

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER 75021**

**ADMINISTRATIVE DOCUMENTS**

ANDA APPROVAL SUMMARY

ANDA: 75-021

DRUG PRODUCT: Acyclovir Tablets

FIRM: Copley Pharmaceutical, Inc.

DOSAGE FORM: Tablet

STRENGTH: 400 mg and 800 mg

CGMP STATEMENT: Included - p. 2971

EIR STATUS UPDATE:

Overall recommendation is acceptable - 4/28/97

BIO STUDY: Satisfactory

A bio study under fasting and food effect conditions was performed on the 800 mg tablet (Lot # 301Z01). The study was found acceptable per E mail dated 5/22/97 from Dr. Z. Whaba, HFD-650. A waiver of in-vovo testing requirements was granted for the 400 mg tablet.

VALIDATION: Satisfactory

The drug substance is a USP 23 item; methods validation is not required.

The request for methods validation for the drug product was originally deferred until the dissolution specification and method were resolved. The request package was forwarded to the Northeast Regional Lab on 11/14/97. Satisfactory 1/14/98.

STABILITY: Satisfactory

The stability testing protocol is satisfactory in regard to testing schedules, conditions and container/closure systems.

Testing includes:

Appearance: 400 mg tablet: Round, blue tablets, debossed "Copley 327" on one side, plain on the other.  
800 mg tablet: Blue capsule shaped tablet, debossed "Copley 301" on one side, plain on the other.

Assay

Dissolution: NLT ) is dissolved in 30 minutes.

Related Substances

Proposed expiration date is 24 months which is supported by the stability data. The data was obtained for the drug product packaged in the proposed market container/closure systems.

ANDA 75-021

LABELING: Satisfactory

labeling is satisfactory for approval - A. Vezza, HFD-613, 11/5/97.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH:

The bio study was performed on lot # 301Z01, 800 mg tablet. The batch size for this lot is                      tablets.

SIZE OF STABILITY BATCHES:

Stability data was submitted for the two ttest batches, i.e.,

Lot # 327Z01, 400 mg tablet,                      tablets  
Lot # 301Z01, 800 mg tablet,                      tablets

PROPOSED PRODUCTION BATCH:

The proposed production batch sizes are                      tablets for each strength.

CHEMIST: Donald Shostak

DATE: 11/14/97  
(Revised 3/5/98)

TEAM LEADER: Ubrani Venkataram

*3/5/98*  
DATE: 11/17/97

x:\wpfile\branch7\shostak\75021n02.sum                      (Disk 17)

FT by: pah/11/24/97  
x:\new\firmam\copley\ltrs&rev\75021.apf

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 75-021

Date of Submission: December 10, 1996

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Acyclovir Tablets 400 mg and 800 mg

Labeling Deficiencies:

1. GENERAL COMMENT

Revise your storage statement to read, "Store between 15° and 25°C (59° and 77°F)...", on all labels and labeling.

2. CONTAINER 400 mg and 800 mg (100s and 250s):

- a. We note that you have submitted an application for acyclovir capsules (ANDA 74-914). We encourage the use of boxing, contrasting colors, or other means to differentiate the expression of strength appearing on the container labels of your tablets from the expression of strength appearing on the container labels of your capsules.
- b. Revise your 400 mg container label to be consistent with your 800 mg tablet container label by revising your storage statement to read, "... and protect from light and ...".

3. INSERT

a. GENERAL COMMENT

- i. Use the abbreviation "mcg" rather than "µg" throughout your insert labeling.
- ii. Italicize the terms "*in vitro*" and "*in vivo*" where they appear in your insert labeling.
- iii. Print "Acyclovir" and "Acyclovir Capsules" in lower case letters, except when appearing at the beginning of a sentence. Please revise accordingly throughout the text of the insert.

b. DESCRIPTION

- i. Revise the first two sentences of the first paragraph to read as follows:

Acyclovir is an antiviral drug.  
Acyclovir capsules and tablets are formulated for oral administration.

- ii. Revise your list of inactive ingredients for your capsule formulation to be consistent with your list of inactive ingredients listed in your capsule application, (ANDA 74-914) and/or comment. Please note that if the alcohol inactives listed for your capsule formulation, (in the insert labeling submitted to ANDA 74-914) are lost in the manufacturing process due to evaporation they need not be listed.
- iii. Include the molecular formula of acyclovir,  $C_8H_{11}N_5O_3$ .
- iv. Make the following revisions in the last paragraph of this section:

- a) ... white to off-white, crystalline ...
- b) ... molecular weight of 225.21 ...
- c) Delete the word "daltons".

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

- i. Revise the third paragraph to read
- ... in aqueous solution; and in a separate study in 20 volunteers, it was shown that acyclovir suspension is bioequivalent to acyclovir capsules. In a different ...
- ii. Delete the text "in 6 volunteers" from the fifth paragraph.

d. INDICATIONS AND USAGE

- i. Genital Herpes Infection (Recurrent Episodes)

Revise the fourth paragraph to read as follows:

... for short periods (see PRECAUTIONS: ...

ii. Chickenpox

In the first sentence of the second paragraph, replace the period with a comma following the words "studies" and "rash".

e. PRECAUTIONS

- i. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise the last sentence of the first paragraph to read:

...schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

ii. Pediatric Use

...in pediatric patients less...

- f. ADVERSE REACTIONS (Observed During Clinical Practice: Nervous)

Revise this subsection to read as follows:

...paresthesia, seizure, somnolence...

g. DOSAGE AND ADMINISTRATION

- i. Chronic Suppressive Therapy for Recurrent Disease -

400 mg (two 200 mg capsules or one 400 mg tablet)...

ii. Acute Treatment of Herpes Zoster

... or one 800 mg ...

iii. Treatment of Chickenpox -

...per dose... [Use bold print]

h. HOW SUPPLIED

- i. Revise your capsule imprints to be consistent with your capsule imprints listed in the HOW SUPPLIED section of the insert labeling for your capsule application, (ANDA 74-914) and/or comment.

- ii. We encourage the inclusion of the following statement in this section:

**CAUTION: Federal law prohibits dispensing without prescription.**

- iii. To be consistent with your finished product specifications and your descriptive format of your 200 mg capsule and 400 mg tablet, revise the description of the 800 mg tablet as follows, and/or comment:

Acyclovir Tablets (capsule shaped, blue tablets) containing 800 mg acyclovir and debossed "Copley 301" on one side and plain on the other side.

- iv. Indicate that your tablets are unscored.

i. **REFERENCES**

- i. Reference 4 - "...by 9-(2-...)", (add hyphen after "9").
- ii. Reference 6 -  
... acyclovir. *Antimicrob Agents Chemother.* ...
- iii. Reference 21 -  
...acyclovir. *J Gen Virol*...
- iv. Reference 31, revise as follows:  
31. Goldberg LH, Kaufman R, Conant MA, et al. Episodic twice daily treatment for recurrent genital herpes. *Am J Med.* 1988; 85:10-13.
- v. Reference 38, revise as follows:  
38. Rotbart HA, Levin MJ, Hayward AR, Immune responses to varicella zoster virus infections in healthy children. *J Infect Dis.* 1993;167:195-199.

Revise your container labels and package insert labeling as described above, then prepare and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed package insert labeling with all differences annotated and explained.

---

**Jerry Phillips**  
**Director**  
**Division of Labeling and Program Support**  
**Office of Generic Drugs**  
**Center for Drug Evaluation and Research**

**NOTE TO THE CHEMIST**

Do you concur with our labeling comment 3(b)(ii) under DESCRIPTION?

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP Z3			X
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?	X		
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X, for unit dose		
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
<b>Labeling(continued)</b>	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in NOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
<b>Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR</b>			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the NOW SUPPLIED section?	X		
<b>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</b>			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration? *Some of the inactive ingredients differ from the RLD.	X*		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
<b>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</b>			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C<sub>max</sub>, T<sub>max</sub>, T 1/2 and date study acceptable)</b>			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		

Was CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. *See FTR, [this request is consistent with other ANDAs].	x*		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**FOR THE RECORD:**

1. This review was based on the labeling of ZOVIRAX® (Glaxo Wellcome: Approved 1/8/97; Revised 5/96).
2. Manufacturing:  
The manufacture is Copley Pharmaceutical, Inc., [Section IX].
3. Patents/Exclusivity  
The patent for the RLD expired on 4/22/97. [Approved Drug Products 17th ed./suppl.1]. No exclusivities. The firm's patent and exclusivity statement is accurate.
4. Storage:  
PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]  
NDA Store at 15°C to 25°C (59° to 77°F) and protect from moisture.  
ANDA Store at controlled room temperature 20°-25°C (68° to 77°F) and protect from light and moisture.
5. Dispensing:  
PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]  
NDA Dispense in a tight container as defined in the U.S.P.  
ANDA Dispense in a tight, light-resistant container as defined in the USP.
6. The chemical name in the DESCRIPTION section differs from the USP, however it is consistent with the RLD. This is acceptable.
7. The firm's list of inactive ingredients listed in DESCRIPTION section are consistent with their composition statement.  
[Vol. B1.1, p. 2841]

8. Container/Closure: 400 mg & 800 mg

100s - HDPE/CRC  
250s - HDPE/CRC  
[Vol. B1.2, p. 3112]

9. The tablet imprints listed in the HOW SUPPLIED section are consistent with the firm's physical description of their drug product in the application.  
[Vol. B1.2, p. 3240 & 3241]

10. CLINICAL PHARMACOLOGY (Pharmacokinetics) section:

We are requesting generic firms to delete the text "in 6 volunteers" from the fifth paragraph, which refers to the influence of food on the absorption.  
[See FTR in file folder].

11. Bioequivalence/Pharmacokinetic data

- Bio. acceptable letter: date 5/20/97 [Vol. B1.1]
- A waiver was granted for the 400 mg tablet.
- Both fasting & fed studies were done.
- Fasting study: results from bio. review of 5/16/97
  - The ANDA & RLD t<sub>1/2</sub> were comparable to each other & to the insert labeling [ANDA t<sub>1/2</sub>: 4.04hr, RLD t<sub>1/2</sub>: 3.97 hr, insert t<sub>1/2</sub>: 2.5 to 3.3 hr]
  - The other pharmacokinetics parameters of the ANDA were comparable to the RLD pharmacokinetics parameters.
- Fed study: results from bio. review of 5/20/97
  - C<sub>max</sub>, T<sub>max</sub> and AUC increased. [The innovator's labeling indicates that in a small, 6-subject study the influence of food on the absorption of acyclovir was not apparent]. See FTR from previous review below.

12. The following is from the previous review/reviewer for this drug product for a different ANDA with minor modifications.

- a. Fasting BE studies were done using the 800 mg tablet. The insert mentions a "no food effect" -

In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent.

Previous reviews of other BE studies have shown that food increases the AUC and C<sub>max</sub> by as much as 40 to 60% for both generic and reference product. Both these parameters were increased after food for the studies submitted to that ANDA as well. The DAVDP has been made aware of the food effect findings and a recommendation to change the Zovirax® labeling has been made.

- b. It was decided in a meeting between OGD and DAVDP that the issue of generic firms participation in the Pregnancy Exposure Registry should be based on BW's decision. This decision was forwarded to the Division of Antiviral Drug Products on 5/1/96 - that generic products not be allowed to refer to the pregnancy registry. The firm did not include this information in their insert.

---

Date of Review: May 19, 1997

Date of Submission: December 10, 1996

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Acyclovir Tablets 400 mg and 800 mg

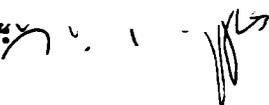
Primary Reviewer:  
Jacqueline White, Pharm.D.

Date:  
5-29-97

Secondary Reviewer:

Date:

5/29/97

Team Leader: 

Date:

5/29/97

cc:

ANDAs 75021na1.1  
DUP/DIVISION FILE  
HFD-613/JWhite/CHoppes/JGrace (no cc:)  
njg/5/29/97/x:\new\...\75021na1.111  
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75021

CORRESPONDENCE

ORIG AMENDMENT

*U/AM*



**COPLEY PHARMACEUTICAL, INC.**

25 John Road, Canton, MA 02021

Phone: (781) 575-7828

Fax: (781) 575-7362

**FAX**

*Regina S. Yeh*

<b>Fax to Number: (301) 443-3839</b>	<b>From: Regina S. Yeh, RAC Senior Regulatory Affairs Associate</b>
<b>Phone Number: (301) 827-5798</b>	<b>Date: 3/4/98</b>
<b>To: Mr. Tim Ames, CSO Office of Generic Drugs Food and Drug Administration 7500 Standish Place Rockville, MD 20855</b>	<b>Pages: 9 including cover</b>

**RE: Telephone Amendment for Acyclovir Tablets, 400 mg and 800 mg  
ANDA # 75-021**

Dear Mr. Ames:

Attached please find a facsimile copy of the telephone amendment for the above subject product. The amendment is regarding the revised raw material specifications and test methods for the Acyclovir drug substance, specifically pertaining to the

Please call me at (781) 575-7828 to confirm the receipt of the faxed material and the acceptability of the revised specifications and test methods. We will submit the hard copies (archival and CMC copies) via Federal Express mail service to Office of Generic Drugs following your telephone confirmation.

Please contact Mr. Nudelman (Director of Regulatory Affairs) at (781) 575-7695 or Regina Yeh at (781) 575-7828 should you have any question regarding the faxed material. Thank You!

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

March 2, 1998

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER (HFD600)  
Food and Drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville MD 20855-2773

Telephone Amendment  
Response to telephone request dated February 23, 1998  
Acyclovir Tablets, 400 mg and 800 mg  
ANDA# 75-021

Dear Mr. Sporn:

Reference is made to the above subject ANDA submitted to the Agency December 10, 1996, to the telephone amendment dated February 10, 1998, and to the Agency's telephone request from Mr. Tim Ames, CSO, Office of Generic Drugs dated February 23, 1998.

In the February 10, 1998 telephone amendment, Copley Pharmaceutical, Inc. had submitted a copy of the manufacturer's statement stating that the [redacted] listed in the USP XXIII (467), Second Supplement, Table I are not used in the synthesis of Acyclovir drug substance. In the February 23, 1998 telephone request, the Agency requests Copley to submit the revised raw material specifications and test methods with regard to the [redacted] based on the information provided by the bulk actives' supplier.

Enclosed in Attachment 1 are the revised raw material specifications and test procedures. The revision incorporates the specific statement: "a letter or COA must be received stating there is no potential for

to be present" for the



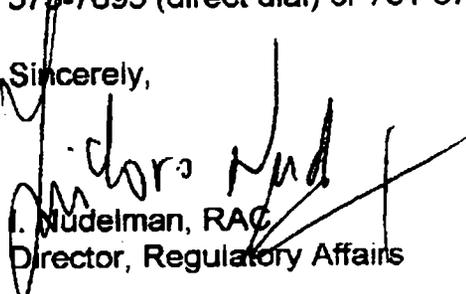
**Copley Pharmaceutical, Inc.**

**Telephone Amendment  
Response to telephone request dated February 6, 1998  
Acyclovir Tablets, 400 mg and 800 mg  
ANDA# 75-021**

page 2

Should there be any question related to this submission please call me at (781) 575-7695 (direct dial) or 781-575-7362 (fax).

Sincerely,

  
J. Rudelman, RAC  
Director, Regulatory Affairs

Enclosures: CMC copy and Archival copy



**Copley Pharmaceutical, Inc.**

**Telephone Amendment  
Response to telephone request dated February 23, 1998  
Acyclovir Tablets, 400 mg and 800 mg  
ANDA# 75-021**

**ATTACHMENT 1**

Revised raw material specifications and test procedures for Acyclovir, USP:

QC18-8214 Raw material test results for Acyclovir, USP (date revised: 2/28/98)

QC14-8214 Raw material test procedure for Acyclovir, USP  
(date revised: 2/28/98)

10/20/97

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER (HFD600)  
Food and Drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville MD 20855-2773

*AM noted  
To Chemistry Review  
than labeling revision  
for revision.  
W.E. 11/3/97*

BIOAVAILABILITY

*no per margo*

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

*FPL*  
ANDA ORIG AMENDMENT  
*jm*

**Supplemental Application  
Response to MINOR Deficiency letter of 6/12/97  
Acyclovir Tablets 400mg and 800mg  
ANDA# 75-021**

Dear Mr. Sporn:

Reference is made to our ANDA# 75-021, to the Agency's CMC deficiency letter of 6/12/97, the letter of 5/20/97 from the Division of Bioequivalence, and to the brand labeling information provided on 8/14/97. Attached is a full response to the Agency's letters including 12 copies of final printed labeling which incorporates the revisions requested by the Agency and the most current brand product labeling approved by the Agency as provided in your 8/14/97 communication.

We trust that this amendment will provide all the information required for final approval of our application. Please contact me for any additional information you may require (direct dial: 781-575-7520, FAX: 781-575-7362).

Sincerely,



W.E. Brochu, Ph.D.  
Director, Regulatory Affairs

**RECEIVED**

**OCT 29 1997**

**GENERIC DRUGS**

JUN 12 1997

ANDA 75-021

38. Chemistry Comments to be Provided to the Applicant

ANDA 75-021

APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Acyclovir Tablets, 400 mg and 800 mg

The deficiencies presented below represent FACSIMILE deficiencies.

Chemistry Deficiencies:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Since the finished drug product is non-USP, satisfactory methods validation must be performed by an FDA laboratory prior to the approval of this ANDA.

Sincerely yours,

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

E L E C T R O N I C M A I L M E S S A G E

Date: 25-Jul-1997 09:30am EDT  
From: Timothy Ames  
AMEST  
Dept: HFD-617 MPN2 113  
Tel No: 301-827-5849 FAX 301-594-3839

TO: Eda Howard ( HOWARDE )

CC: Mark Anderson ( ANDERSONM )

Subject: FWD: Overdue Faxes

Eda,

Please convert the following FACSIMILE AMENDMENT faxes to MINOR AMENDMENT (NM) status as of the date the FAs were sent, as the firms failed to respond within the 30 day time period.

ANDA 75-021-FA issued 6/12/97 convert to NM as of that date.

tim

*done! zj DMW  
7.25.97  
1.1*

FACSIMILE AMENDMENT

JUN 12 1997

ANDA/AADA: 75-021



OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

TO: APPLICANT Copley Pharm. Inc PHONE 617-827-8114 575 7363  
ATTN: Barbara Gaudreau FAX 617-827-1239 75-7362  
Robert William Brochu

FROM: Tim Ames, PROJECT MANAGER (301-594-0309) 827-5849

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 12/10/96, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Acyclovir Tablets, 400mg + 800mg.

Reference is also made to your amendment(s) dated \_\_\_\_\_

Attached are 6 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

**SPECIAL INSTRUCTIONS:**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.** If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

X:\new\ogdadmin\faxtrak\faxcov.fax

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 75-021

Date of Submission: December 10, 1996

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Acyclovir Tablets 400 mg and 800 mg

**Labeling Deficiencies:**

**1. GENERAL COMMENT**

Revise your storage statement to read, "Store between 15° and 25°C (59° and 77°F)...", on all labels and labeling.

**2. CONTAINER 400 mg and 800 mg (100s and 250s):**

a. We note that you have submitted an application for acyclovir capsules (ANDA 74-914). We encourage the use of boxing, contrasting colors, or other means to differentiate the expression of strength appearing on the container labels of your tablets from the expression of strength appearing on the container labels of your capsules.

b. Revise your 400 mg container label to be consistent with your 800 mg tablet container label by revising your storage statement to read, "... and protect from light and ...".

**3. INSERT**

**a. GENERAL COMMENT**

- i. Use the abbreviation "mcg" rather than "µg" throughout your insert labeling.
- ii. Italicize the terms "in vitro" and "in vivo" where they appear in your insert labeling.
- iii. Print "Acyclovir" and "Acyclovir Capsules" in lower case letters, except when appearing at the beginning of a sentence. Please revise accordingly throughout the text of the insert.

b. DESCRIPTION

- i. Revise the first two sentences of the first paragraph to read as follows:

Acyclovir is an antiviral drug.  
Acyclovir capsules and tablets are formulated for oral administration.

- ii. Revise your list of inactive ingredients for your capsule formulation to be consistent with your list of inactive ingredients listed in your capsule application, (ANDA 74-914) and/or comment. Please note that if the alcohol inactives listed for your capsule formulation, (in the insert labeling submitted to ANDA 74-914) are lost in the manufacturing process due to evaporation they need not be listed.
- iii. Include the molecular formula of acyclovir,  $C_8H_{11}N_5O_3$ .
- iv. Make the following revisions in the last paragraph of this section:
- a) ... white to off-white, crystalline ...
  - b) ... molecular weight of 225.21 ...
  - c) Delete the word "daltons".

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

- i. Revise the third paragraph to read
- ... in aqueous solution; and in a separate study in 20 volunteers, it was shown that acyclovir suspension is bioequivalent to acyclovir capsules. In a different ...
- ii. Delete the text "in 6 volunteers" from the fifth paragraph.

d. INDICATIONS AND USAGE

- i. Genital Herpes Infection (Recurrent Episodes)
- Revise the fourth paragraph to read as follows:
- ... for short periods (see PRECAUTIONS: ...

ii. Chickenpox

In the first sentence of the second paragraph, replace the period with a comma following the words "studies" and "rash".

e. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise the last sentence of the first paragraph to read:

...schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

ii. Pediatric Use

...in pediatric patients less...

f. ADVERSE REACTIONS (Observed During Clinical Practice: *Nervous*)

Revise this subsection to read as follows:

...paresthesia, seizure, somnolence...

g. DOSAGE AND ADMINISTRATION

i. Chronic Suppressive Therapy for Recurrent Disease -

400 mg (two 200 mg capsules or one 400 mg tablet)...

ii. Acute Treatment of Herpes Zoster

... or one 800 mg ...

iii. Treatment of Chickenpox -

...per dose... [Use bold print]

h. HOW SUPPLIED

i. Revise your capsule imprints to be consistent with your capsule imprints listed in the HOW SUPPLIED section of the insert labeling for your capsule application, (ANDA 74-914) and/or comment.

ii. We encourage the inclusion of the following statement in this section:

**CAUTION: Federal law prohibits dispensing without prescription.**

- iii. To be consistent with your finished product specifications and your descriptive format of your 200 mg capsule and 400 mg tablet, revise the description of the 800 mg tablet as follows, and/or comment:

Acyclovir Tablets (capsule shaped, blue tablets) containing 800 mg acyclovir and debossed "Copley 301" on one side and plain on the other side.

- iv. Indicate that your tablets are unscored.

**i. REFERENCES**

- i. Reference 4 - "...by 9-(2-...)", (add hyphen after "9").
- ii. Reference 6 -  

... acyclovir. *Antimicrob Agents Chemother.* ...
- iii. Reference 21 -  

...acyclovir. *J Gen Virol*...
- iv. Reference 31, revise as follows:  

31. Goldberg LH, Kaufman R, Conant MA, et al. Episodic twice daily treatment for recurrent genital herpes. *Am J Med.* 1988; 85:10-13.
- v. Reference 38, revise as follows:  

38. Rotbart HA, Levin MJ, Hayward AR, Immune responses to varicella zoster virus infections in healthy children. *J Infect Dis.* 1993;167:195-199.

Revise your container labels and package insert labeling as described above, then prepare and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed package insert labeling with all differences annotated and explained.

---

Jerry Phillips  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

ANDA 75-021

Copley Pharmaceutical, Inc.  
Attention: Robert Kelly  
25 John Road  
Canton Commerce Center  
Canton, MA 02021

FEB 3 1997



Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Acyclovir Tablets, 400 mg and 800 mg

DATE OF APPLICATION: December 10, 1996

DATE OF RECEIPT: December 11, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames  
Project Manager  
(301) 594-0310

Sincerely yours,

*Jerry Phillips* *2/3/97*  
Jerry Phillips  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

505(j)(2)(a)(ok)  
Cynthia Marie H. Weikel  
1/8/97

**Copley  
Pharmaceutical  
Inc.**

25 John Road  
Canton, Massachusetts 02021  
(617) 821-6111  
Mailroom Fax: (617) 821-4068

December 10, 1996

Mr. Douglas Sporn  
Director, Office of Generic Drugs  
CDER  
Food and Drug Administration  
Metro Park North II  
Room 150  
7500 Standish Place  
Rockville MD 20855-2773

**Acyclovir Tablets 400 mg and 800 mg  
ANDA Submission**

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, Copley Pharmaceutical, Inc. respectfully submits for your Division's review and approval our Abbreviated New Drug Application (ANDA) for Acyclovir Tablets, 400 mg and 800 mg strengths.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are:

(617) 575-7363 (direct dial)

(617) 575-7362 (fax).

Thank you for your prompt handling of this submission.

Sincerely,



Robert Kelly  
Manager, Regulatory Affairs

Enclosures:

Archive Copy (blue folder): 8 volumes

Bioequivalence Copy (orange folder): 7 volumes

Chemistry, Manufacturing, Controls Copy (red folder): 2 volumes

Methods Validation (2 copies, separate binders)

**RECEIVED**

**DEC 11 1996**

**GENERIC DRUGS**