CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74914

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-914

JG PRODUCT: Acyclovir Capsules

FIRM: Copley Pharmaceutical, Inc.

DOSAGE FORM: Hard Gelatin Capsule

STRENGTH: 200 mg

CGMP STATMENT: Submitted 6/18/96 p. 2737

EIR STATUS UPDATE: All firms acceptable 10/15/96 and 12/20/96

BIO STUDY: **Pending Sign-off**

The two bio studies under fasting and nonfasting conditions were found satisfactory on 9/13/96 by Dr. M. Makary, HFD-658.

The applicant intends to use the following dissolution method:

USP Apparatus II (Paddles)
Speed: 100rpm
Medium: 900 mL 0.1N Hcl

Specification: NLT _ %(Q) is dissolved in 30 minutes

The specification is as per the E-mail of 12/6/96 from M. Anderson regarding dissolution specifications for Acyclovir Capsules and Tablets.

The method used by Copley is acceptable to the Div. Of Bioequivalence - refer to the E-mail dated 10/10/97. from L. Ouderkirk.

VALIDATION: Satisfactory

Methods validation on the finished drug product was found satisfactory by the New York Regional Laboratory on 9/22/97.

STABILITY: Satisfactory

The stability testing protocol, methods and post-approval commitment are satisfactory

The proposed stability specifications are:

Appearance: Blue opaque cap and body printed in black ink "Copley 299 Acyclovir 200"

Assay: 90.0% - 110.0% of labeled amount.

Dissolution: NLT %(Q) of the labeled amount is dissolved

in 30 minutes

Related Substances: NMT % Guanine; NMT % Other Individual Related substances and NMT % Total Related Substances.

Moisture: NMT %

The proposed expiration date is 24 months which is supported by the data.

LABELING: ~~Pending~~ Satisfactory

Insert labeling was found unsatisfactory - J. White, HFD-613, 8/11/97; C. Hoppes, HFD-613, 8/12/97. A telephone amendment was requested per memo of telecon - J. White, HFD-613, 8/14/97. Labeling satisfactory 11/5/97.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH:

The bio studies were performed on lot # 299Z01, ( ) capsules.

SIZE OF STABILITY BATCHES:

The stability studies were performed on lot # 299Z01 ( ) capsules.

PROPOSED PRODUCTION BATCH:

The proposed production batch size is ( ) capsules. A blank batch record was submitted for this batch size. The manufacturing process will be the same as for the test batch.

Finished Product Specifications:

Appearance: Blue opaque cap & body printed in black ink Copley 299 Acyclovir 200"

Identification: ( ) retentin time for acyclovir in the assay preparation is identical to that obtained for acyclovir in the standard preparation.

Assay: 90.0% - 110.0% of the labeled amount of acyclovir.

Uniformity of Dosage: Meets USP 23 <905> requirements.

Related Substances: NMT (% guanine; NMT (% Other Related Substances; NMT (% Total Related Substances.

ANDA 74-914

Moisture: NMT (%

Dissolution: NLT %(Q) is dissolved in 30 minutes.

(/S/ 11/6/97

CHEMIST: Donald Shostak DATE: 10/20/97

/S/ 11/7/97

TEAM LEADER: Ubrani Venkataram DATE: 10/27/97

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FT by: pah/11/5/97
x:\new\firmsam\copley\ltrs&rev\74914n02.apf

APPROVAL SUMMARY

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 74-914

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceutical, Inc.
25 John Road
Canton, MA 02021

4. LEGAL BASIS FOR SUBMISSION
The listed reference drug is Zovirax® Capsules manufactured by Burroughs Wellcome, NDA 18-828

Copley will market Acyclovir capsules 200 mg following expiration of US Patent 4,199,574 (April 22, 1997).

The reference listed drug is no longer entitled to exclusivity

(Refer to p. 00010)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Submitted: June 18, 1996

FDA:
Acknowledgement: August 9, 1996
Letter (Div. of Bioequivalence): September 25, 1996

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

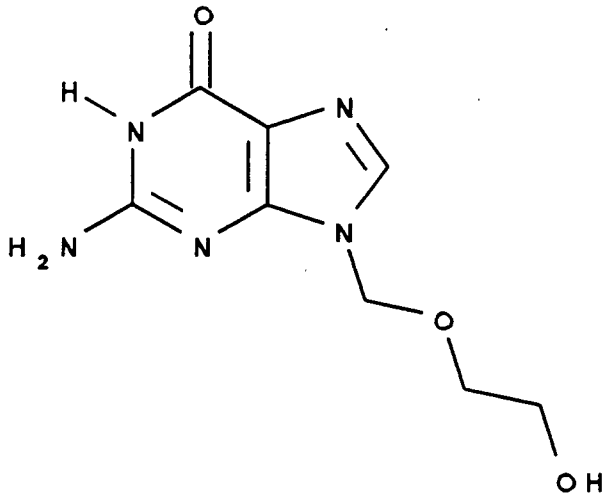
13. DOSAGE FORM
Capsule Hard Gelatin)

14. POTENCY
Rx

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

$C_8H_{11}N_5O_3$; M.W. = 225.21



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

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. The application is deficient in regard to CMC, container/closure and stabiity issues.

b. Labeling is unsatisfactory J. White, HFD-613, 11/19/96.

c. Methods validation for the drug product is deferred until the applicant provided a copy of the method for moisture determination.

d. EIR satisfactory 10/15/96 for Solchem and Copley; EER pending for ancillary firms.

e. Bio studies satisfactory, but dissolution testing incomplete - bio review 9/13/96

18. CONCLUSIONS AND RECOMMENDATIONS

This application is NOT APPROVABLE. The amendment will be MAJOR.

19. REVIEWER: Donald Shostak

DATE COMPLETED: November 22, 1996

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Chem Review #1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-914 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Acyclovir Capsules 200 mg

A. Deficiencies:

1. Organic Volatile Impurities and Sulfur Dioxide testing was not submitted on Corn Starch NF. Please submit.

2. Sodium starch glycollate is listed as a compoment but does not appear in the composition statement. Please clarify.

3. Please describe in more detail the cap liner used. The information submitted appears to be for the inner safety seal.

4. Please revise the statemet on p. 2791 regarding the submission of a Changes Being Effected supplement for the deletion of(testing. A CBE supplement would not be appropriate for this change.

5. In regard to the amounts of total related substances found at release testing we feel that the specification of NMT % is too high. Please comment.

6. Please submit a copy of the method for moisture determination in the finished drug product.

7. In regard to the stability testing, we have the following comments:

   a. Based on the amounts of guanine and total related substances found during accelerated stability testing, we feel the limits of % for each are too high. Please comment.

   b. Specifications should be established for individual related substances and identification should be made where known impurities exist. (Refer to p. 2898).

   c. If 25° - 30°C is used as the room temperature conditions, the humidity conditions should be monitored and reported.

MAJOR AMENDMENT CLOSING PARAGRAPHS

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies and comments provided. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiciencies identified during the review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

cc: ANDA 74-914
Dup Jacket
Division File
Field Copy

Endorsements: (Drafts & final with dates)

HFD-647/DShostak/11/22/96 D Shostak 12/2/96

HFD-647/JSimmons/11//20/96 J Simmons 12.9.96

HFD-647/TAmes/11/29/96

HFD-640/FHolcombe (final only)

FT by: pah/12/2/96
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x:\wpfile\branch7\shostak\74914n01.RDS (Disk 14)

NOT APPROVABLE - MAJOR

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-914

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceutical, Inc.
25 John Road
Canton, MA 02021

4. LEGAL BASIS FOR SUBMISSION
The listed reference drug is Zovirax® Capsules manufactured by Glaxo Wellcome, NDA 18-828

Copley will market Acyclovir capsules 200 mg following expiration of US Patent 4,199,574 (April 22, 1997).

The reference listed drug is no longer entitled to exclusivity

(Refer to p. 00010)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Acyclovir Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Submitted: June 18, 1996
Amendment: February 14, 1997 (Subject of this review)
Amendment (Labeling): May 2, 1997
New Corresp. August 8, 1997 (Dissolution): Subject of this review
New Corresp. August 11, 1997 (Dissolution): Subject of this review

FDA:
Acknowledgement: August 9, 1996
Letter (Div. of Bioequivalence): September 25, 1996
Letter; C.R. # 1: December 17, 1996

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

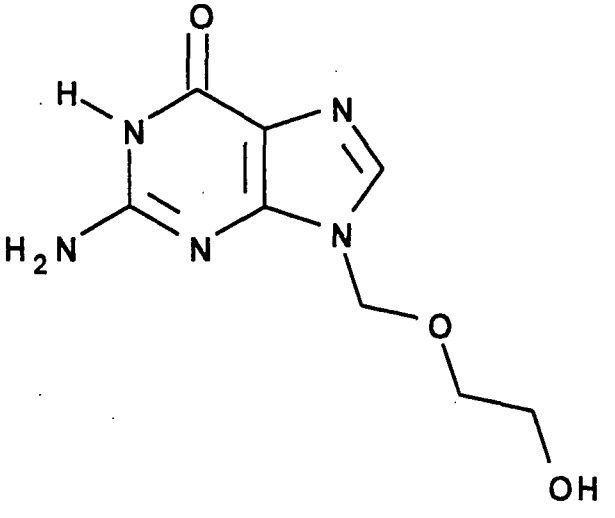
13. DOSAGE FORM
Capsule (Hard Gelatin)

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

$C_8H_{11}N_5O_3$; M.W. = 225.21



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

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. CMC issues are satisfactory
b. EIR acceptable for all firms 10/15/96 and 12/20/96.
c. Labeling satisfactory 11/5/97.
d. Final signoff by Div. Of Bioequivalence pending as of 10/17/97/
e. Methods validation satisfactory 9/22/97.
f. DMF status - refer to item # 37.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA can be approved upon sign-off by the Div. of Bioequivalence.

19. REVIEWER:
Donald Shostak

DATE COMPLETED:
October 20, 1997
(Revised 11/6/97 - labeling)

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Chem Review #2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* X Original FollowUp FUR	DATE November 15, 1996	PHONE NO. 594-0305	EER ID #
REQUESTORS NAME: Don Shostak/Tim Ames	DIVISION: OGD DC II		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: 74-914			
BRAND NAME:	ESTABLISHED NAME: Acyclovir		
DOSAGE STRENGTH: Capsule, 200 mg			STERILE Yes X No
PROFILE CLASS: CHG	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: Copley Pharmaceutical, Inc.			
APPLICANT'S ADDRESS: 25 John Road Canton Commerce Center Canton, MA 02021			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY ~	
1.	Testing of active & inactive ingredients and finished dosage form				
2.	Testing of active and inactive ingredients and finished dosage form				
3.	Testing of active and inactive ingredients and finished dosage form				
4.					
5.					

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)*	DATE	PHONE	EER ID #
Original ☐ FollowUp ☐ FUR	July 10, 1996	NO.594-0305	

REQUESTORS NAME Tim Ames	DIVISION: Office of Generic Drugs	MAIL CODE: HFD-647

APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-914

BRAND NAME: Zovirax	ESTABLISHED NAME: Acyclovir

DOSAGE STRENGTH: Capsules, 200 mg	STERILE ☐Yes ☒ No

PROFILE CLASS: CHG	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*

APPLICANT'S NAME: Copley Pharmaceutical, Inc

APPLICANT'S ADDRESS: 25 John Road
Canton Commerce Center
Canton, MA 02021

COMMENTS :

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY	
1. applicant	manufacturer of finished dosage form, testing and packaging	cru			
2	manufacturer of NDS	10685 csn			
3.					
4.					
5.					

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	COMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 74-914 HFD-647/Div. File, HFD-617/JWilson, HFD-647/Tim Ames
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CDER Establishment Evaluation Report for November 26, 1997

Application: **ANDA 74914/000**
Stamp: **19-JUN-1996** Regulatory Due:
Applicant: **COPLEY PHARM**
CANTON COMMERCE CENTER
25 JOHN RD
CANTON, MA 02021

Priority:
Org Code: **600**
Action Goal:
District Goal: **19-AUG-1997**
Brand Name:
Established Name: **ACYCLOVIR**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **200 MG**

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 20-DEC-1996 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 15-OCT-1996 by M. EGAS (HFD-322) 301-594-0095

Establishment:

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 20-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Establishment: **1221807**
COPLEY PHARMACEUTICAL INC
CANTON COMMERCE CENTER
25 JOHN RD
CANTON, MA 02021

DMF No:

AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 15-OCT-1996**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 20-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER

Establishment:

DMF No:

AADA No:

ACTON, MA 01720

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 20-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No: **10685**

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 26-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
