg (See Table 2 for pharmacokinetic parameters). There was no evidence of cidofovir accumulation after 4 weeks of repeated administration of 3 mg/kg/week (n = 5) without probenecid. In patients with normal renal function approximately 80 to 100% of the VISTIDE dose was recovered unchanged in urine within 24 hr (n = 27). The renal clearance of cidofovir was greater than creatinine clearance, indicating renal tubular secretion contributes to the elimination of cidofovir.

The pharmacokinetics of cidofovir administered with probenecid were evaluated in 12 HIV-infected patients with or without asymptomatic CMV infection and 10 patients with relapsing CMV retinitis. Dose-independent pharmacokinetics were observed for cidofovir, administered with probenecid, after one hr infusions of 3.0 (n = 12), 5.0 (n = 6), and 7.5 (n = 4) mg/kg (See Table 2). Approximately 70 to 85% of the VISTIDE dose administered with concomitant probenecid was excreted as unchanged drug within 24 hr. When VISTIDE was administered with probenecid, the renal clearance of cidofovir was reduced to a level consistent with creatinine clearance, suggesting that probenecid blocks active renal tubular secretion of cidofovir.

Table 2. Cidofovir Pharmacokinetic Parameters Following 3.0 and 5.0 mg/kg Infusions, Without and With Probenecid*

PARAMETERS	VISTIDE ADMINISTERED WITHOUT PROBENECID		VISTIDE ADMINISTERED WITH PROBENECID	
	3 mg/kg (n = 10)	5 mg/kg (n = 2)	3 mg/kg (n = 12)	5 mg/kg (n = 6)
AUC (μg•hr/mL)	20.0 ± 2.3	28.3	25.7 ± 8.5	40.8 ± 9.0
Cmax (end of infusion) (μg/mL)	7.3 ± 1.4	11.5	9.8 ± 3.7	19.6 ± 7.2
Vdss (mL/kg)	537 ± 126 (n = 12)		410 ± 102 (n = 18)	
Clearance (mL/min/1.73 m^2)	179 ± 23.1 (n = 12)		148 ± 38.8 (n = 18)	
Renal Clearance (mL/min/1.73 m^2)	150 ± 26.9 (n = 12)		98.6 ± 27.9 (n = 11)	

* See DOSAGE AND ADMINISTRATION

In vitro, cidofovir was less than 6% bound to plasma or serum proteins over the cidofovir concentration range 0.25 to 25 μg/mL. CSF concentrations of cidofovir following intravenous infusion of VISTIDE 5 mg/kg with concomitant probenecid and intravenous hydration were undetectable (< 0.1 μg/mL, assay detection threshold) at 15 minutes after the end of a 1 hr infusion in one patient whose corresponding serum concentration was 8.7 μg/mL.

DRUG-DRUG INTERACTIONS

Zidovudine

The pharmacokinetics of zidovudine were evaluated in 10 patients receiving zidovudine alone or with intravenous cidofovir (without probenecid). There was no evidence of an effect of cidofovir on the pharmacokinetics of zidovudine.

SPECIAL POPULATIONS

Renal Insufficiency

Pharmacokinetic data collected from subjects with creatinine clearance values as low as 11 mL/min indicate that cidofovir clearance decreases proportionally with creatinine clearance.

High-flux hemodialysis has been shown to reduce the serum levels of cidofovir by approximately 75%.

Initiation of therapy with VISTIDE is contraindicated in patients with serum creatinine > 1.5 mg/dL, a calculated creatinine clearance ≤ 55 mL/min or a urine protein ≥ 100 mg/dL (equivalent to ≥2+ proteinuria) (See CONTRAINDICATIONS).

Geriatric/Gender/Race

The effects of age, gender, and race on cidofovir pharmacokinetics have not been investigated.

INDICATION AND USAGE

VISTIDE is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). THE SAFETY AND EFFICACY OF VISTIDE HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER CMV INFECTIONS (SUCH AS PNEUMONITIS OR GASTROENTERITIS), CONGENITAL OR NEONATAL CMV DISEASE, OR CMV DISEASE IN NON-HIV-INFECTED INDIVIDUALS.

DESCRIPTION OF CLINICAL TRIALS

Three phase II/III controlled trials of VISTIDE have been conducted in HIV-infected patients with CMV retinitis.

Delayed Versus Immediate Therapy (Study 105). In stage 1 of this open-label trial, conducted by the Studies of the Ocular Complications of AIDS (SOCA) Clinical Research Group, 29 previously untreated patients with peripheral CMV retinitis were randomized to either immediate treatment with VISTIDE (5 mg/kg once a week for 2 weeks, then 3 mg/kg every other week) or to have VISTIDE delayed until progression of CMV retinitis[13]. In stage 2 of this trial, an additional 35 previously untreated patients with peripheral CMV retinitis were randomized to either immediate treatment with VISTIDE (5 mg/kg once a week for 2 weeks, then 5 mg/kg every other week) immediate treatment with VISTIDE (5 mg/kg once a week for 2 weeks, then 3 mg/kg every other week), or to have VISTIDE delayed until progression of CMV retinitis. Of the 64 patients in this study, 12 were randomized to 5 mg/kg maintenance therapy, 26 to 3 mg/kg maintenance therapy, and 26 to delayed therapy. Of the 12 patients enrolled in the 5 mg/kg maintenance group, 5 patients progressed, 5 patients discontinued therapy and 2 patients had no progression at study completion. Based on masked readings of retinal photographs, the median [95% confidence interval (CI)] time to retinitis progression was not reached (25, not reached) for the 5 mg/kg maintenance group. Median (95% CI) time to the alternative endpoint of retinitis progression or study drug discontinuation was 44 days (24, 207) for the 5 mg/kg maintenance group. Patients receiving 5 mg/kg maintenance had delayed time to retinitis progression compared to patients receiving 3 mg/kg maintenance or deferred therapy.

Delayed Versus Immediate Therapy (Study 106). In an open-label trial, 48 previously untreated patients with peripheral CMV retinitis were randomized to either immediate treatment with VISTIDE (5 mg/kg once a week for 2 weeks, then 5 mg/kg every other week), or to have VISTIDE delayed until progression of CMV retinitis[14]. Patient baseline characteristics and disposition are shown in Table 3. Of 25 and 23 patients in the immediate and delayed groups respectively, 23 and 21 were evaluable for retinitis progression as determined by retinal photography. Based on masked readings of retinal photographs, the median [95% confidence interval (CI)] times to retinitis progression were 120 days (40, 134) and 22 days (10, 27) for the immediate and delayed therapy groups, respectively. This difference was statistically significant. However, because of the limited number of patients remaining on treatment over time (3 of 25

patients received VISTIDE for 120 days or longer). the median time to progression for the immediate therapy group was difficult to precisely estimate Median (95% CI) times to the alternative endpoint of retinitis progression or study drug discontinuation (including adverse events, withdrawn consent, and systemic CMV disease) were 52 days (37, 85) and 22 days (13, 27) for the immediate and delayed therapy groups, respectively This difference was statistically significant. Time to progression estimates from this study may not be directly comparable to estimates reported for other therapies

Table 3. Patient Characteristics and Disposition (Study 106)

	Immediate Therapy (n = 25)	Delayed Therapy (n = 23)
Baseline Characteristics		
Age (years)	38	38
Sex (M/F)	24/1	22/1
Median CD4 Cell Count	6	9
Endpoints		
CMV Retinitis Progression	10	18
Discontinued Due to Adverse Event	6	0
Withdrew Consent	3[a]	1
Discontinued Due to Intercurrent Illness	2[b]	1[b]
Discontinued Based on Ophthalmological Examination	1[c]	1[c]
No Progression at Study Completion	1	0
Not Evaluable at Baseline	2	2

[a] One patient died 2 weeks after withdrawing consent

[b] Two patients on immediate therapy were diagnosed with CMV disease and discontinued from study One patient on delayed therapy was diagnosed with CMV gastrointestinal disease

[c] CMV retinitis progression not confirmed by retinal photography.

Dose-response study of VISTIDE (Study 107) In an open-label trial, 100 patients with relapsing CMV retinitis were randomized to receive 5 mg/kg once a week for 2 weeks and then either 5 mg/kg (n = 49) or 3 mg/kg (n = 51) every other week Enrolled patients had been diagnosed with CMV retinitis an average of 390 days prior to randomization and had received a median of 3 8 prior courses of systemic CMV therapy Eighty-four of the 100 patients were considered evaluable for progression by serial retinal photographs (43 randomized to 5 mg/kg and 41 randomized to 3 mg/kg) Twenty-six and 21 patients discontinued therapy due to either an adverse event, intercurrent illness, excluded medication, or withdrawn consent in the 5 mg/kg and 3 mg/kg groups, respectively Thirty-eight of the 100 randomized patients had progressed according to masked assessment of serial retinal photographs (13 randomized to 5 mg/kg and 25 randomized to 3 mg/kg) Using retinal photographs, the median (95% CI) times to retinitis progression for the 5 mg/kg and 3 mg/kg groups were 115 days (70, not reached) and 49 days (35, 52), respectively This difference was statistically significant Similar to Study 106, the median time to retinitis progression for the 5 mg/kg group was difficult to precisely estimate due to the limited number of patients remaining on treatment over time (4 of the 49 patients in the 5 mg/kg group were treated for 115 days or longer) Median (95% CI) times to the alternative endpoint of retinitis progression or study drug discontinuation were 49 days (38, 63) and 35 days (27, 39) for the 5 mg/kg and 3 mg/kg groups, respectively This difference was statistically significant.

CONTRAINDICATIONS

Initiation of therapy with VISTIDE is contraindicated in patients with a serum creatinine > 1 5 mg/dL, a calculated creatinine clearance ≤ 55 mL/min, or a urine protein ≥ 100 mg/dL (equivalent to ≥ 2+ proteinuria)

VISTIDE is contraindicated in patients receiving agents with nephrotoxic potential Such agents must be discontinued at least seven days prior to starting therapy with VISTIDE.

VISTIDE is contraindicated in patients with hypersensitivity to cidofovir

VISTIDE is contraindicated in patients with a history of clinically severe hypersensitivity to probenecid or other sulfa-containing medications

Direct intraocular injection of VISTIDE is contraindicated, direct injection of cidofovir has been associated with iritis, ocular hypotony, and permanent impairment of vision

WARNINGS

Nephrotoxicity: Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to VISTIDE administration Cases of acute renal failure resulting in dialysis and/or contributing to death have occurred with as few as one or two doses of VISTIDE Renal function (serum creatinine and urine protein) must be monitored within 48 hours prior to each dose of VISTIDE. Dose adjustment or discontinuation is required for changes in renal function (serum creatinine and/or urine protein) while on therapy. Proteinuria, as measured by urinalysis in a clinical laboratory, may be an early indicator of VISTIDE-related nephrotoxicity Continued administration of VISTIDE may lead to additional proximal tubular cell injury, which may result in glycosuria decreases in serum phosphate, uric acid, and bicarbonate, elevations in serum creatinine, and/or acute renal failure, in some cases, resulting in the need for dialysis Patients with these adverse events occurring concurrently and meeting a criteria of Fanconi's syndrome have been reported Renal function that did not return to baseline after drug discontinuation has been observed in clinical studies of VISTIDE

Intravenous normal saline hydration and oral probenecid must accompany each VISTIDE infusion Probenecid is known to interact with the metabolism or renal tubular excretion of many drugs (see PRECAUTIONS) The safety of VISTIDE has not been evaluated in patients receiving other known potentially nephrotoxic agents, such as intravenous aminoglycosides (e g , tobramycin, gentamicin, and amikacin), amphotericin B, foscarnet, intravenous pentamidine vancomycin, and non-steroidal anti-inflammatory agents (see DOSAGE AND ADMINISTRATION)

Preexisting Renal Impairment: Initiation of therapy with VISTIDE is contraindicated in patients with a baseline serum creatinine > 1 5 mg/dL, a creatinine clearance ≤ 55 mL/min, or a urine protein ≥ 100 mg/dL (equivalent to ≥ 2+ proteinuria).

Hematological Toxicity: Neutropenia may occur during VISTIDE therapy Neutrophil count should be monitored while receiving VISTIDE therapy

Decreased Intraocular Pressure/Ocular Hypotony: Decreased intraocular pressure may occur during VISTIDE therapy, and in some instances has been associated with decreased visual acuity Intraocular pressure should be monitored during VISTIDE therapy

Metabolic Acidosis: Decreased serum bicarbonate associated with proximal tubule injury and renal wasting syndrome (including Fanconi's syndrome) have been reported in patients receiving VISTIDE (see ADVERSE REACTIONS) Cases of metabolic acidosis in association with liver dysfunction and pancreatitis resulting in death have been reported in patients receiving VISTIDE.

PRECAUTIONS

General

Due to the potential for increased nephrotoxicity, doses greater than the recommended dose must not be administered and the frequency or rate of administration must not be exceeded (see DOSAGE AND ADMINISTRATION)

VISTIDE is formulated for intravenous infusion only and must not be administered by intraocular injection Administration of VISTIDE by infusion must be accompanied by oral probenecid and intravenous saline prehydration (see DOSAGE AND ADMINISTRATION).

Uveitis/Iritis

Uveitis or iritis was reported in clinical trials and during postmarketing in patients receiving VISTIDE therapy Treatment with topical corticosteroids with or without topical cycloplegic agents should be considered Patients should be monitored for signs and symptoms of uveitis/iritis during VISTIDE therapy.

Information for Patients

Patients should be advised that VISTIDE is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during and following treatment. Patients receiving VISTIDE should be advised to have regular follow-up ophthalmologic examinations Patients may also experience other manifestations of CMV disease despite VISTIDE therapy

HIV-infected patients may continue taking antiretroviral therapy, but those taking zidovudine should be advised to temporarily discontinue zidovudine administration or decrease their zidovudine dose by 50%, on days of VISTIDE administration only, because probenecid reduces metabolic clearance of zidovudine.

Patients should be informed of the major toxicity of VISTIDE, namely renal impairment, and that dose modification, including reduction, interruption, and possibly discontinuation, may be required Close monitoring of renal function (routine urinalysis and serum creatinine) while on therapy should be emphasized

The importance of completing a full course of probenecid with each VISTIDE dose should be emphasized. Patients should be warned of potential adverse events caused by probenecid (e g , headache, nausea, vomiting, and hypersensitivity reactions) Hypersensitivity/allergic reactions may include rash, fever, chills and anaphylaxis Administration of probenecid after a meal or use of antiemetics may decrease the nausea. Prophylactic or therapeutic antihistamines and/or acetaminophen can be used to ameliorate hypersensitivity reactions

Patients should be advised that cidofovir causes tumors, primarily mammary adenocarcinomas, in rats VISTIDE should be considered a potential carcinogen in humans (See Carcinogenesis, Mutagenesis, & Impairment of Fertility) Women should be advised of the limited enrollment of women in clinical trials of VISTIDE

Patients should be advised that VISTIDE caused reduced testes weight and hypospermia in animals. Such changes may occur in humans and cause infertility Women of childbearing potential should be advised that cidofovir is embryotoxic in animals and should not be used during pregnancy. Women of childbearing potential should be advised to use effective contraception during and for 1 month following treatment with VISTIDE Men should be advised to practice barrier contraceptive methods during and for 3 months after treatment with VISTIDE

Drug Interactions

Probenecid Probenecid is known to interact with the metabolism or renal tubular excretion of many drugs (e g , acetaminophen, acyclovir angiotensin-converting enzyme inhibitors aminosalicylic acid, barbiturates, benzodiazepines bumetanide clofibrate, methotrexate, famotidine, furosemide, nonsteroidal anti-inflammatory agents, theophylline, and zidovudine) Concomitant medications should be carefully assessed Zidovudine should either be temporarily discontinued or decreased by 50% when coadministered with probenecid on the day of VISTIDE infusion

Nephrotoxic agents Concomitant administration of VISTIDE and agents with nephrotoxic potential [e g , intravenous aminoglycosides (e g , tobramycin, gentamicin, and amikacin), amphotericin B, foscarnet, intravenous pentamidine, vancomycin, and non steroidal anti-inflammatory agents] is contraindicated Such agents must be discontinued at least seven days prior to starting therapy with VISTIDE.

Carcinogenesis, Mutagenesis, & Impairment of Fertility

Chronic, two-year carcinogenicity studies in rats and mice have not been carried out to evaluate the carcinogenic potential of cidofovir However, a 26-week toxicology study evaluating once weekly subscapular subcutaneous injections of cidofovir in rats was terminated at 19 weeks because of the induction, in females, of palpable masses the first of which was detected after six doses. The masses were diagnosed as mammary adenocarcinomas which developed at doses as low as 0 6 mg/kg/week, equivalent to 0.04 times the human systemic exposure at the recommended intravenous VISTIDE dose based on AUC comparisons

In a 26-week intravenous toxicology study in which rats received 0 6, 3, or 15 mg/kg cidofovir once weekly, a significant increase in mammary adenocarcinomas in female rats as well as a significant incidence of Zymbal's gland carcinomas in male and female rats were seen at the high dose but not at the lower two doses. The high dose was equivalent to 1 1 times the human systemic exposure at the recommended dose of VISTIDE, based on comparisons of AUC measurements In light of the results of these studies, cidofovir should be considered to be a carcinogen in rats as well as a potential carcinogen in humans.

Cynomolgus monkeys received intravenous cidofovir, alone and in conjunction with concomitant oral probenecid, intravenously once weekly for 52 weeks at doses resulting in exposures of approximately 0.7 times the human systemic exposure at the recommended dose of VISTIDE No tumors were detected. However, the study was not designed as a carcinogenicity study due to the small number of animals at each dose and the short duration of treatment.

No mutagenic response was observed in microbial mutagenicity assays involving *Salmonella typhimurium* (Ames) and *Escherichia coli* in the presence and absence of metabolic activation. An increase in micronucleated polychromatic erythrocytes *in vivo* was seen in mice receiving ≥ 2000 mg/kg, a dosage approximately 65-fold higher than the maximum recommended clinical intravenous VISTIDE dose based on body surface area estimations. Cidofovir induced chromosomal aberrations in human peripheral blood lymphocytes *in vitro* without metabolic activation At the 4 cidofovir levels tested, the percentage of damaged metaphases and number of aberrations per cell increased in a concentration-dependent manner.

Studies showed that cidofovir caused inhibition of spermatogenesis in rats and monkeys However, no adverse effects on fertility or reproduction were seen following once weekly intravenous injections of cidofovir in male rats for 13 consecutive weeks at doses up to 15 mg/kg/week (equivalent to 1 1 times the recommended human dose based on AUC comparisons). Female rats dosed intravenously once weekly at 1 2 mg/kg/week (equivalent to 0.09 times the recommended human dose based on AUC)

or higher, for up to 6 weeks prior to mating and for 2 weeks post mating had decreased litter sizes and live births per litter and increased early resorptions per litter. Peri- and post-natal development studies in which female rats received subcutaneous injections of cidofovir once daily at doses up to 1.0 mg/kg/day from day 7 of gestation through day 21 postpartum (approximately 5 weeks) resulted in no adverse effects on viability, growth, behavior, sexual maturation or reproductive capacity in the offspring.

Pregnancy: Category C

Cidofovir was embryotoxic (reduced fetal body weights) in rats at 1.5 mg/kg/day and in rabbits at 1.0 mg/kg/day, doses which were also maternally toxic, following daily intravenous dosing during the period of organogenesis. The no-observable-effect levels for embryotoxicity in rats (0.5 mg/kg/day) and in rabbits (0.25 mg/kg/day) were approximately 0.04 and 0.05 times the clinical dose (5 mg/kg every other week) based on AUC, respectively. An increased incidence of fetal external, soft tissue and skeletal anomalies (meningocele, short snout, and short maxillary bones) occurred in rabbits at the high dose (1.0 mg/kg/day) which was also maternally toxic. There are no adequate and well-controlled studies in pregnant women. VISTIDE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether cidofovir is excreted in human milk. Since many drugs are excreted in human milk and because of the potential for adverse reactions as well as the potential for tumorigenicity shown for cidofovir in animal studies, VISTIDE should not be administered to nursing mothers. The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Pediatric Use

Safety and effectiveness in children have not been studied. The use of VISTIDE in children with AIDS warrants extreme caution due to the risk of long-term carcinogenicity and reproductive toxicity. Administration of VISTIDE to children should be undertaken only after careful evaluation and only if the potential benefits of treatment outweigh the risks.

Geriatric Use

No studies of the safety or efficacy of VISTIDE in patients over the age of 60 have been conducted. Since elderly individuals frequently have reduced glomerular filtration, particular attention should be paid to assessing renal function before and during VISTIDE administration (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

1. ***Nephrotoxicity:*** Renal toxicity, as manifested by ≥ 2+ proteinuria, serum creatinine elevations of ≥ 0.4 mg/dL, or decreased creatinine clearance ≤ 55 mL/min, occurred in 79 of 135 (59%) patients receiving VISTIDE at a maintenance dose of 5 mg/kg every other week. Maintenance dose reductions from 5 mg/kg to 3 mg/kg due to proteinuria or serum creatinine elevations were made in 12 of 41 (29%) patients who had not received prior therapy for CMV retinitis (Study 106) and in 19 of 74 (26%) patients who had received prior therapy for CMV retinitis (Study 107). Prior foscarnet use has been associated with an increased risk of nephrotoxicity; therefore, such patients must be monitored closely (see CONTRAINDICATIONS, WARNINGS, DOSAGE AND ADMINISTRATION).

- ***Neutropenia:*** In clinical trials, at the 5 mg/kg maintenance dose, a decrease in absolute neutrophil count to ≤ 500 cells/mm^3 occurred in 24% of patients. Granulocyte colony stimulating factor (GCSF) was used in 39% of patients.

- ***Decreased Intraocular Pressure/Ocular Hypotony:*** Among the subset of patients monitored for intraocular pressure changes, a ≥ 50% decrease from baseline intraocular pressure was reported in 17 of 70 (24%) patients at the 5 mg/kg maintenance dose. Severe hypotony (intraocular pressure of 0-1 mm Hg) has been reported in 3 patients. Risk of ocular hypotony may be increased in patients with preexisting diabetes mellitus.

- ***Anterior Uveitis/Iritis:*** Uveitis or iritis has been reported in clinical trials and during postmarketing in patients receiving VISTIDE therapy. Uveitis or iritis was reported in 15 of 135 (11%) patients receiving 5 mg/kg maintenance dosing. Treatment with topical corticosteroids with or without topical cycloplegic agents may be considered. Patients should be monitored for signs and symptoms of uveitis/iritis during VISTIDE therapy.

- ***Metabolic Acidosis:*** A diagnosis of Fanconi's syndrome, as manifested by multiple abnormalities of proximal renal tubular function, was reported in 1% of patients. Decreases in serum bicarbonate to ≤ 16 mEq/L occurred in 16% of cidofovir-treated patients. Cases of metabolic acidosis in association with liver dysfunction and pancreatitis resulting in death have been reported in patients receiving VISTIDE.

In clinical trials, VISTIDE was withdrawn due to adverse events in 39% of patients treated with 5 mg/kg every other week as maintenance therapy.

The incidence of adverse reactions reported as serious in three controlled clinical studies in patients with CMV retinitis, regardless of presumed relationship to drug, is listed in Table 4.

Table 4. Serious Clinical Adverse Events or Laboratory Abnormalities Occurring in > 5% of Patients

	N = 135[a] # patients (%)
Proteinuria (≥ 100 mg/dL)	68 (50)
Neutropenia (≤ 500 cells/mm^3)	33 (24)
Decreased Intraocular Pressure[b]	17 (24)
Decreased Serum Bicarbonate (≤ 16 mEq/L)	21 (16)
Fever	19 (14)
Infection	16 (12)
Creatinine Elevation (≥ 2.0 mg/dL)	16 (12)
Pneumonia	12 (9)
Dyspnea	11 (8)
Nausea with Vomiting	10 (7)

[a] Patients receiving 5 mg/kg maintenance regimen in Studies 105, 106 and 107.

[b] Defined as decreased intraocular pressure (IOP) to ≤ 50% that at baseline. Based on 70 patients receiving 5 mg/kg maintenance dosing (Studies 105, 106 and 107), for whom baseline and follow-up IOP determinations were recorded.

The most frequently reported adverse events regardless of relationship to study drugs (cidofovir or probenecid) or severity are shown in Table 5.

The following additional list of adverse events/intercurrent illnesses have been observed in clinical studies of VISTIDE and are listed below regardless of causal relationship to VISTIDE. Evaluation of these reports was difficult because of the diverse manifestations of the underlying disease and because most patients received numerous concomitant medicines.

Body as a Whole: abdominal pain, accidental injury, AIDS, allergic reaction, back pain, catheter blocked, cellulitis, chest pain, chills and fever, cryptococcosis, cyst, death, face edema, flu-like syndrome, hypothermia, injection site reaction, malaise, mucous membrane disorder, neck pain, overdose, photosensitivity reaction, sarcoma, sepsis.

Cardiovascular System: cardiomyopathy, cardiovascular disorder, congestive heart failure, hypertension, hypotension, migraine, pallor, peripheral vascular disorder, phlebitis, postural hypotension, shock, syncope, tachycardia, vascular disorder, edema.

Digestive System: cholangitis, colitis, constipation, esophagitis, dyspepsia, dysphagia, fecal incontinence, flatulence, gastritis, gastrointestinal hemorrhage, gingivitis, hepatitis, hepatomegaly, hepatosplenomegaly, jaundice, abnormal liver function, liver damage, liver necrosis, melena, pancreatitis, proctitis, rectal disorder, stomatitis, aphthous stomatitis, tongue discoloration, mouth ulceration, tooth caries.

Endocrine System: adrenal cortex insufficiency.

Hemic & Lymphatic System: hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, lymphoma like reaction, pancytopenia, splenic disorder, splenomegaly, thrombocytopenia, thrombocytopenic purpura.

Metabolic & Nutritional System: cachexia, dehydration, edema, hypercalcemia, hyperglycemia, hyperkalemia, hyperlipemia, hypocalcemia, hypoglycemia, hypoglycemic reaction, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, increased alkaline phosphatase, increased BUN, increased lactic dehydrogenase, increased SGOT, increased SGPT, peripheral edema, respiratory alkalosis, thirst, weight loss, weight gain.

Musculoskeletal System: arthralgia, arthrosis, bone necrosis, bone pain, joint disorder, leg cramps, myalgia, myasthenia, pathological fracture.

Nervous System: abnormal dreams, abnormal gait, acute brain syndrome, agitation, amnesia, anxiety, ataxia, cerebrovascular disorder, confusion, convulsion, delirium, dementia, depression, dizziness, drug dependence, dry mouth, encephalopathy, facial paralysis, hallucinations, hemiplegia, hyperesthesia, hypertonia, hypotony, incoordination, increased libido, insomnia, myoclonus, nervousness, neuropathy, paresthesia, personality disorder, somnolence, speech disorder, tremor, twitching, vasodilatation, vertigo.

Respiratory System: asthma, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, hypoxia, increased sputum, larynx edema, lung disorder, pharyngitis, pneumothorax, rhinitis, sinusitis.

Skin & Appendages: acne, angioedema, dry skin, eczema, exfoliative dermatitis, furunculosis, herpes simplex, nail disorder, pruritus, rash, seborrhea, skin discoloration, skin disorder, skin hypertrophy, skin ulcer, sweating, urticaria.

Special Senses: abnormal vision, amblyopia, blindness, cataract, conjunctivitis, corneal lesion, corneal opacity, diplopia, dry eyes, ear disorder, ear pain, eye disorder, eye pain, hyperacusis, iritis, keratitis, miosis, otitis externa, otitis media, refraction disorder, retinal detachment, retinal disorder, taste perversion, tinnitus, uveitis, visual field defect, hearing loss.

Urogenital System: decreased creatinine clearance, dysuria, glycosuria, hematuria, kidney stone, mastitis, metorrhagia, nocturia, polyuria, prostatic disorder, toxic nephropathy, urethritis, urinary casts, urinary incontinence, urinary retention, urinary tract infection.

Table 5. All Clinical Adverse Events, Laboratory Abnormalities or Intercurrent Illnesses Regardless of Severity Occurring in > 15% of Patients

	N = 115[a] # patients (%)
Any Adverse Event	115 (100)
Proteinuria (≥ 30 mg/dL)	101 (88)
Nausea +/- Vomiting	79 (69)
Fever	67 (58)
Neutropenia (< 750 cells/mm^3)	50 (43)
Asthenia	50 (43)
Headache	34 (30)
Rash	34 (30)
Infection	32 (28)
Alopecia	31 (27)
Diarrhea	30 (26)
Pain	29 (25)
Creatinine Elevation (> 1.5 mg/dL)	28 (24)
Anemia	28 (24)
Anorexia	26 (23)
Dyspnea	26 (23)
Chills	25 (22)
Increased Cough	22 (19)
Oral Moniliasis	21 (18)

[a] Patients receiving 5 mg/kg maintenance regimen in Studies 106 and 107.

Reporting of Adverse Reactions

Malignancies or serious adverse reactions that occur in patients who have received VISTIDE should be reported to Gilead in writing to the Director of Clinical Research, Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 or by calling 1-800-GILEAD-5 (445-3235), or to FDA MedWatch 1-800-FDA-1088/fax 1-800-FDA-0178.

OVERDOSAGE

Two cases of cidofovir overdose have been reported. These patients received single doses of VISTIDE at 16.3 mg/kg and 17.4 mg/kg, respectively, with concomitant oral probenecid and intravenous hydration. In both cases, the patients were hospitalized and received oral probenecid (one gram three times daily) and vigorous intravenous hydration with normal saline for 3 to 5 days. Significant changes in renal function were not observed in either patient.

DOSAGE AND ADMINISTRATION

VISTIDE MUST NOT BE ADMINISTERED BY INTRAOCULAR INJECTION.

Dosage

THE RECOMMENDED DOSAGE, FREQUENCY, OR INFUSION RATE MUST NOT BE

EXCEEDED VISTIDE MUST BE DILUTED IN 100 MILLILITERS 0 9% (NORMAL) SALINE PRIOR TO ADMINISTRATION TO MINIMIZE POTENTIAL NEPHROTOXICITY, PROBENECID AND INTRAVENOUS SALINE PREHYDRATION MUST BE ADMINISTERED WITH EACH VISTIDE INFUSION

Induction Treatment The recommended induction dose of VISTIDE for patients with a serum creatinine of ≤ 1 5 mg/dL, a calculated creatinine clearance > 55 mL/min, and a urine protein < 100 mg/dL (equivalent to < 2+ proteinuria) is 5 mg/kg body weight (given as an intravenous infusion at a constant rate over 1 hr) administered once weekly for two consecutive weeks Because serum creatinine in patients with advanced AIDS and CMV retinitis may not provide a complete picture of the patient's underlying renal status, it is important to utilize the Cockcroft-Gault formula to more precisely estimate creatinine clearance (CrCl) As creatinine clearance is dependent on serum creatinine and patient weight, it is necessary to calculate clearance prior to initiation of VISTIDE CrCl (mL/min) should be calculated according to the following formula.

$$\text{Creatinine clearance for males} = \frac{[140\text{-age (years)}] \times [\text{body wt (kg)}]}{72 \times [\text{serum creatinine (mg/dL)}]}$$

$$\text{Creatinine clearance for females} = \frac{[140\text{-age (years)}] \times [\text{body wt (kg)}] \times 0.85}{72 \times [\text{serum creatinine (mg/dL)}]}$$

Maintenance Treatment The recommended maintenance dose of VISTIDE is 5 mg/kg body weight (given as an intravenous infusion at a constant rate over 1 hr), administered once every 2 weeks

Dose Adjustment

Changes in Renal Function During VISTIDE Therapy The maintenance dose of VISTIDE must be reduced from 5 mg/kg to 3 mg/kg for an increase in serum creatinine of 0 3 - 0 4 mg/dL above baseline. VISTIDE therapy must be discontinued for an increase in serum creatinine of ≥ 0 5 mg/dL above baseline or development of ≥ 3+ proteinuria.

Preexisting Renal Impairment VISTIDE is contraindicated in patients with a serum creatinine concentration > 1.5 mg/dL, a calculated creatinine clearance ≤ 55 mL/min, or a urine protein ≥ 100 mg/dL (equivalent to ≥ 2+ proteinuria)

Probenecid Probenecid must be administered orally with each VISTIDE dose Two grams must be administered 3 hr prior to the VISTIDE dose and one gram administered at 2 and again at 8 hr after completion of the 1 hr VISTIDE infusion (for a total of 4 grams)

Ingestion of food prior to each dose of probenecid may reduce drug-related nausea and vomiting. Administration of an antiemetic may reduce the potential for nausea associated with probenecid ingestion. In patients who develop allergic or hypersensitivity symptoms to probenecid, the use of an appropriate prophylactic or therapeutic antihistamine and/or acetaminophen should be considered (see CONTRAINDICATIONS).

Hydration Patients must receive at least one liter of 0 9% (normal) saline solution intravenously with each infusion of VISTIDE. The saline solution should be infused over a 1-2 hr period immediately before the VISTIDE infusion. Patients who can tolerate the additional fluid load should receive a second liter If administered, the second liter of saline should be initiated either at the start of the VISTIDE infusion or immediately afterwards, and infused over a 1 to 3 hr period

Method of Preparation and Administration

Inspect vials visually for particulate matter and discoloration prior to administration If particulate matter or discoloration is observed, the vial should not be used With a syringe, extract the appropriate volume of VISTIDE from the vial and transfer the dose to an infusion bag containing 100 mL 0.9% (normal) saline solution. Infuse the entire volume intravenously into the patient at a constant rate over a 1 hr period Use of a standard infusion pump for administration is recommended.

It is recommended that VISTIDE infusion admixtures be administered within 24 hr of preparation and that refrigerator or freezer storage not be used to extend this 24 hr limit

If admixtures are not intended for immediate use, they may be stored under refrigeration (2-8°C) for no more than 24 hr. Refrigerated admixtures should be allowed to equilibrate to room temperature prior to use

The chemical stability of VISTIDE admixtures was demonstrated in polyvinyl chloride composition and ethylene/propylene copolymer composition commercial infusion bags, and in glass bottles **No data are available to support the addition of other drugs or supplements to the cidofovir admixture for concurrent administration.**

VISTIDE is supplied in single-use vials Partially used vials should be discarded (see Handling and Disposal)

Compatibility with Ringer's solution, Lactated Ringer's solution or bacteriostatic infusion fluids has not been evaluated.

Handling and Disposal

Due to the mutagenic properties of cidofovir, adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration, and disposal of VISTIDE The National Institutes of Health presently recommends that such agents be prepared in a Class II laminar flow biological safety cabinet and that personnel preparing drugs of this class wear surgical gloves and a closed front surgical-type gown with knit cuffs If VISTIDE contacts the skin, wash membranes and flush thoroughly with water Excess VISTIDE and all other materials used in the admixture preparation and administration should be placed in a leak-proof, puncture-proof container. The recommended method of disposal is high temperature incineration

Patient Monitoring

Serum creatinine and urine protein must be monitored within 48 hours prior to each dose White blood cell counts with differential should be monitored prior to each dose In patients with proteinuria, intravenous hydration should be administered and the test repeated Intraocular pressure, visual acuity and ocular symptoms should be monitored periodically

HOW SUPPLIED

VISTIDE (cidofovir injection) 75 mg/mL for intravenous infusion, is supplied as a non-preserved solution in single-use clear glass vials as follows

NDC 61958-0101-1 375 mg in a 5 mL vial in a single-unit carton

VISTIDE should be stored at controlled room temperature 20°-25°C (68°-77°F)

CAUTION Federal law prohibits dispensing without prescription

Manufactured by
Ben Venue Laboratories, Inc
Bedford, OH 44146-0568

Manufactured for and distributed by
Gilead Sciences, Inc
333 Lakeside Drive
Foster City, CA 94404

VISTIDE® (cidofovir injection) is covered by U.S Patent No 5,142,051 and its foreign counterparts Other patents pending.

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58-0866

-R13-Rev. June, 2000

700571-11

FOSCAVIR®

(foscarnet sodium) Injection

Rx only

WARNING

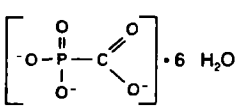
RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF FOSCAVIR. FREQUENT MONITORING OF SERUM CREATININE, WITH DOSE ADJUSTMENT FOR CHANGES IN RENAL FUNCTION, AND ADEQUATE HYDRATION WITH ADMINISTRATION OF FOSCAVIR, IS IMPERATIVE. (See ADMINISTRATION section; Hydration.)

SEIZURES, RELATED TO ALTERATIONS IN PLASMA MINERALS AND ELECTROLYTES, HAVE BEEN ASSOCIATED WITH FOSCAVIR TREATMENT. THEREFORE, PATIENTS MUST BE CAREFULLY MONITORED FOR SUCH CHANGES AND THEIR POTENTIAL SEQUELAE. MINERAL AND ELECTROLYTE SUPPLEMENTATION MAY BE REQUIRED.

FOSCAVIR IS INDICATED FOR USE ONLY IN IMMUNOCOMPROMISED PATIENTS WITH CMV RETINITIS AND MUCOCUTANEOUS ACYCLOVIR-RESISTANT HSV INFECTIONS. (See INDICATIONS section.)

DESCRIPTION

FOSCAVIR is the brand name for foscarnet sodium. The chemical name of foscarnet sodium is phosphonoformic acid, trisodium salt. Foscarnet sodium is a white crystalline powder containing 6 equivalents of water of hydration with an empirical formula of $Na_3CO_5P \cdot 6\ H_2O$ and a molecular weight of 300.1. The structural formula is



FOSCAVIR has the potential to chelate divalent metal ions, such as calcium and magnesium, to form stable coordination compounds. FOSCAVIR INJECTION is a sterile, isotonic aqueous solution for intravenous administration only. The solution is clear and colorless. Each milliliter of FOSCAVIR contains 24 mg of foscarnet sodium hexahydrate in Water for Injection USP. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH of the solution to 7.4. FOSCAVIR INJECTION contains no preservatives.

VIROLOGY

Mechanism of Action: FOSCAVIR is an organic analogue of inorganic pyrophosphate that inhibits replication of herpesviruses *in vitro* including cytomegalovirus (CMV) and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).

FOSCAVIR exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerases at concentrations that do not affect cellular DNA polymerases. FOSCAVIR does not require activation (phosphorylation) by thymidine kinase or other kinases and therefore is active *in vitro* against HSV TK deficient mutants and CMV UL97 mutants. Thus, HSV strains resistant to acyclovir or CMV strains resistant to ganciclovir may be sensitive to FOSCAVIR. However, acyclovir or ganciclovir resistant mutants with alterations in the viral DNA polymerase may be resistant to FOSCAVIR and may not respond to therapy with FOSCAVIR. The combination of FOSCAVIR and ganciclovir has been shown to have enhanced activity *in vitro*.

Antiviral Activity *in vitro* and *in vivo*: The quantitative relationship between the *in vitro* susceptibility of human cytomegalovirus (CMV) or herpes simplex virus 1 and 2 (HSV-1 and HSV-2) to FOSCAVIR and clinical response to therapy has not been established and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending on the assay method used, cell type employed and the laboratory performing the test. A number of sensitive viruses and their IC_{50} values are listed below (Table 1).

TABLE 1

FOSCARNET Inhibition of virus multiplication in cell culture	
Virus	IC_{50} (μM)
CMV	50–800*
HSV-1, HSV-2	10–130
Ganciclovir resistant CMV	190
HSV-TK negative mutant	67
HSV-DNA polymerase mutants	5–443

* Mean = 269 μM

Statistically significant decreases in positive CMV cultures from blood and urine have been demonstrated in two studies (FOS-03 and ACTG-015/915) of patients treated with FOSCAVIR. Although median time to progression of CMV retinitis was increased in patients treated with FOSCAVIR, reductions in positive blood or urine cultures have not been shown to correlate with clinical efficacy in individual patients.

TABLE 2

BLOOD AND URINE CULTURE RESULTS FROM CMV RETINITIS PATIENTS*

Blood	+CMV	-CMV
Baseline	27	34
End of Induction**	1	60
Urine	**+CMV**	**-CMV**
Baseline	52	6
End of Induction**	21	37

* A total of 77 patients was treated with FOSCAVIR in two clinical trials (FOS-03 and ACTG-015/915). Not all patients had blood or urine cultures done and some patients had results from both cultures.

** (60 mg/kg FOSCAVIR TID for 2–3 weeks)

Resistance: Strains of both HSV and CMV that are resistant to FOSCAVIR can be readily selected *in vitro* by passage of wild type virus in the presence of increasing concentrations of the drug. All FOSCAVIR resistant mutants are known to be generated through mutation in the viral DNA polymerase gene. CMV strains with double mutations conferring resistance to both FOSCAVIR and ganciclovir have been isolated from patients with AIDS. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetics of foscarnet have been determined after administration as an intermittent intravenous infusion during induction therapy in AIDS patients with CMV retinitis. Observed plasma foscarnet concentrations in four studies (FOS-01, ACTG-015, FP48PK, FP49PK) are summarized in Table 3.

TABLE 3

Foscarnet Pharmacokinetic Characteristics*

Parameter	60 mg/kg Q8h	90 mg/kg Q12h
C_{max} at steady-state (μM)	589 ± 192 (24)	623 ± 132 (19)
C_{trough} at steady-state (μM)	114 ± 91 (24)	63 ± 57 (17)
Volume of distribution (L/kg)	0.41 ± 0.13 (12)	0.52 ± 0.20 (18)
Plasma half-life (hr)	4.0 ± 2.0 (24)	3.3 ± 1.4 (18)
Systemic clearance (L/hr)	6.2 ± 2.1 (24)	7.1 ± 2.7 (18)
Renal clearance (L/hr)	5.6 ± 1.9 (5)	6.4 ± 2.5 (13)
CSF:plasma ratio	0.69 ± 0.19 (9)†	0.66 ± 0.11 (5)‡

* Values expressed as mean ± S.D. (number of subjects studied) for each parameter.

† 50 mg/kg Q8h for 28 days, samples taken 3 hrs after end of 1 hr infusion (Astra Report 815-04 AC025-1)

‡ 90 mg/kg Q12h for 28 days, samples taken 1 hr after end of 2 hr infusion (Hengge et al., 1993)

Distribution: *In vitro* studies have shown that 14 – 17% of foscarnet is protein bound at plasma drug concentrations of 1 – 1000 μM.

The foscarnet terminal half-life determined by urinary excretion was 87.5 ± 41.8 hours, possibly due to release of foscarnet from bone. Postmortem data on several patients in European clinical trials provide evidence that foscarnet does accumulate in bone in humans, however, the extent to which this occurs has not been determined. In animal studies (mice), 40% of an intravenous dose of FOSCAVIR was deposited in bone in young animals and 7% was deposited in adult animals.

Special Populations:

Adults with Impaired Renal Function: The pharmacokinetic properties of foscarnet have been determined in a small group of adult subjects with normal and impaired renal function, as summarized in Table 4.

TABLE 4

Pharmacokinetic Parameters (mean ± S.D.) After a Single 60 mg/kg Dose of FOSCAVIR in 4 Groups* of Adults with Varying Degrees of Renal Function

Parameter	Group 1 (N=6)	Group 2 (N=6)	Group 3 (N=6)	Group 4 (N=4)
Creatinine clearance (mL/min)	108 ± 16	68 ± 8	34 ± 9	20 ± 4
Foscarnet CL (mL/min/kg)	2.13 ± 0.71	1.33 ± 0.43	0.46 ± 0.14	0.43 ± 0.26
Foscarnet half-life (hr)	1.93 ± 0.12	3.35 ± 0.87	13.0 ± 4.05	25.3 ± 18.7

* Group 1 patients had normal renal function defined as a creatinine clearance (CrCl) of >80 mL/min. Group 2 CrCl was 50 – 80 mL/min. Group 3 CrCl was 25 – 49 mL/min and Group 4 CrCl was 10 – 24 mL/min.

Total systemic clearance (CL) of foscarnet decreased and half-life increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of foscarnet in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

CMV Retinitis. A prospective, randomized, controlled clinical trial (FOS-03) was conducted in 24 patients with AIDS and CMV retinitis comparing treatment with FOSCAVIR to no treatment. Patients received induction treatment of FOSCAVIR, 60 mg/kg every 8 hours for 3 weeks, followed by maintenance treatment with 90 mg/kg/day until retinitis progression (appearance of a new lesion or advancement of the border of a posterior lesion greater than 750 microns in diameter). All diagnoses and determinations of retinitis progression were made from masked reading of retinal photographs. The 13 patients randomized to treatment with FOSCAVIR had a significant delay in progression of CMV retinitis compared to untreated controls. Median times to retinitis progression from study entry were 93 days (range 21 – >364) and 22 days (range 7 – 42), respectively.

In another prospective clinical trial of CMV retinitis in patients with AIDS (ACTG-915), 33 patients were treated with two to three weeks of FOSCAVIR induction (60 mg/kg TID) and then randomized to either 90 mg/kg/day or 120 mg/kg/day maintenance therapy. The median times from study entry to retinitis progression were not significantly different between the treatment groups: 96 (range 14 – >176) days and 140 (range 16 – >233) days, respectively.

In study ACTG 129/FGCRT SOCA study 107 patients with newly diagnosed CMV retinitis were randomized to treatment with FOSCAVIR (induction, 60 mg/kg TID for 2 weeks, maintenance 90 mg/kg QD) and 127 were randomized to treatment with ganciclovir (induction 5 mg/kg BID, maintenance 5 mg/kg QD) The median time to progression on the two drugs was similar (Fos=59 and Gcv=56 days)

Relapsed CMV Retinitis: The CMV Retinitis Retreatment Trial (ACTG 228/SOCA CRRT) was a randomized, open-label comparison of FOSCAVIR or ganciclovir monotherapy to the combination of both drugs for the treatment of persistently active or relapsed CMV retinitis in patients with AIDS Subjects were randomized to one of the three treatments FOSCAVIR 90 mg/kg BID induction followed by 120 mg/kg QD maintenance (Fos), ganciclovir 5 mg/kg BID induction followed by 10 mg/kg QD maintenance (Gcv), or the combination of the two drugs, consisting of continuation of the subject's current therapy and induction dosing of the other drug (as above), followed by maintenance with FOSCAVIR 90 mg/kg QD plus ganciclovir 5 mg/kg QD (Cmb) Assessment of retinitis progression was performed by masked evaluation of retinal photographs The median times to retinitis progression or death were 39 days for the FOSCAVIR group, 61 days for the ganciclovir group and 105 days for the combination group For the alternative endpoint of retinitis progression (censoring on death), the median times were 39 days for the FOSCAVIR group, 61 days for the ganciclovir group and 132 days for the combination group Due to censoring on death, the latter analysis may overestimate the treatment effect Treatment modifications due to toxicity were more common in the combination group than in the FOSCAVIR or ganciclovir monotherapy groups (see ADVERSE REACTIONS section)

Mucocutaneous Acyclovir-Resistant HSV Infections: In a controlled trial, patients with AIDS and mucocutaneous, acyclovir-resistant HSV infection were randomized to either FOSCAVIR (N=8) at a dose of 40 mg/kg TID or vidarabine (N=6) at a dose of 15 mg/kg per day Eleven patients were non-randomly assigned to receive treatment with FOSCAVIR because of prior intolerance to vidarabine Lesions in the eight patients randomized to FOSCAVIR healed after 11 to 25 days; seven of the 11 patients non-randomly treated with FOSCAVIR healed their lesions in 10 to 30 days Vidarabine was discontinued because of intolerance (N=4) or poor therapeutic response (N=2) In a second trial forty AIDS patients and three bone marrow transplant recipients with mucocutaneous, acyclovir-resistant HSV infections were randomized to receive FOSCAVIR at a dose of either 40 mg/kg BID or 40 mg/kg TID Fifteen of the 43 patients had healing of their lesions in 11 to 72 days with no difference in response between the two treatment groups

INDICATIONS

CMV Retinitis: FOSCAVIR is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) Combination therapy with FOSCAVIR and ganciclovir is indicated for patients who have relapsed after monotherapy with either drug SAFETY AND EFFICACY OF FOSCAVIR HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER CMV INFECTIONS (e g PNEUMONITIS GASTROENTERITIS) CONGENITAL OR NEONATAL CMV DISEASE OR NON-IMMUNOCOMPROMISED INDIVIDUALS

Mucocutaneous Acyclovir-Resistant HSV Infections: FOSCAVIR is indicated for the treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients SAFETY AND EFFICACY OF FOSCAVIR HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER HSV INFECTIONS (e g , RETINITIS, ENCEPHALITIS), CONGENITAL OR NEONATAL HSV DISEASE, OR HSV IN NON-IMMUNOCOMPROMISED INDIVIDUALS

CONTRAINDICATIONS

FOSCAVIR is contraindicated in patients with clinically significant hypersensitivity to foscarnet sodium

WARNINGS

Renal Impairment: THE MAJOR TOXICITY OF FOSCAVIR IS RENAL IMPAIRMENT (see ADVERSE REACTIONS section) Renal impairment is most likely to become clinically evident during the second week of induction therapy but may occur at any time during FOSCAVIR treatment Renal function should be monitored carefully during both induction and maintenance therapy (see PATIENT MONITORING section) Elevations in serum creatinine are usually but not always reversible following discontinuation or dose adjustment of FOSCAVIR Safety and efficacy data for patients with baseline serum creatinine levels greater than 2 8 mg/dL or measured 24-hour creatinine clearances <50 mL/min are limited

BECAUSE OF FOSCAVIR'S POTENTIAL TO CAUSE RENAL IMPAIRMENT, DOSE ADJUSTMENT BASED ON SERUM CREATININE IS NECESSARY Hydration may reduce the risk of nephrotoxicity It is recommended that 750–1000 mL of normal saline or 5% dextrose solution should be given prior to the first infusion of FOSCAVIR to establish diuresis With subsequent infusions, 750–1000 mL of hydration fluid should be given with 90-120 mg/kg of FOSCAVIR, and 500 mL with 40–60 mg/kg of FOSCAVIR Hydration fluid may need to be decreased if clinically warranted

After the first dose the hydration fluid should be administered concurrently with each infusion of FOSCAVIR

Mineral and Electrolyte Abnormalities: FOSCAVIR has been associated with changes in serum electrolytes including hypocalcemia hypophosphatemia, hyperphosphatemia hypomagnesemia and hypokalemia (see ADVERSE REACTIONS section) FOSCAVIR may also be associated with a dose-related decrease in ionized serum calcium which may not be reflected in total serum calcium This effect is likely to be related to chelation of divalent metal ions such as calcium by foscarnet Patients should be advised to report symptoms of low ionized calcium such as perioral tingling, numbness in the extremities and paresthesias Particular caution and careful management of serum electrolytes is advised in patients with altered calcium or other electrolyte levels before treatment and especially in those with neurologic or cardiac abnormalities and those receiving other drugs known to influence minerals and electrolytes (see PATIENT MONITORING and Drug Interactions sections) Physicians should be prepared to treat these abnormalities and their sequelae such as tetany seizures or cardiac disturbances The rate of FOSCAVIR infusion may also affect the decrease in ionized calcium **Therefore, an infusion pump must be used for administration to prevent rapid intravenous infusion (see DOSAGE AND ADMINISTRATION section).** Slowing the infusion rate may decrease or *prevent symptoms*

Seizures: Seizures related to mineral and electrolyte abnormalities have been associated with FOSCAVIR treatment (see WARNING section, Mineral and Electrolyte Abnormalities) Several cases of seizures were associated with death Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions

PRECAUTIONS

General: Care must be taken to infuse solutions containing FOSCAVIR only into veins with adequate blood flow to permit rapid dilution and distribution to avoid local irritation (see DOSAGE AND ADMINISTRATION) Local irritation and ulcerations of penile epithelium have been reported in male patients receiving FOSCAVIR, possibly related to the presence of drug in the urine One case of vulvovaginal ulcerations in a female receiving FOSCAVIR has been reported Adequate hydration with close attention to personal hygiene may minimize the occurrence of such events

Hemopoietic System: Anemia has been reported in 33% of patients receiving FOSCAVIR in controlled studies Granulocytopenia has been reported in 17% of patients receiving FOSCAVIR in controlled studies however, only 1% (2/189) were terminated from these studies because of neutropenia

Information for Patients

CMV Retinitis Patients should be advised that FOSCAVIR is not a cure for CMV retinitis and that they may continue to experience progression of retinitis during or following treatment They should be advised to have regular ophthalmologic examinations

Mucocutaneous Acyclovir-Resistant HSV Infections Patients should be advised that FOSCAVIR is not a cure for HSV infections While complete healing is possible, relapse occurs in most patients Because relapse may be due to acyclovir-sensitive HSV, sensitivity testing of the viral isolate is advised In addition, repeated treatment with FOSCAVIR has led to the development of resistance associated with poorer response In the case of poor therapeutic response, sensitivity testing of the viral isolate also is advised

General Patients should be informed that the major toxicities of foscarnet are renal impairment electrolyte disturbances, and seizures, and that dose modifications and possibly discontinuation may be required The importance of close monitoring while on therapy must be emphasized Patients should be advised of the importance of reporting to their physicians symptoms of perioral tingling numbness in the extremities or paresthesias during or after infusion as possible symptoms of electrolyte abnormalities Should such symptoms occur the infusion of FOSCAVIR should be stopped, appropriate laboratory samples for assessment of electrolyte concentrations obtained and a physician consulted before resuming treatment The rate of infusion must be no more than 1 mg/kg/minute The potential for renal impairment may be minimized by accompanying FOSCAVIR administration with hydration adequate to establish and maintain a diuresis during dosing

Drug Interactions: A possible drug interaction of FOSCAVIR and intravenous pentamidine has been described. Concomitant treatment of four patients in the United Kingdom with FOSCAVIR and intravenous pentamidine may have caused hypocalcemia; one patient died with severe hypocalcemia. Toxicity associated with concomitant use of aerosolized pentamidine has not been reported.

Because of foscarnet's tendency to cause renal impairment, the use of FOSCAVIR should be avoided in combination with potentially nephrotoxic drugs such as aminoglycosides, amphotericin B and intravenous pentamidine (see above) unless the potential benefits outweigh the risks to the patient

Abnormal renal function has been observed in clinical practice during the use of FOSCAVIR and ritonavir, or FOSCAVIR, ritonavir, and saquinavir (See DOSAGE and ADMINISTRATION)

Since FOSCAVIR decreases serum concentrations of ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with particular caution

Ganciclovir The pharmacokinetics of foscarnet and ganciclovir were not altered in 13 patients receiving either concomitant therapy or daily alternating therapy for maintenance of CMV disease

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in rats and mice at oral doses of 500 mg/kg/day and 250 mg/kg/day. Oral bioavailability in unfasted rodents is < 20% No evidence of oncogenicity was reported at plasma drug levels equal to 1/3 and 1/5 respectively, of those in humans (at the maximum recommended human daily dose) as measured by the area-under-the-time/concentration curve (AUC)

FOSCAVIR showed genotoxic effects in the BALB/3T3 *in vitro* transformation assay at concentrations greater than 0 5 mcg/mL and an increased frequency of chromosome aberrations in the sister chromatid exchange assay at 1000 mcg/mL A high dose of foscarnet (350 mg/kg) caused an increase in micronucleated polychromatic erythrocytes *in vivo* in mice at doses that produced exposures (area under curve) comparable to that anticipated clinically

Pregnancy: Teratogenic Effect

Pregnancy Category C FOSCAVIR did not adversely affect fertility and general reproductive performance in rats The results of pen- and post-natal studies in rats were also negative However these studies used exposures that are inadequate to define the potential for impairment of fertility at human drug exposure levels

Daily subcutaneous doses up to 75 mg/kg administered to female rats prior to and during mating during gestation, and 21 days post-partum caused a slight increase (< 5%) in the number of skeletal anomalies compared with the control group Daily subcutaneous doses up to 75 mg/kg administered to rabbits and 150 mg/kg administered to rats during gestation caused an increase in the frequency of skeletal anomalies/variations On the basis of estimated drug exposure (as measured by AUC), the 150 mg/kg dose in rats and 75 mg/kg dose in rabbits were approximately one-eighth (rat) and one-third (rabbit) the estimated maximal daily human exposure These studies are inadequate to define the potential teratogenicity at levels to which women will be exposed

There are no adequate and well controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, FOSCAVIR should be used during pregnancy only if clearly needed

Nursing Mothers: It is not known whether FOSCAVIR is excreted in human milk, however in lactating rats administered 75 mg/kg FOSCAVIR was excreted in maternal milk at concentrations three times higher than peak maternal blood concentrations

Pediatric Use: The safety and effectiveness of FOSCAVIR in pediatric patients have not been established FOSCAVIR is deposited in teeth and bone and deposition is greater in young and growing animals FOSCAVIR has been demonstrated to adversely affect development of tooth enamel in mice and rats The effects of this deposition on skeletal development have not been studied Since deposition in human bone has also been shown to occur, it is likely that it does so to a greater degree in developing bone in pediatric patients Administration to pediatric patients should be undertaken only after careful evaluation and only if the potential benefits for treatment outweigh the risks

Geriatric Use: No studies of the efficacy or safety of FOSCAVIR in persons 65 years of age or older have been conducted However, FOSCAVIR has been used in patients age 65 years of age and older The pattern of adverse events seen in these patients is consistent across all age groups This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored (See DOSAGE AND ADMINISTRATION)

ADVERSE REACTIONS

THE MAJOR TOXICITY OF FOSCAVIR IS RENAL IMPAIRMENT (see WARNINGS section) Approximately 33% of 189 patients with AIDS and CMV retinitis who received FOSCAVIR (60 mg/kg TID), without adequate hydration developed significant impairment of renal function (serum creatinine ≥ 2 0 mg/dL) The incidence of renal impairment in subsequent clinical trials in which 1000 mL of normal saline or 5% dextrose solution was given with each infusion of FOSCAVIR was 12% (34/280)

FOSCAVIR has been associated with changes in serum electrolytes including hypocalcemia (15–30%) hypophosphatemia (8–26%) and hyperphosphatemia (6%) hypomagnesemia (15–30%) and hypokalemia (16–48%) (see WARNINGS section) The higher percentages were derived from those patients receiving hydration

FOSCAVIR treatment was associated with seizures in 18/189 (10%) AIDS patients in the initial five controlled studies (see WARNINGS section). Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions predisposing the patient to seizures. The rate of seizures did not increase with duration of treatment. Three cases were associated with overdoses of FOSCAVIR (see OVERDOSAGE section).

In five controlled U.S. clinical trials the most frequently reported adverse events in patients with AIDS and CMV retinitis are shown in Table 5. These figures were calculated without reference to drug relationship or severity.

TABLE 5 — Adverse Events Reported in Five Controlled US Clinical Trials

	n = 189		n = 189
Fever	65%	**Abnormal Renal Function**	27%
Nausea	47%	**Vomiting**	26%
Anemia	33%	**Headache**	26%
Diarrhea	30%	**Seizures**	10%

From the same controlled studies, adverse events categorized by investigator as "severe" are shown in Table 6. Although death was specifically attributed to FOSCAVIR in only one case, other complications of FOSCAVIR (i.e., renal impairment, electrolyte abnormalities, and seizures) may have contributed to patient deaths (see WARNINGS section).

TABLE 6 — Severe Adverse Events

	n = 189
Death	14%
Abnormal Renal Function	14%
Marrow Suppression	10%
Anemia	9%
Seizures	7%

From the five initial U.S. controlled trials of FOSCAVIR, the following list of adverse events has been compiled regardless of causal relationship to FOSCAVIR. Evaluation of these reports was difficult because of the diverse manifestations of the underlying disease and because most patients received numerous concomitant medications.

Incidence 5% or Greater

Body as a Whole: fever, fatigue, rigors, asthenia, malaise, pain, infection, sepsis, death

Central and Peripheral Nervous System: headache, paresthesia, dizziness, involuntary muscle contractions, hypoesthesia, neuropathy, seizures including grand mal seizures (see WARNINGS)

Gastrointestinal System: anorexia, nausea, diarrhea, vomiting, abdominal pain

Hematologic: anemia, granulocytopenia, leukopenia (see PRECAUTIONS)

Metabolic and Nutritional: mineral and electrolyte imbalances (see WARNINGS) including hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia

Psychiatric: depression, confusion, anxiety

Respiratory System: coughing, dyspnea

Skin and Appendages: rash, increased sweating

Urinary: alterations in renal function including increased serum creatinine, decreased creatinine clearance, and abnormal renal function (see WARNINGS)

Special Senses: vision abnormalities

Incidence between 1% and 5%

Application Site: injection site pain, injection site inflammation

Body as a Whole: back pain, chest pain, edema, influenza-like symptoms, bacterial infections, moniliasis, fungal infections, abscess

Cardiovascular: hypertension, palpitations, ECG abnormalities including sinus tachycardia, first degree AV block and non-specific ST-T segment changes, hypotension, flushing, cerebrovascular disorder (see WARNINGS)

Central and Peripheral Nervous System: tremor, ataxia, dementia, stupor, generalized spasms, sensory disturbances, meningitis, aphasia, abnormal coordination, leg cramps, EEG abnormalities (see WARNINGS)

Gastrointestinal: constipation, dysphagia, dyspepsia, rectal hemorrhage, dry mouth, melena, flatulence, ulcerative stomatitis, pancreatitis

Hematologic: thrombocytopenia, platelet abnormalities, thrombosis, white blood cell abnormalities, lymphadenopathy

Liver and Biliary: abnormal A-G ratio, abnormal hepatic function, increased SGPT, increased SGOT

Metabolic and Nutritional: hyponatremia, decreased weight, increased alkaline phosphatase, increased LDH, increased BUN, acidosis, cachexia, thirst, hypercalcemia (see WARNINGS)

Musculo-Skeletal: arthralgia, myalgia

Neoplasms: lymphoma-like disorder, sarcoma

Psychiatric: insomnia, somnolence, nervousness, amnesia, agitation, aggressive reaction, hallucination

Respiratory System: pneumonia, sinusitis, pharyngitis, rhinitis, respiratory disorders, respiratory insufficiency, pulmonary infiltration, stridor, pneumothorax, hemoptysis, bronchospasm

Skin and Appendages: pruritus, skin ulceration, seborrhea, erythematous rash, maculo-papular rash, skin discoloration

Special Senses: taste perversions, eye abnormalities, eye pain, conjunctivitis

Urinary System: albuminuria, dysuria, polyuria, urethral disorder, urinary retention, urinary tract infections, acute renal failure, nocturia, facial edema

Selected adverse events occurring at a rate of less than 1% in the five initial U.S. controlled clinical trials of FOSCAVIR include: syndrome of inappropriate antidiuretic hormone secretion, pancytopenia, hematuria, dehydration, hypoproteinemia, increases in amylase and creatinine phosphokinase, cardiac arrest, coma, and other cardiovascular and neurologic complications.

Selected adverse event data from the Foscarnet vs. Ganciclovir CMV Retinitis Trial (FGCRT), performed by the Studies of the Ocular Complications of AIDS (SOCA) Research Group, are shown in Table 7 (see CLINICAL TRIALS section).

TABLE 7 — FGCRT: SELECTED ADVERSE EVENTS*

EVENT	GANCICLOVIR			FOSCARNET		
	No. of Events	No. of Patients	Rates‡	No. of Events	No. of Patients	Rates‡
Absolute neutrophil count decreasing to < 0.50 x 10^9 per liter	63	41	1.30	31	17	0.72
Serum creatinine increasing to > 260 µmol per liter (>2.9 mg/dL)	6	4	0.12	13	9	0.30
Seizure†	21	13	0.37	19	13	0.37
Catheterization-related infection	49	27	1.26	51	28	1.46
Hospitalization	209	91	4.74	202	75	5.03

* Values for the treatment groups refer only to patients who completed at least one follow-up visit – i.e. 113 to 119 patients in the ganciclovir group and 93 to 100 in the foscarnet group. "Events" denotes all events observed and "patients" the number of patients with one or more of the indicated events.

† Final frozen SOCA I database dated October 1991.

‡ Per person-year at risk.

Selected adverse events from ACTG Study 228 (CRRT) comparing combination therapy with FOSCAVIR or ganciclovir monotherapy are shown in Table 8. The most common reason for a treatment change in patients assigned to either FOSCAVIR or ganciclovir was retinitis progression. The most frequent reason for a treatment change in the combination treatment group was toxicity.

TABLE 8

CRRT: Selected Adverse Events

	Foscavir N=88			Ganciclovir N=93			Combination N=93		
	No. Events	No. Pts †	Rate‡	No. Events	No. Pts †	Rate‡	No. Events	No. Pts †	Rate‡
Anemia (Hgb <70 g/L)	11	7	0.20	9	7	0.14	19	15	0.33
Neutropenia§									
ANC <0.75 x 10^9 cells/L	86	32	1.53	95	41	1.51	107	51	1.91
ANC <0.50 x 10^9 cells/L	50	25	0.91	49	28	0.80	50	28	0.85
Thrombocytopenia									
Platelets <50 x 10^9/L	28	14	0.50	19	8	0.43	40	15	0.56
Platelets <20 x 10^9/L	1	1	0.01	6	2	0.05	7	6	0.18
Nephrotoxicity Creatinine > 260 µmol/L (>2.9 mg/dL)	9	7	0.15	10	7	0.17	11	10	0.20
Seizures	6	6	0.17	7	6	0.15	10	5	0.18
Hospitalizations	86	53	1.86	111	59	2.36	118	64	2.36

†Pts. = patients with event; ‡Rate = events/person/year; §ANC = absolute neutrophil count

Adverse events that have been reported in post-marketing surveillance include: ventricular arrhythmia, prolongation of QT interval, diabetes insipidus (usually nephrogenic), renal calculus and muscle disorders including myopathy, myositis, muscle weakness and rare cases of rhabdomyolysis. Cases of vesiculobullous eruptions including erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson Syndrome have been reported. In most cases, patients were taking other medications that have been associated with toxic epidermal necrolysis or Stevens-Johnson Syndrome.

OVERDOSAGE

In controlled clinical trials performed in the United States, overdosage with FOSCAVIR was reported in 10 out of 189 patients. All 10 patients experienced adverse events and all except one made a complete recovery. One patient died after receiving a total daily dose of 12.5 g for three days instead of the intended 10.9 g. The patient suffered a grand mal seizure and became comatose. Three days later the patient expired with the cause of death listed as respiratory/cardiac arrest. The other nine patients received doses ranging from 1.14 times to 8 times their recommended doses with an average of 4 times their recommended doses. Overall, three patients had seizures, three patients had renal function impairment, four patients had paresthesias either in limbs or perorally, and five patients had documented electrolyte disturbances primarily involving calcium and phosphate.

The pattern of adverse events associated with overdose in post-marketing surveillance is consistent with the symptoms previously observed during foscarnet therapy.

There is no specific antidote for FOSCAVIR overdose. Hemodialysis and hydration may be of benefit in reducing drug plasma levels in patients who receive an overdosage of FOSCAVIR, but the effectiveness of these interventions has not been evaluated. The patient should be observed for signs and symptoms of renal impairment and electrolyte imbalance. Medical treatment should be instituted if clinically warranted.

DOSAGE AND ADMINISTRATION

CAUTION—DO NOT ADMINISTER FOSCAVIR BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF FOSCAVIR MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS. CARE SHOULD BE TAKEN TO AVOID UNINTENTIONAL OVERDOSE BY CAREFULLY CONTROLLING THE RATE OF INFUSION. THEREFORE, AN INFUSION PUMP MUST BE USED IN SPITE OF THE USE OF AN INFUSION PUMP, OVERDOSES HAVE OCCURRED.

ADMINISTRATION

FOSCAVIR is administered by controlled intravenous infusion, either by using a central venous line or by using a peripheral vein. The standard 24 mg/mL solution may be used with or without dilution when using a central venous catheter for infusion. When a peripheral vein catheter is used, the 24 mg/mL solution must be diluted to 12 mg/mL with 5% dextrose in water or with a normal saline solution prior to administration to avoid local irritation of peripheral veins. Since the dose of FOSCAVIR is calculated on the basis of body weight, it may be desirable to remove and discard any unneeded quantity from the bottle before starting with the infusion to avoid overdosage. Dilutions and/or removals of excess quantities should be accomplished under aseptic conditions. Solutions thus prepared should be used within 24 hours of first entry into a sealed bottle. *To reduce the risk of nephrotoxicity, creatinine clearance (mL/min/kg) should be calculated even if serum creatinine is within the normal range, and doses should be adjusted accordingly.*

Hydration: Hydration may reduce the risk of nephrotoxicity. It is recommended that 750–1000 mL of normal saline or 5% dextrose solution should be given prior to the first infusion of FOSCAVIR to establish diuresis. With subsequent infusions, 750–1000 mL of hydration fluid should be given with 90–120 mg/kg of FOSCAVIR, and 500 mL with 40–60 mg/kg of FOSCAVIR. Hydration fluid may need to be decreased if clinically warranted.

After the first dose, the hydration fluid should be administered concurrently with each infusion of FOSCAVIR.

Compatibility with Other Solutions/Drugs: Other drugs and supplements can be administered to a patient receiving FOSCAVIR. However, care must be taken to ensure that FOSCAVIR is only administered with normal saline or 5% dextrose solution and that no other drug or supplement is administered concurrently via the same catheter. Foscarnet has been reported to be chemically incompatible with 30% dextrose, amphotericin B, and solutions containing calcium such as Ringer's lactate and TPN. Physical incompatibility with other IV drugs has also been reported including acyclovir sodium, ganciclovir, trimetrexate glucuronate, pentamidine isethionate, vancomycin, trimethoprim/sulfamethoxazole, diazepam, midazolam, digoxin, phenytoin, leucovorin, and prochlorperazine. Because of foscarnet's chelating properties, a precipitate can potentially occur when divalent cations are administered concurrently in the same catheter.

Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored or contain particulate matter should not be used.

Accidental Exposure: Accidental skin and eye contact with foscarnet sodium solution may cause local irritation and burning sensation. If accidental contact occurs, the exposed area should be flushed with water.

DOSAGE

THE RECOMMENDED DOSAGE, FREQUENCY, OR INFUSION RATES SHOULD NOT BE EXCEEDED. ALL DOSES MUST BE INDIVIDUALIZED FOR PATIENTS' RENAL FUNCTION.

Induction Treatment: The recommended initial dose of FOSCAVIR for patients with normal renal function is:

- For CMV retinitis patients, either 90 mg/kg (1-1/2 to 2 hour infusion) every twelve hours or 60 mg/kg (minimum one hour infusion) every eight hours over 2-3 weeks depending on clinical response.
- For acyclovir-resistant HSV patients, 40 mg/kg (minimum one hour infusion) either every 8 or 12 hours for 2-3 weeks or until healed.

An infusion pump must be used to control the rate of infusion. Adequate hydration is recommended to establish a diuresis (see Hydration for recommendation), both prior to and during treatment to minimize renal toxicity (see WARNINGS), provided there are no clinical contraindications.

Maintenance Treatment: Following induction treatment the recommended maintenance dose of FOSCAVIR for CMV retinitis is 90 mg/kg/day to 120 mg/kg/day (individualized for renal function) given as an intravenous infusion over 2 hours. Because the superiority of the 120 mg/kg/day has not been established in controlled trials, and given the likely relationship of higher plasma foscarnet levels to toxicity, it is recommended that most patients be started on maintenance treatment with a dose of 90 mg/kg/day. Escalation to 120 mg/kg/day may be considered should early reinduction be required because of retinitis progression. Some patients who show excellent tolerance to FOSCAVIR may benefit from initiation of maintenance treatment at 120 mg/kg/day earlier in their treatment.

An infusion pump must be used to control the rate of infusion with all doses. Again, hydration to establish diuresis both prior to and during treatment is recommended to minimize renal toxicity provided there are no clinical contraindications (see WARNINGS).

Patients who experience progression of retinitis while receiving FOSCAVIR maintenance therapy may be retreated with the induction and maintenance regimens given above or with a combination of FOSCAVIR and ganciclovir (see CLINICAL TRIALS section). **Because of physical incompatibility, FOSCAVIR and ganciclovir must NOT be mixed.**

Use in Patients with Abnormal Renal Function: FOSCAVIR should be used with caution in patients with abnormal renal function because reduced plasma clearance of foscarnet will result in elevated plasma levels (see CLINICAL PHARMACOLOGY). In addition, FOSCAVIR has the potential to further impair renal function (see WARNINGS). Safety and efficacy data for patients with baseline serum creatinine levels greater than 2.8 mg/dL or measured 24-hour creatinine clearances < 50 mL/min are limited.

Renal function must be monitored carefully at baseline and during induction and maintenance therapy with appropriate dose adjustments for FOSCAVIR as outlined below (see Dose Adjustment and PATIENT MONITORING). During FOSCAVIR therapy if creatinine clearance falls below the limits of the dosing nomograms (0.4 mL/min/kg), FOSCAVIR should be discontinued, the patient hydrated, and monitored daily until resolution of renal impairment is ensured.

Dose Adjustment: FOSCAVIR dosing must be individualized according to the patient's renal function status. Refer to Table 9 below for recommended doses and adjust the dose as indicated. Even patients with serum creatinine in the normal range may require dose adjustment; therefore, the dose should be calculated at baseline and frequently thereafter.

To use this dosing guide, actual 24-hour creatinine clearance (mL/min) must be divided by body weight (kg), or the estimated creatinine clearance in mL/min/kg can be calculated from serum creatinine (mg/dL) using the following formula (modified Cockcroft and Gault equation):

$$\text{For males } \frac{140 - \text{age}}{\text{serum creatinine} \times 72} \text{ (} \times 0.85 \text{ for females)} = \text{mL/min/kg}$$

TABLE 9
FOSCAVIR DOSING GUIDE
INDUCTION

	HSV: Equivalent to		CMV: Equivalent to	
CrCl (mL/min/kg)	80 mg/kg/day total (40 mg/kg Q12h)	120 mg/kg/day total (40 mg/kg Q8h)	180 mg/kg/day total (60 mg/kg Q8h)	(90 mg/kg Q12h)
> 1.4	40 Q12h	40 Q8h	60 Q8h	90 Q12h
>1.0–1.4	30 Q12h	30 Q8h	45 Q8h	70 Q12h
>0.8–1.0	20 Q12h	35 Q12h	50 Q12h	50 Q12h
>0.6–0.8	35 Q24h	25 Q12h	40 Q12h	60 Q24h
>0.5–0.6	25 Q24h	40 Q24h	60 Q24h	60 Q24h
≥0.4–0.5	20 Q24h	35 Q24h	50 Q24h	50 Q24h
<0.4	Not Recommended	Not Recommended	Not Recommended	Not Recommended

MAINTENANCE

	CMV: Equivalent to	
CrCl (mL/min/kg)	90 mg/kg/day (once daily)	120 mg/kg/day (once daily)
>1.4	90 Q24h	120 Q24h
>1.0–1.4	70 Q24h	90 Q24h
>0.8–1.0	50 Q24h	65 Q24h
>0.6–0.8	90 Q48h	185 Q48h
>0.5–0.6	60 Q48h	80 Q48h
≥0.4–0.5	50 Q48h	65 Q48h
<0.4	Not Recommended	Not Recommended

> means "greater than"; ≥ means "greater than or equal to"; < means "less than"

PATIENT MONITORING

The majority of patients will experience some decrease in renal function due to FOSCAVIR administration. Therefore it is recommended that creatinine clearance, either measured or estimated using the modified Cockcroft and Gault equation based on serum creatinine, be determined at baseline, 2–3 times per week during induction therapy and at least every one to two weeks during maintenance therapy, with FOSCAVIR dose adjusted accordingly (see Dose Adjustment). More frequent monitoring may be required for some patients. It is also recommended that a 24-hour creatinine clearance be determined at baseline and periodically thereafter to ensure correct dosing (assuming verification of an adequate collection using creatinine index). FOSCAVIR should be discontinued if creatinine clearance drops below 0.4 mL/min/kg.

Due to FOSCAVIR's propensity to chelate divalent metal ions and alter levels of serum electrolytes, patients must be monitored closely for such changes. It is recommended that a schedule similar to that recommended for serum creatinine (see above) be used to monitor serum calcium, magnesium, potassium and phosphorus. Particular caution is advised in patients with decreased total serum calcium or other electrolyte levels before treatment, as well as in patients with neurologic or cardiac abnormalities, and in patients receiving other drugs known to influence serum calcium levels. Any clinically significant metabolic changes should be corrected. Also, patients who experience mild (e.g., perioral numbness or paresthesias) or severe (e.g. seizures) symptoms of electrolyte abnormalities should have serum electrolyte and mineral levels assessed as close in time to the event as possible.

Careful monitoring and appropriate management of electrolytes, calcium, magnesium and creatinine are of particular importance in patients with conditions that may predispose them to seizures (see WARNINGS).

HOW SUPPLIED

FOSCAVIR (foscarnet sodium) INJECTION, 24 mg/mL for intravenous infusion, is supplied in glass bottles as follows:

NDC 0186-1906-01 500 mL bottles, cases of 12

NDC 0186-1905-01 250 mL bottles, cases of 12

FOSCAVIR INJECTION should be stored at controlled room temperature, 15 – 30°C (59 – 86°F), and should be protected from excessive heat (above 40°C) and from freezing. FOSCAVIR INJECTION should be used only if the bottle and seal are intact, a vacuum is present, and the solution is clear and colorless.

Manufactured for AstraZeneca LP, Wilmington, DE 19850
By Abbott Laboratories, North Chicago, IL 60064

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