CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74914

ADMINISTRATIVE DOCUMENTS

THIS UPDATED LABELING REVIEW SUPERSEDES THE PREVIOUS LABELING REVIEW FOR SUBMISSIONS DATED 2/14/97 AND 5/2/97.

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

ANDA Number: 74-914

Date of Submission: February 14, 1997 and May 2, 1997

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Acyclovir Capsules, 200 mg

Labeling Deficiencies:

INSERT

1. General Comment

   Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of the reference listed drug Zovirax® (Glaxo Wellcome Inc.; revised; March 1997 and approved May 29, 1997).

   [Please note: Previous labeling comments, [i.e., Revise the molecular weight to in accord with USP 23, use "mcg" rather than "μg", italicize *"in vitro"* and *"in vivo"*..., comments under HOW SUPPLIED] still apply to your ANDA.]

2. DESCRIPTION

   a. Revise the sentence of the first paragraph to read as follows:

      Acyclovir is an antiviral drug.

   b. You may delete from your list of inactive ingredients.

3. DOSAGE AND ADMINISTRATION (Treatment of Chickenpox)

   Bold the subsection heading.

4. **HOW SUPPLIED**

We encourage you to include the following statement in this section, "CAUTION: Federal law prohibits dispensing without prescription."

Revise your 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 further 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 reference listed drug 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

Enclosure: Insert labeling of the reference listed drug

M E M O R A N D U M

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

DATE: July 23, 1997

FROM: Don Shostak, Review Chemist, HFD-647 D. Shostak 7/23/97

THRU: Sema Basaran, Ph.D., Team Leader (Acting), HFD-647 S. Basaran 7/23/97

SUBJECT: Methods Validation Request for ANDA 74-914 (Acyclovir Capsules, 200 mg)

TO: Ella Walker, Supv. Chemist, HFR-NE560

Enclosed is one copy of the analytical methods for Acyclovir Capsules, 200 mg. Since this drug product is non-USP, methods validation is required prior to the approval of the ANDA. Also enclosed are copies of the components/composition statement, certificate of analysis and Form 2871a.

I have also enclosed a copy the applicant's original method for dissolution testing. We are requesting that the dissolution testing be performed by both procedures. Please note that the specification for dissolution testing should be:

> Not less than ` `%(Q) of the labeled amount of acyclovir is dissolved in 30 minutes.

The applicant is aware of the above dissolution specification.

The applicant's manufacturing facility address as indicated in the ANDA is:

Copley Pharmaceutical Inc.
Canton Commerce Center
25 John Road
Canton, MA 02021

Administrative contact: William E. Brochu, Ph.D.
Director, Regulatory Affairs
Telephone: (617) 575-7520

The drug product will be packaged in bottles of 100 capsules.

Please comment on the suitability of the analytical methods.

2.1

RECORD OF TELEPHONE CONVERSATION

I initiated a call to Dr. William Brochu of Copley Pharmaceutical Inc. He was out of the office, therefore I left a message for Mr. David Patan [voice mail] informing him that the our Office would fax the labeling comments and that the firm's response should be submitted as a telephone labeling amendment.

DATE 8/14/97

ANDA NUMBER
74914

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR x_ FDA

MADE _ BY TELE. _ IN PERSON

PRODUCT NAME
acyclovir capsules

FIRM NAME
Copley Pharmaceutical Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
message for Mr. David Patan

TELEPHONE NUMBER
617 821 6111 [fax 617 821 4068]

SIGNATURE
/S/

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 8/8/97

NDA NUMBER: 74-914

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: ACYCLOVIR CAPSULES

FIRM NAME: COPLEY

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: DR WILLIAM BROCHU DIR. REG. AFFAIRS

TELEPHONE NO.: 617-575-7520

I called Dr Brochu in regard to his FAX of 8/8/97 to correct a misunderstanding of the dissolution requirement for Acyclovir Capsules. In his FAX it was stated that the specification is NLT ((Q) in 30 minutes resulting in % being dissolved. The requirement is actually NLT % (Q) in 30 minutes resulting in % being dissolved.

Dr Brochu will discuss this specification with his Q/A people and get back with me via FAX. If he feels that Copley may not be able to easily meet the specification he will discuss the issue with Florence Tang, Deputy Director Div of Chemistry II.

This issue was discussed with Lucia Tang, Acting Team Leader Branch 6 and the call was made with her concurrence.

SIGNATURE: /S/

DIVISION: DIV. CHEM II HFD 647

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? There are at least 9 copies in the blue volume.

Container Labels: 200 mg - 100s: Satisfactory in final print as of the 2/14/97 submission.

Professional Package Insert Labeling: Satisfactory in final print as of the 5/2/97 submission.

NOTE: Bio. still incomplete.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Zovirax® Capsules

NDA Number: 18-829

NDA Drug Name: Zovirax®

NDA Firm: Glaxo Wellcome Inc.

Date of Approval of NDA Insert and supplement #:S-010- Approved 1/8/97; Revised 5/96.

Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: ZOVIRAX® (Glaxo Wellcome)

NOTE TO THE CHEMIST

1. The list of inactive ingredients listed in the DESCRIPTION section have been revised. Do you concur?

   Chemist/D.S. response: Concur 7/18/97

2. Do you concur with our labeling comment #1b under "Revisions needed post-approval" 1b?

   Chemist/D.S. response: Concur 7/18/97

3. The capsule imprints listed in the HOW SUPPLED section has been revised. Do you concur?

   Chemist/D.S. response: Concur 7/18/97

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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 23/suppl.6		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		
Error Prevention Analysis			
PROPRIETARY NAME			
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
PACKAGING -See applicant's packaging configuration in FTR			
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	
LABELING			

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	
Error Prevention Analysis: *LABELING* (Continued)	**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 HOW 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
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
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 of the innovator differ from this ANDA].	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	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

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?			
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	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. [See FTR in file folder]	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. Storage/Dispensing recommendations:

   Storage recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]

   NDA: -Store at 15° to 25°C(59° to 77°F) and protect from moisture.

   ANDA: Store at 15° to 25°C(59° to 77°F) and protect from light and moisture.

   Dispensing recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]

   NDA: Tight, light resistant container

   ANDA:Tight, light resistant container

3. Patents

   RLD's patent expired 4/22/97.

4. Components/Composition

The list of inactive ingredients in the DESCRIPTION section is consistent with the firm's revised composition and component statement.
[Vol. 2.1, p. 12]

5. Container/Closure

100s - CRC
[Vol. 1.2, p. 2809 & Vol. 2.1, p. 13]

6. The firm has revised the capsule imprints listed in the HOW SUPPLIED section and they are consistent with their finished product specifications report in Vol. 2.1, p.20.

7. PACKAGE SIZE

NDA - 100s & unit dose 100s
ANDA - 100s

8. The firm has a pending ANDA for a tablet formulation (75021), with a shared insert.

9. Bioequivalence/Pharmacokinetic data

-Bio. INCOMPLETE letter: date 9/25/96 [Vol. 1.1]
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 9/13/96
  -The ANDA & RLD t1/2 were comparable to each other & to the insert labeling [ANDA t1/2: 3.36 hr, RLD t1/2: 3.47 hr, insert t1/2: 2.5 to 3.3 hr]
-Fed study: results from bio. review of 9/25/96
  -Cmax decreased and Tmax increased. AUC~about the same. [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.

10. The following information is from a previous review/reviewer FTR.

a. The insert mentions 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 Cmax 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 this 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.

Date of Review: May 20, 1997 [Review updated 8/5/97-due to new RLD insert labeling-]

Date of Submission: February 14, 1997 and May 2, 1997

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Acyclovir Capsules 200 mg

Primary Reviewer:
Jacqueline White, Pharm.D. Date: 8/7/97

Secondary Reviewer: Date:

Team Leader: Date: 8/12/97

for/ John Grace

cc:
ANDA 74914ap.1
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes/JGrace (no cc:)
njg/8/6/97/x:\new\...\74914new.1
Review

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 7/18/97

NDA NUMBER: 74-914

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: ACYCLOVIR CAPSULES

FIRM NAME: COPLEY

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: DR WILLIAM BROCHU DIR. REG AFFAIRS

TELEPHONE NO.: 617-575-7520

I called Dr Brochu in regard to the dissolution information in the 6/14/97 amendment. I noted that Copley, in response to a Div of Bio letter of 9/25/96 changed their dissolution method and specification to that referred in the 9/25/96 letter from the Div of Bio. I informed Dr Brochu that the specification for capsules should be NLT 70(Q) in 30 minutes. Since Copley validated this method (JULY-AUG 1996 PF) they now have 2 validated methods but will have to let us know which one they prefer to use as the official method.

This telecon was initiated after discussion with Dr Sevva Basaran, acting Team Leader Branch 6. It was concluded that Copley misunderstood the letter from the Div of Bio as meaning the Div of Bio wanted Copley to use the July-Aug 1996 PF method and specification.

The call was made after discussion with Dr Basaran and with her concurrence

SIGNATURE: /S/

DIVISION: DIV CHEM II HFD 647

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION

I received a call from Ann Kuan on 4/15/97 regarding ANDA 74914. She inquired if there were any labeling deficiencies for this application. I informed her that a new adverse reaction was recently approved in January for the reference listed drug. I stated that the new adverse reaction was "seizure", under the *Nervous* subsection and should be revised to read "...paresthesia, seizure,...". I asked her some questions regarding our previous letter. She then requested that I speak with Bozena Wasil. I briefly asked Bozena Wasil -Should ethyl acetate, saranex, silicone or polystyrene be listed in the DESCRIPTION section as inactive ingredients? about the changes in the DESCRIPTION and HOW SUPPLIED sections of the insert labeling. I informed her that our review was not completed. However, the firm could submit revised final printed insert labeling with the above revision as a telephone amendment.

DATE 4/15/97

ANDA NUMBER
74914

IND NUMBER

TELECON

INITIATED BY **MADE**
_X APPLICANT/ _ BY
SPONSOR **TELE.**

FDA _ IN
PERSON

PRODUCT NAME
Acyclovir capsules

FIRM NAME
Copley

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ann Kuan &
Bozena Wasil

TELEPHONE NUMBER

SIGNATURE
/S/

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-914** Date of Submission: **October 29, 1997**

Applicant's Name: **Copley Pharmaceutical, Inc.**

Established Name: **Acyclovir Capsules, 200 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 200 mg - 100s
Satisfactory in final print as of the 2/14/97 submission.

Professional Package Insert Labeling:
Satisfactory in final print as of the 10/29/97 submission.

Post-approval revisions: PI - VIROLOGY, Antiviral Activities - "herpesviruses" (one word); PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility - third paragraph - "cytogenetic" (spelling).

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Zovirax® Capsules

NDA Number: 18-829

NDA Drug Name: Zovirax®

NDA Firm: Glaxo Wellcome Inc.

Date of Approval of NDA Insert and supplement #: 5/29/97 (S-020)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: ZOVIRAX® (Glaxo Wellcome)

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 23		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		
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
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	
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? FOR UNIT DOSE Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
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	
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 HOW 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

	Yes	No	N/A
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
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?		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	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
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	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		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 5/29/97; Revised 3/97).

2. Storage/Dispensing recommendations:

   Storage recommendations:

   PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]

   NDA: -Store at 15° to 25°C (59° to 77°F) and protect from moisture.

ANDA: - Store at 15° to 25°C (59° to 77°F) and protect from light and moisture.

Dispensing recommendations:

PF: Preserve in tight containers. [Vol. 22, no.4/copy in file folder-1996]
NDA: Tight, light resistant container
ANDA: Tight, light resistant container

3. Patents

RLD's patent expired 4/22/97.

4. Components/Composition

The list of inactive ingredients in the DESCRIPTION section is consistent with the firm's revised composition and component statement. [Vol. 2.1, p. 12]

5. Container/Closure

100s - CRC [Vol. 1.2, p. 2809 & Vol. 2.1, p. 13]

6. The firm has revised the capsule imprints listed in the HOW SUPPLIED section and they are consistent with their finished product specifications report in Vol. 2.1, p.20.

7. PACKAGE SIZE

NDA - 100s & unit dose 100s
ANDA - 100s

8. The firm has a pending ANDA for a tablet formulation (75-021), with a shared insert.

9. Bioequivalence/Pharmacokinetic data

-Bio. PENDING SIGN-OFF
-Both fasting & fed studies were done.
-Fasting study: results from bio. review of 9/13/96
  -The ANDA & RLD $t_{1/2}$ were comparable to each other & to the insert labeling [ANDA $t_{1/2}$: 3.36 hr, RLD $t_{1/2}$: 3.47 hr, insert $t_{1/2}$: 2.5 to 3.3 hr]
-Fed study: results from bio. review of 9/25/96
  -C_{max} decreased and T_{max} increased. AUC~about the same. [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.

10. The following information is from a previous review/reviewer FTR.

a. The insert mentions 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_{max} 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 this 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.

Date of Review: 11-4-97 Date of Submission: 10-29-97

Primary Reviewer: Adolph Vezza /S/ Date: 11/5/97

Team Leader: Charlie Hoppes /S/ Date: 11/5/97

cc:
ANDA 74-914
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc:)
aev/11/4/97|X:\NEW\FIRMSAM\COPLEY\LTRS&REV\74914.APL
Review

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

Date of Review: September, 1996

Date of Submission: June 18, 1996

Primary Reviewer: Jacqueline White, Pharm.D.

Secondary Reviewer: Chan Park, Ph.D.

ANDA Number: 74-914 Review Cycle: First [Draft]

Applicant's Name [as seen on 356(h)]: Copley Pharmaceutical, Inc.

Manufacturer's Name (If different than applicant):

Proprietary Name: None

Established Name: Acyclovir Capsules 200 mg

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 100s

Satisfactory in draft.

2. INSERT:

a. General Comments

i. When abbreviating micrograms we encourage you to use the abbreviation "mcg" rather than "μg". Please revise your insert labeling accordingly.

ii. Throughout your labeling print *"in vitro"* and *"in vivo"* in italic print.

iii. Print "Acyclovir" and "Acyclovir Capsules" in lower case letters, except when it appears at the beginning of a sentence. Please revise accordingly throughout the text of the insert.

b. DESCRIPTION

i. Include the molecular formula of acyclovir, $C_8H_{11}N_5O_3$.

ii. Please note there are now two official USP 23/NF 18 monographs for lactose. Please revise accordingly.

iii. We note you have listed "sodium starch glycolate" in your Component Statement. However, it is not listed in the Composition Statement nor in this section. Please comment and/or revise.

iv. Include the dyes in the imprinting ink in the list of inactive ingredients.

v. To be in accord with USP 23/NF 18, make the following revisions in the last paragraph:

> ...a white to off-white crystalline powder with a molecular weight of 225.21, and ...

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

Delete the third paragraph, "A single ... solution".

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

e. CONTRAINDICATIONS

... of the formulation.
[singular]

f. PRECAUTIONS

Pediatric Use

... in pediatric patients less ...

g. DOSAGE AND ADMINISTRATION

Treatment of Chickenpox

Revise this subsection to read as follows:

Children (2 years of age and older): 20 mg/kg **per dose** orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

h. HOW SUPPLIED

i. We note the description of your finished dosage form in the Finished Product Specifications is not consistent with the description of your drug product in this section, (i.e., "Copley 299, Acyclovir 200" verses "Copley Acyclovir 200"). Please comment and/or revise.

ii. Add a "semicolon" following the text "... Acyclovir 200".

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 package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed container labels. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept "printers proof" for the insert only for tentative approval of an application.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further 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 your last submission with all differences annotated and explained.

NOTE TO THE CHEMIST

1. Do you concur with our labeling comment under DESCRIPTION, 2(b)(iii)? Concur 11/22/96 /S/

2. Please review our labeling comment under HOW SUPPLIED regarding a discrepancy. Concur /S/ 12/4/96

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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.		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?			
Error Prevention Analysis			
PROPRIETARY NAME			
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
PACKAGING -See applicant's packaging configuration in FTR			
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	
LABELING			
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	
Error Prevention Analysis: *LABELING* (Continued)	**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 HOW 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
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
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 of the innovator differ from this ANDA].	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? [See FTR]	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? [See FTR]	x		
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	x		
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
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?			
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. [See comment under DESCRIPTION].	x		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [pending]			

Insert labeling references a food effect or a no-effect? If so, was a food study done? [SEE FTR]		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	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. [See FTR].			

FOR THE RECORD:

1. Labeling review was based on the labeling of ZOVIRAX® (Burroughs Wellcome: Approved 9/7/95; Revised 5/95). print-out.

2. Dispensing recommendations:

   USP: Not USP [However, USP packaging and storage for acyclovir is "Preserve in tight containers].
   NDA: Tight, light resistant container
   ANDA:Tight, light resistant container

   Storage recommendations:

   NDA: -Store at 15° to 25°C(59° to 77°F) and protect from moisture. [Insert]

   -Store at 15° to 25°C(59° to 77°F) and protect from light and moisture. [Container & Carton]

   ANDA: Store at 15° to 25°C(59° to 77°F) and protect from light and moisture. [For, container label and insert labeling].

3. Patents/Exclusivity

   RLD patent expires 4/22/97. The firm's patent certification and exclusivity statement is accurate.

4. Components/Composition

   The list of inactive ingredients in the DESCRIPTION section is not consistent with the firm's components statement. See comment under DESCRIPTION and NOTE TO THE CHEMIST. [Vol. 1.1, p. 000028].

5. Container/Closure

   100s - CRC
   [Vol. 1.2, p. 2809]

6. The firm's description of the appearance of the capsule imprint in the HOW SUPPLIED section is NOT consistent with the firm's descriptive appearance of their finished dosage form. See comment under DESCRIPTION and NOTE TO THE CHEMIST. [Vol. B1.10, p.3279]

7. PACKAGE SIZE

NDA - 100s & unit dose 100s
ANDA - 100s

8. The following information is from a previous review/reviewer FTR.

a. The insert mentions 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 Cmax 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 this 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.

/S/
Reviewer

11-19-96 / 11-19-96
Date

/S/
Team Leader,
Labeling Review Branch

11/22/96
Date

cc: ANDA 74-914
Division File
HFD-613/JWhite/CPark\JGrace (no cc)
njg/11/12/96/x:\new\...\Apothecon...\74914na1.l
Review