

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20460/S008
Trade Name: Cytovene
Generic Name: Gancoclovir
Sponsor: Roche Global Development
Approval Date: December 12, 1997
Indication: CMV disease prevention in solid organ transplant recipients and immunosuppressed patients

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20460/S008

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	Included	Pending Completion	Not Prepared	Not Required
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Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20460/S008

APPROVAL LETTER



NDA 20-460/S-008

Roche Global Development
Palo Alto
Attn: Barbara S.T. Reynolds, Ph.D.
Regulatory Program Director
3401 Hillview Avenue
Palo Alto, CA 94304

DEC 12 1997

Dear Dr. Reynolds:

Please refer to your June 2, 1997, supplemental New Drug Application (NDA) submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Cytovene® (ganciclovir) 500mg capsules.

We acknowledge receipt of your amendments dated:

September 30, 1997	November 17, 1997	November 25, 1997
October 16, 1997	November 20, 1997	

This supplemental application provides for a 500mg strength of Cytovene (ganciclovir capsules).

We have completed our review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the November 25, 1997 draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed label (FPL) must be identical to the November 25, 1997 draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved NDA 20-460/S-008." Approval of this labeling is not required before it is used.

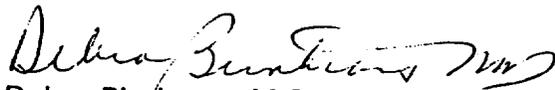
Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

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

If you have any questions, please contact Terrie L. Crescenzi, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Debra Birnkrant".

Debra Birnkrant, M.D.

Acting Director

Division of Antiviral Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

Concurrence:

HFD530/ADepDir/Dempsey *AD 12/12/97*
HFD-530/MTL/Behrman *ES 12/11/97*
HFD-530/MO/Martin *GM 11/22/97*
HFD-530/ChemTL/Miller *SM 12/11/97*
HFD-530/Chem/Lo *Ko Lo 12/11/97*
HFD-530/BiopharmTL/Jenkins *SP 12/11/97*
HFD-530/Biopharm/Sekar *vj 12/11/97*
HFD-530/SCSO/ADeCicco *D 12.11.97*
HFD-530/CSO/Crescenzi *@ 12/10/97*

cc:

HFD-530/Original NDA 20-460/S-008
HFD-530/Division File
HF-2/MedWatch (with draft/final labeling)
HFD-2/Lumpkin
HFD-80
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
District Office
HFD-222/New Drug Chemistry Division Director
HFD-530/Behrman
HFD-530/Martin
HFD-530/Crescenzi
HFD-530/Lo
HFD-530/Sekar

Approval Date:

Approval (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20460/S008

MEDICAL REVIEW(S)

NDA20-460/SE2-008

Date submitted: 2 Jun 97
Date received: 5 Jun 97
Date assigned: 6 Jun 97
MOR completed: 18 Nov 97

Medical Officer Review of Supplemental NDA

Applicant: Syntex (USA) Inc
3401 Hillview Ave
Palo Alto, CA 94304-1397

Drug: Chemical: 9-(1,3-dihydroxy-2-propoxymethyl) guanine
Generic: ganciclovir
Trade: Cytovene®

Route: Oral

Dosage form: 500 mg capsule

Purpose: To support approval of a new dosage strength

Supplement Contents: The supplement contains: (a) proposed labelling changes; (b) chemistry section; and (c) PK section. The PK section includes 2 PK studies: (i) GANS 2636- A phase I study to evaluate the bioequivalence of two formulations of oral ganciclovir (500 mg capsule and 250 mg capsule) in HIV positive subjects, and (ii) GANS 2686 - A phase I bioequivalence study of oral ganciclovir capsules in HIV- and CMV-seropositive subjects.

Related INDs, NDAs:

Resume The supplement contains 2 PK studies intended to support approval of a new dosage strength of ganciclovir.

Other Reviews

Chemistry: Please see Dr. Ko-Yu Lo's review

Pharmacokinetics: Please see Dr. Vanitha Sekar's review.

Proposed Labelling Changes

Clinical Studies:

A. GANS2636: A phase I study to evaluate the bioequivalence of two formulations of oral ganciclovir (500 mg capsule and 250 mg capsule) in HIV positive subjects.

A. Objective: To determine the bioequivalence under steady-state conditions of the 500 mg capsule formulation compared with the 250 mg capsule formulation at a dose of 1000 mg Q8H following a meal or snack, as assessed by the AUC_{0-8} and observed C_{max} in HIV + subjects.

B. Study Design: Single center, open label, randomized two-way crossover study of 15-21 days duration. Subjects were randomized to either the 250 mg or 500 mg capsule regimen, followed the next week by the other regimen. On Days 1-4 and 8-11, subjects received GCV, 1000 mg Q8H. A washout period (Days 5-7) separated the two regimens.

C. Study Population: A total of 14 subjects, all males were enrolled, mean age 36 yrs (range: 25-51 yrs). These subjects were seropositive for HIV and CMV, but asymptomatic for AIDS.

D. Conduct of the Study

Enrollment: All 14 enrolled subjects completed the trial.

Withdrawals: none

E. Safety results: *Deaths*. None. *Serious Adverse Events*. None.

Adverse Events: Similar numbers of adverse events were observed in each of the treatment groups. A single hemic/lymphatic event, lymphadenopathy, was observed in each treatment group. Fluctuations in ANC in individual patients were minor and not evidently related to treatment group.

Comment: This study raises no formulation-related or other safety concerns.

F. Pharmacokinetics results: The study report concludes that "the 250 gm and 500 mg capsule formulations of oral ganciclovir were bioequivalent for AUC_{0-8} and C_{max} ." Please see Dr. Sekar's review.

B. GANS 2686: A phase I bioequivalence study of oral ganciclovir capsules in HIV- and CMV-seropositive subjects.

A. Objective: to determine bioequivalence of oral ganciclovir capsules having different dissolution characteristics and crystal form compositions under steady state conditions at a dose of 1000 mg Q8H.

B. Study Design: open-label, randomized, four-way crossover design. Four regimens in random order, all administered 1000 mg Q8H for 10 doses (Days 1-4, 8-11, 15-18, 22-25) are compared:

Regimen A (ref.), oral GCV, 250 mg caps, storage: 25°C, ambient RH x 18 mo (Lot955731)

Regimen B, oral GCV, 500 mg caps, storage: 25°C/60%RH x 9 mo (Lot 1450021)

Regimen C, oral GCV, 500 mg caps, storage: 30°C/60%Rh x 8.5 mo (Lot 1446461).

Regimen D, oral GCV, 500 mg caps, storage: 40°C/70%RH x 8.5 mo (Lot 1446481)

C. Study Population: Twenty-four subjects (23 M, 1 F), aged 22-51 yrs, were randomized.

D. Conduct of the Study

Enrollment: Of 24 subjects enrolled, 21 completed the study.

Protocol violations: Entry criteria were met by all subjects.

Withdrawals: Three subjects terminated the study early, 2 for adverse events (facial swelling-see Premature Terminations, below) and 1 for personal reasons.

E. Safety results

Deaths. There were no deaths.

Serious Adverse Events. There were no serious adverse events.

Premature terminations. Two subjects are described as having had severe facial swelling, each after receiving 2 of the 4 regimens. Because of concern that facial swelling might relate to study drug, the Principle Investigator prematurely terminated both subjects from the study.

In both instances, facial swelling was identified during evaluation prior to dosing at the third dosing period. One subject had received Regimens B and C, and the other, Regimens A and B during the first two dosing periods.

Comment: In controlled trials, facial swelling is not an event that has been found to relate to GCV therapy. In this study, the GCV treatment in Period 2 in both cases involved the 500 mg capsule dosing form; the capsules were, however, from a different drug lot in each case. Facial swelling was not reported in these subjects while on GCV therapy, but after 3 days following the last GCV dose in the previous dosing period. Thus, facial swelling, if related to GCV therapy in this case, would presumably relate specifically to the 500 mg dosing form, and is a relatively delayed event.

The Applicant was asked to provide additional information and to comment on facial swelling in these two subjects. The Applicant notes that Subject 833 had had a history of facial rashes and dry skin, and that facial swelling was accompanied by rash in this instance. A causative relationship to study drug was not established or ruled out, and a rechallenge was not attempted. Subject 844 had unilateral facial swelling, with a raised area on the buccal mucosa; four days later following the application of warm compresses, "oral drainage (pus)" was reported for this subject.

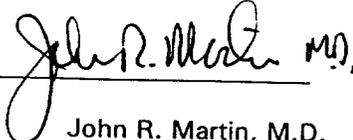
It seems unlikely that facial swelling in these subjects is related to GCV treatment.

F. Pharmacokinetics results. Please see Dr. Sekar's review.

Labelling Comments: Please see Chemistry and Biopharmaceutics reviews for comments. No modifications to the propose labelling need to be made based on the clinical review of the Application.

Conclusions: In Study GANS 2686, two subjects who had received the 500 mg dosage form of GCV were discontinued from the study because of severe facial swelling. No such adverse event was described in Study GANS 2636. It is considered unlikely that facial swelling is related to treatment with the 500 mg dosage form of GCV. No other safety concerns were identified.

Recommendation: It is recommended that this Supplemental Application be approved.


John R. Martin, M.D.
Medical Officer

concurrences:

HFD-530/ActDivDir/DBirnkrant *DB 12-12-97*
HFD-530/TL/RBehrman *ESD 12-10-97*

cc:

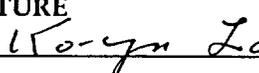
NDA
HFD-530
HFD-530/ActDivDir/DBirnkrant
HFD-530/TL/RBehrman
HFD-530/CSO/TCrescenzi
HFD-530/Chem/KYLo
HFD-530/Biopharm/VSekar
HFD-530/MO/JMartin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20460/S008

CHEMISTRY REVIEW(S)

DRAFT

SUPPLEMENTAL NDA CHEMIST'S REVIEW		1. ORGANIZATION HFD-530		2. NDA NUMBER 20-460			
		3. NAME AND ADDRESS OF APPLICANT (City and State) Syntex (U.S.A.) Inc. 3401 Hillview Avenue, M/S S1-200 Palo Alto, CA 94304				4. AF NUMBER	
5. SUPPLEMENT(S) NUMBER(S) DATE(S) SE2-008 6/2/97				6. NAME OF DRUG CYTOVENE ^R		7. NONPROPRIETARY NAME Ganciclovir	
				8. SUPPLEMENT(S) PROVIDES FOR: A 500 mg strength of CYTOVENE (ganciclovir capsules)			
10. PHARMACOLOGICAL CATEGORY Antiviral		11. HOW DISPENSED <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		12. RELATED IND/NDA/DMF(S) NDA 20-460 Original			
13. DOSAGE FORM (S) Capsules		14. POTENCY(IES) 500 mg					
15. CHEMICAL NAME AND STRUCTURE 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine				16. RECORDS AND REPORTS Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No			
17. COMMENTS NDA 20-460/SE2-008 provides for a 500 mg strength of CYTOVENE (ganciclovir capsules). The 500 mg capsules is identical in composition to the marketed 250 mg capsules, except for capsule shell size, color, and final fill weight, and is a direct scale-up of the 250 mg capsules. This submission contains the following information: 1. CMC information for the 500 mg capsules 2. Bioequivalence studies to compare the bioavailability of the 250 mg and 500 mg capsules. 3. Labeling (package insert, and container and carton labels)							
18. CONCLUSIONS AND RECOMMENDATIONS The chemistry section of this supplement is approved.							
19. REVIEWER							
NAME Ko-Yu Lo, Ph.D.		SIGNATURE 		DATE COMPLETED 12/5/97			
20. CONCURRENCE: HFD-530/SMiller							
DISTRIBUTION	<input checked="" type="checkbox"/>	Original Jacket	<input checked="" type="checkbox"/>	Division File	<input checked="" type="checkbox"/> KLo		
	<input checked="" type="checkbox"/>	TCrescenzi	<input checked="" type="checkbox"/>	JMartin			

**REQUEST FOR CATEGORICAL EXCLUSION FROM AN ENVIRONMENTAL
ASSESSMENT FOR GANCICLOVIR CAPSULES, 500 MG
(SUPPLEMENT TO NDA 20-460)**

Pursuant to Title 21 CFR 25.24(c)(2), Syntex (U.S.A.) Inc., 3401 Hillview Ave., Palo Alto, California, 94304 requests a categorical exclusion from the requirement for the preparation of an environmental assessment for Ganciclovir Capsules, 500 mg. Under 21 CFR § 25.24(c)(2), a supplement to an NDA may be categorically excluded from the preparation of an Environmental Assessment "if the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect and if data available to the agency do not establish that, at the expected levels of exposure, the substance may be toxic to organisms in the environment."

A 250 mg capsule formulation for oral administration of ganciclovir is currently approved (NDA 20-460) in the United States under the name Cytovene® (ganciclovir capsules). It was originally indicated for prevention of CMV disease in individuals with advanced HIV infection at risk of developing CMV disease, and also as an alternative to the IV formulation for maintenance treatment of CMV retinitis in immunocompromised individuals, including individuals with AIDS. A supplement to NDA 20-460 for the additional indication of the prevention of CMV disease in solid organ transplant recipients was approved by the FDA in November 1996 (Supplement #SE1-006).

This Request for Categorical Exclusion from an Environmental Assessment Report is submitted in support of a supplement to NDA 20-460 for Ganciclovir Capsules, 500 mg. In this supplement, the only changes are increasing the ganciclovir capsule dosage strength from 250 mg to 500 mg, and the size and color of the gelatin capsule. The proposed capsule is a #0 two-piece hard gelatin capsule consisting of an opaque green body and yellow cap. It contains FD&C Blue #2, Yellow Iron Oxide, Titanium Oxide, and Gelatin (the same ingredients as are found in the 250 mg capsule). Although the dosage strength of the proposed 500 mg capsules is greater than the approved 250 mg capsules, the daily dosage of ganciclovir will not increase as fewer capsules will be administered; nor will the drug be administered for longer durations or for different indications than already approved. Thus, the proposed action is not expected to result in an increase of production of ganciclovir and is therefore not expected to increase the amount of ganciclovir and its metabolites entering the environment through product use.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20460/S008

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 20460 (008)
DRUG: Cytovene® (ganciclovir)
APPLICANT: Syntex Research
TYPE: Supplement
VOLUME(S): 1, 8 - 13

REVIEWER: Vanitha J. Sekar, Ph.D.
FORMULATION: 500 mg capsules
SUBMISSION DATE: June 5, 1997
LOGGED IN: June 16, 1997
FINAL REVIEW: December 5, 1997

TABLE OF CONTENTS**SYNOPSIS**

STUDY NUMBER GANS 2638

STUDY NUMBER GANS 2686

DISSOLUTION METHOD AND SPECIFICATION FOR 500 MG GANCICLOVIR

APPENDIX 1: INDIVIDUAL DATA FROM STUDY GANS 2636

APPENDIX 2: INDIVIDUAL DATA FROM STUDY GANS 2686

APPENDIX 3: PROPOSED LABELING REVISIONS AND DRAFT PACKAGE INSERT

SYNOPSIS:

Background: Ganciclovir is a synthetic nucleoside analog that inhibits replication of human herpes viruses. Intravenous ganciclovir is approved for the treatment of CMV retinitis in AIDS patients and for the prevention of CMV disease in transplant patients. The oral formulation is indicated as an alternative to the intravenous formulation for maintenance therapy 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 a more rapid progression is balanced by the benefit associated with avoiding daily infusions. The maintenance dose for oral ganciclovir is 1000 mg t.i.d. with food. Alternatively, a regimen of 500 mg q3h 6 times a day with food, while awake, may be used.

The absolute bioavailability of ganciclovir after oral administration is low (~5% to 9%). Plasma protein binding for ganciclovir is low (1 to 2%). Approximately 90% of an orally administered dose of ganciclovir is excreted unchanged in urine and feces within 5 days of administration. When administered orally, ganciclovir exhibits linear pharmacokinetics up to a total daily dose of 4g/day. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. The average half life following intravenous and oral ganciclovir is approximately 3.5 and 5 hours, respectively.

Summary: This document contains reviews of two bioequivalence studies submitted as a supplement to NDA 20460. The current formulation for oral ganciclovir, which has been approved by the U.S. Food and Drug Administration, is a 250 mg hard gelatin capsule. In order to increase the convenience of dosing with oral ganciclovir, a 500 mg capsule formulation has been developed. Both formulations contain the same ingredients in the same proportions and use the same type of hard gelatin capsule. The only differences between the

formulations are the fill weights, capsule sizes, and capsule colors.

Composition of Ganciclovir 500 mg Capsules

Ingredient	Wt. Per capsule (mg)	% w/w	Function
Ganciclovir	500		Active Ingredient
Povidone			
Croscarmellose sodium NF			
Magnesium Stearate			
Purified water			
Total fill weight (theoretical)			

Study GANS2638 was a pivotal study conducted to determine the bioequivalence under steady state conditions of the 500 mg capsule formulation (at a dose of 1000 mg q8h) of ganciclovir to the 250 mg capsule formulation (at a dose of 1000 mg q8h). This was a single center, open label, randomized, two way crossover study in 14 HIV-positive male subjects. Assessment of bioequivalence was done using 90% confidence limits for the pharmacokinetic parameters AUC_{0-8} and C_{max} . AUC_{0-8} and C_{max} passed the criteria for bioequivalence. The statistical analysis indicated that the T_{max} for the reference (250 mg capsule) was significantly longer than for the test (500 mg capsule).

Ganciclovir Computed Parameter 90% Confidence Intervals (Study GAN2638)

Computed Parameter	Ratio (B/A)	Lower Limit	Upper Limit
$\ln AUC_{0-8}$	98.2%		
$\ln C_{max}$	102.1%		

Study GANS2686 was initiated as a result of the discovery of a new crystal form of ganciclovir in both the 250 mg and 500 mg capsules. The discovery was made after the approval of the 250 mg capsule NDA. Some capsule lots for which the hydrated Phase II crystal form of ganciclovir converts to the Phase III crystal form over time show a decrease in dissolution rate under ambient storage conditions. The trend of dissolution slowing under ambient storage conditions has not been observed for lots without the Phase III crystal form. The study was conducted to determine the bioequivalence of four treatments (A, B, C and D) of oral ganciclovir having different dissolution characteristics, storage conditions and crystal form compositions. Treatment A was the reference and B, C and D were the test treatments. The study was performed under steady state conditions, at a dose of 1000 mg q8h. This was a single center, open label, randomized, four way crossover study in 24 HIV-positive subjects. Assessment of bioequivalence was done using 90% confidence limits for the pharmacokinetic parameters, AUC_{0-8} , and C_{max} . The 90% confidence intervals showed that AUC_{0-8} and C_{max} passed the criteria for bioequivalence for treatments B and C. For treatment D, AUC_{0-8} passed

the criteria for bioequivalence, but C_{max} did not. The statistical analysis indicated that the T_{max} for the test treatment (D) was significantly longer than for the reference (A).

GANS 2686 Study Treatments, Storage Conditions, *In-Vitro* Dissolution and Crystal Composition.

Treatment	Dosage strength	Storage Conditions		Mean \pm SD (% Dissolved at 45 min)		Polymorph composition (% Phase Crystals)		
		$^{\circ}$ C/%RH	Months	Water	0.1 N HCL	I	II	III
A (Reference)	250 mg	25/Ambient	18	102 \pm 1.16	102 \pm 0.937	52	48	0
B (Test)	500 mg	25/60	9	83.6 \pm 4.62	99.4 \pm 1.08	0	24	76
C (Test)	500 mg	30/60	8.5	62.0 \pm 4.70	88.7 \pm 3.08	0	Trace	100
D (Test)	500 mg	40/75	8.5	39.8 \pm 11.2	25.0 \pm 3.10	Trace	Trace	100

Ganciclovir Computed Parameter 90% Confidence Intervals (Study GAN2686)

Comparison of B vs A

Computed Parameter	Ratio (B/A)	Lower Limit	Upper Limit
$\ln AUC_{0-4}$	94.2%	-----	-----
$\ln C_{max}$	89.5%	-----	-----

Comparison of C vs A

Computed Parameter	Ratio (C/A)	Lower Limit	Upper Limit
$\ln AUC_{0-4}$	96.0%	-----	-----
$\ln C_{max}$	90.6%	-----	-----

Comparison of D vs A

Computed Parameter	Ratio (C/A)	Lower Limit	Upper Limit
$\ln AUC_{0-4}$	86.4%	-----	-----
$\ln C_{max}$	78.5%	-----	-----

Dissolution Method and Specification for Ganciclovir 500 mg Capsules: The recommended dissolution method for the ganciclovir 500 mg capsules utilizes

This method is the same as that for the approved 250 mg capsule. The proposed specification for ganciclovir 500 mg is Q= dissolved in 45 minutes. The specification proposed is than the current specification for the 250 mg capsule of Q= dissolved in 45 minutes.

The applicant has based this specification (Q= in 45 minutes) primarily on results from bioequivalence study GANS 2686 which showed that 500 mg capsules with dissolution rate of in 45 minutes were bioequivalent to the currently marketed 250 mg capsules. However, review of the dissolution data for the lots used in the bioavailability studies and for

the stability lots suggest that $Q=$ in 45 minutes would be appropriate.

Conclusions: For the pivotal bioequivalence study, GANS2638, the test treatment (500 mg) passed the criteria for bioequivalence. For GANS2686, test treatments B and C passed the criteria for bioequivalence, however, treatment D did not. (For treatment D, AUC_{0-8} passed the criteria for bioequivalence, but C_{max} did not). Treatment D also exhibited the slowest dissolution characteristics. The storage conditions (elevated temperature and high relative humidity) and the predominance of Phase III crystals for Treatment D may be a reason for the poor dissolution characteristics for this treatment. The test product in the pivotal study GANS 2638 was from the same batch as the test product for Treatment D in GAN2686. In the pivotal study GANS 2638, the capsules were stored at 25°C and ambient RH (as opposed to study GANS 2686 where the storage conditions were 40°C and 75% RH). In the pivotal study GANS 2638, both C_{max} and AUC_{0-8} for the test product met the bioequivalence criteria. -The results from this study suggest that the 500 mg ganciclovir capsules should not be stored at conditions greater than that of ambient temperature and relative humidity (this conclusion was also made by the chemistry reviewer).

Labeling: The proposed labeling revisions are acceptable.

Note: An Intra-division CPB briefing was held on October 31, 1997.

Attendees: Dr. John Lazor, Dr. Janice Jenkins, Dr. Dennis Bashaw, Dr. Frank Pelsor, Dr. Funmi Ajayi, Ms. Terrie Cresenzi

Based on the discussions at the briefing, the following comments were addressed to the applicant.

COMMENTS TO APPLICANT:

1. Based on the dissolution data (release data) for the 500 mg capsule lots used in the two bioavailability studies (GANS 2638 and GANS 2686) and the data for the stability lots (12514-1, 12516-1, 1195001, 1195051, 1195091), we feel that a dissolution specification of $Q=$ in 45 minutes would be appropriate for the 500 mg ganciclovir capsules. (This specification is also the current interim dissolution specification for the 250 mg ganciclovir capsules).
2. The dissolution data for the 3 registration batches (1500571, 1500581, 1500591) stored at ambient conditions with and without desiccant suggest that the presence of desiccant in the container prevents slowing of the dissolution profile (which is observed under conditions where no desiccant is present). We feel that the dissolution data for batches stored with desiccant meet the requirements of $Q=$ in 45 minutes (even after storage for 12 months).
3. Treatments C and D (from Study GANS 2686) have similar polymorphic composition (predominantly Phase III crystals). Therefore, the presence of Phase III crystals does not

explain the slowing of dissolution for treatment D. We feel that the slowing of dissolution may be associated with the hard gelatin shell of the capsules, and we would like you to study the dissolution profiles for the four study treatments from Study GANS 2686, in particular treatment D with and without enzymes (two-tier dissolution testing). Since your initial test medium is water, we would like for you to perform the two-tier dissolution test in water. Also, we would like you to perform the two-tier dissolution test using another medium such as 0.1N HCl/pepsin or pH 6.8 buffer/pancreatin.

Note: A teleconference was held with applicant on November 20, 1997 to discuss the above issues (as well as other issues related to CMC). There was agreement between the applicant and the agency regarding setting the dissolution specification for the 500 mg ganciclovir capsules at $Q =$ dissolved in 45 minutes. Following the teleconference, the applicant submitted dissolution data for capsules from treatments C and D (from Study GANS 2686) using two-tier dissolution testing with 0.1N HCl/pepsin as the medium. These data (attached as Appendix 4) were generated to investigate how much of the dissolution is due to capsule fill versus capsule shell effects. These data suggest that for treatment C, the dissolution is faster in 0.1N HCl/pepsin compared to water or 0.1N HCL alone suggesting that in this case the dissolution slowing was primarily due to the capsule shell effects. For treatment C, the proposed dissolution specification of $Q =$ in 45 minutes is met when dissolution is performed in simulated gastric fluid medium. However, for treatment D, the dissolution rate in simulated gastric fluid is moderately faster than in 0.1N HCL, but about the same as it is in water. For treatment D, the proposed dissolution specification of $Q =$ in 45 minutes is not met even when dissolution is performed in simulated gastric fluid medium. This suggests that the dissolution slowing in this case may be attributable to capsule fill effects.

Recommendation: The applicant has adequately addressed the requirements of the Division of Pharmaceutical Evaluation III for approval of the 500 mg ganciclovir capsules as an additional dosage form.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Vanitha Jayaraman Sekar 12/5/97

Vanitha J. Sekar, Ph.D.
Reviewer, Antiviral Drugs Section, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: *Janice Barnett Jenkins 12/10/97*
Janice B. Jenkins, Ph.D.
Team Leader, Antiviral Drugs Section, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-530 NDA 20460 (SE2-008)
/MO/J.Martin
/CSO/T.Crescenzi
/Biopharm/V.Sekar
/TL Biopharm/J.Jenkins
HFD-340 /Viswanathan
✓ HFD-880 /DPEIII
✓ CDR (Attn: Barbara Murphy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20460/S008

ADMINISTRATIVE DOCUMENTS

DEBARMENT CERTIFICATION

Syntex (USA) Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 306(a) and (b), in connection with this application.

PATENT INFORMATION FOR SUPPLEMENT TO NDA NO. 20-460

- | | | |
|----|--|----------------------|
| 1) | Active Ingredient(s): | ganciclovir |
| 2) | Strength(s): | 500 mg capsules |
| 3) | Trade Name: | CYTOVENE |
| 4) | Dosage Form and Route of Administration: | capsule; oral |
| 5) | Applicant (Firm) Name: | Syntex (U.S.A.) Inc. |
| 6) | NDA Supplement Number: | S-008 |
| 7) | First Approval Date of original NDA: | 12/22/94 |
| | First Approval Date of Supplemental NDA: | Not yet approved* |
| 8) | Exclusivity: | Not applicable |
| 9) | Patent Information: | See Attachment |

CONFIDENTIAL INFORMATION

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

Rev. 12/97

ATTACHMENT

First U.S. Patent Number: 4,355,032

Expiration Date: June 23, 2003

Type of Patent-Indicate all that apply:

- | | | | |
|----|--|-------------------|----------------------|
| 1. | Drug Substance (Active Ingredient) | <u>X</u> <u>Y</u> | <u> </u> <u>N</u> |
| 2. | Drug Product (Composition/Formulation) | <u>X</u> <u>Y</u> | <u> </u> <u>N</u> |
| 3. | Method of Use | <u>X</u> <u>Y</u> | <u> </u> <u>N</u> |

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

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

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

The undersigned declares that the above stated United States Patent Number **4,355,032** covers the composition, formulation and/or method of use of ganciclovir This product is:

 X currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

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

Second U.S. Patent Number: 4,423,050

Expiration Date: May 21, 2001

Type of Patent-Indicate all that apply:

- | | | |
|---|---------------------------------------|----------------------------|
| 1. Drug Substance (Active Ingredient) | <input type="checkbox"/> Y | <input type="checkbox"/> N |
| 2. Drug Product (Composition/Formulation) | <input type="checkbox"/> Y | <input type="checkbox"/> N |
| 3. Method of Use | <input checked="" type="checkbox"/> Y | <input type="checkbox"/> N |

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

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

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

The undersigned declares that the above stated United States Patent Number **4,423,050** covers the composition, formulation and/or method of use of ganciclovir. This product is:

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

OR

the subject of this application for which approval is being sought.)

Third U.S. Patent Number: 4,507,305

Expiration Date: May 21, 2001

Type of Patent-Indicate all that apply:

- | | | |
|---|---------------------------------------|----------------------------|
| 1. Drug Substance (Active Ingredient) | <input type="checkbox"/> Y | <input type="checkbox"/> N |
| 2. Drug Product (Composition/Formulation) | <input type="checkbox"/> Y | <input type="checkbox"/> N |
| 3. Method of Use | <input checked="" type="checkbox"/> Y | <input type="checkbox"/> N |

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

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

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

The undersigned declares that the above stated United States Patent Number 4,507,305 covers the composition, formulation and/or method of use of ganciclovir. This product is:

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

OR

the subject of this application for which approval is being sought.)

Fourth U.S. Patent Number: 4,642,346

Expiration Date: June 24, 2005

Type of Patent-Indicate all that apply:

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

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

Name of Patent Owner: Syntex (U.S.A.) Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

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

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____.
This product is:

_____ currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

_____ the subject of this application for which approval is being sought.)

Signed: 

Date: December 11, 1997

Title: Chief Patent Counsel, Hoffmann-La Roche Inc.

Telephone Number: (973) 235-3656

A copy of the above information should be submitted with the NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit that information within 30 days of the date of issuance of the patent.

EXCLUSIVITY SUMMARY FOR NDA # 20-460 / SE2-008

Trade Name Cytovene
Applicant Name Syntex (USA) Inc
Approval Date If Known

Generic Name ganciclovir
HFD # 530

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES / NO /

b) Is it an effectiveness supplement?

YES / NO /

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

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

YES / NO /

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

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

d) Did the applicant request exclusivity?

YES / / NO / X /

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES / / NO / /

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

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

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

YES /__ / NO /__ /

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

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES", GO TO PART III.

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

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

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

YES /__ / NO /__ /

IF "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying in that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES /__ / NO /__ /

If "no", state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES /__ / NO /__ /

(1) If the answer to 2(b) is "yes", do you personally know of any reason to disagree with the applicant's conclusion?

YES / / NO / /

If yes, explain: _____

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

YES / / NO / /

If yes, explain: _____

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /__/ NO /__/

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

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

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /__/ NO /__/

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

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

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

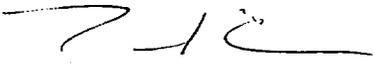
Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

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

YES / / NO / /

If yes, explain: _____



Signature of
Project Manager

10 Dec 97

Date

Signature of
Acting Division Director

Date

cc: Orig NDA Div File HFD-85

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-460 Supplement # 008 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Cytovene (ganciclovir capsules) Action: AP AE NA

Applicant Syntex (U.S.A.), Inc. Therapeutic Class _____

Indication(s) previously approved CMV disease prevention in solid organ transplant recipients and immunosuppressed patients, and treatment of CMV disease in organ transplant recipients and immunosuppressed patients.

Pediatric information in labeling of approved indication(s) is adequate X inadequate ____

Indication in this application Provides for a 500mg strength of Cytovene (ganciclovir capsules) (For supplements, answer the following questions in relation to the proposed indication.)

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing.
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

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

John R. Mader, M.D.
Signature of Preparer and Title

11 Dec 97
Date

cc: Orig NDA/PLA/PMA # 20-460/S-008
Div File
NDA/PLA Action Package
HFD-006/ SOLmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)