CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 18828/S010

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Approval Package for:

Application Number:NDA 18828/S010

Trade Name: Zovirax Suspension

Generic Name: (acyclovir)

Sponsor: Burroughs Wellcome Co.

Approval Date: February 26, 1992

INDICATION: Provide for the use of Zovirax suspension, capsules and tablets in the treatment of primary varicella infections.

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Application Number: NDA 18828/S010

APPROVAL LETTER

NDA 19-909/S-003
NDA 18-828/S-010
NDA 20-089/S-002

FEB 26 1992

Mr. Donald A. Knight
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Knight:

Please refer to your supplemental New Drug Applications (NDAs) dated October 18, 1990 (19-909/S-003 and 18-828/S-010) and February 11, 1992 (20-089/S-002), submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zovirax (acyclovir) Suspension, Capsules and Tablets, respectively.

In addition, please refer to your letter dated February 11, 1992 in which you agree to do additional post-marketing studies of acyclovir suspension, capsules and tablets in the treatment of chickenpox in normal children as outlined in Appendix C of this submission.

We also acknowledge receipt of your additional communication dated February 24, 1992, in which you further define and reaffirm your commitment to conduct the postmarketing studies referred to in your February 11, 1992 letter. In this communication you also agree to revise Attachment E of the draft labeling submitted in your February 21, 1992 communication as follows:

> **Treatment of Chickenpox:** 20 mg/kg (not to exceed 800mg) orally, 4 times daily for 5 days. "Therapy should be initiated at the earliest sign or symptom."

These supplemental applications provide for the use of Zovirax suspension, capsules and tablets in the treatment of primary varicella infections.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling dated February 21, 1992 as revised. Accordingly, these applications, with the labeling revisions above, are approved, effective as of the date of this letter.

These revisions are terms of the supplemental NDA approval. Marketing these products before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the products misbranded and an unapproved new drug.

Please submit twelve (12) copies of the FPL when it is available. This submission should be designated for administrative purposes an "FPL Supplement" to the approved NDAs. Approval of the supplement by FDA is not required before the labeling is used.

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

Sincerely yours,

/S/ 2/26/92

David W. Feigal, Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18828/S010

ADMINISTRATIVE DOCUMENTS

MEMORANDUM OF TELEPHONE CONVERSATION FEB 10 1992

NDA: 19,909/S-003 & S-004; 18-828/S-010 & S-012; 20-089/S-001

DATE: February 4, 1992

PRODUCT: Zovirax Suspension, Capsules and Tablets

SPONSOR: Burroughs Wellcome Co.

PARTICIPANTS: DAVDP
Donna Freeman, M.D. DSF 2/10/92
Dianne Murphy, M.D.
Carole Broadnax, CSO CB 2/10/92

and

Burroughs Wellcome
Sandra Lehrman, M.D.
Gray Davis, Ph.D.
Beverly Atwood, Pharm.D.
Elizabeth Andrews
Joan Drucker, M.D.
Karen Biron, Ph.D.
Nancy Bower
Dennis Troy, Marketing

SUBJECT: Follow-up to DAVDP's letter (NDA 19-909/S-003) to BW dated January 10, 1992, regarding labeling changes and requests for post-marketing studies of acyclovir suspension.

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Dr. Freeman initiated this call and had the following comments regarding BW's revised draft package insert dated January 23, 1992, and their draft response to post-marketing studies (copies attached).

Labeling - Attachment B

1. Please **bold** "within 24 hours" on lines three (3) and fifteen for ease of reading.

2. Dr. Freeman noted that it is confusing to sort out the results of the two (2) studies (e.g., patients ages 2 to 12 years and patients ages 13 to 18 years) referred to in the second paragraph (line 14). She stated that she will have to review specific sections of the NDA again to make sure these studies are properly represented in the labeling.

3. Dr Freeman commented that the material in lines 25 through 28 is in the NDA, but that inclusion of these results is new to the proposed labeling.

Labeling - Attachment C

4. Dr. Freeman requested that BW delete the first line of the **Herpes Zoster Infections** (line 23) and the **Chickenpox** (line 28) paragraphs. She commented that without the first sentence, the Herpes Zoster paragraph is fine. She asked BW to include a statement in the Chickenpox paragraph concerning their lack of information on the long term effects of treatment intervention on normal children with chickenpox.

5. From line 21 on, Dr. Freeman commented that BW should come up with phrasing that, in general, the disease is well tolerated and the degree of benefit from acyclovir is not dramatic. Dr. Lehrman stated that BW will put the phrase "one day" back in the labeling. Dr. Murphy commented that the greatest concern of the Advisory Committee is that the long term benefit of acyclovir is not known. Dr. Lehrman responded that the reason they have referred the reader back to the INDICATIONS AND USAGE section is so that they can judge for themselves what the differences are. Dr. Freeman stated that this may be difficult for the lay reader and that she is concerned that promotional materials are based on the way the label is written. Dr. Lehrman responded that BW will work on this.

BW's draft response to post-marketing studies

6. Regarding resistance, Dr. Freeman commented that virus isolated from a child pre-treatment is good and that the success of post-treatment isolation attempts may be so low as to not be worth the effort. She suggested that maybe virus could be obtained from peripheral blood. Dr. Biron responded that lesions are the most fertile culture area and that trying to obtain virus from blood will complicate things. She stated that she will need data from Dr. Balfour's study to determine how far into treatment the yield is good.

Dr. Freeman proposed the following:

1) Initiate a family study and look at the index case, and then specifically the exposed siblings. She commented that the drug will probably be used prophylactically even though it is not labeled for this.

2) Look at the sensitivity of isolates from the exposed siblings to monitor for insensitive virus if the drug is being used prophylactically. Such a study might be set up within a Health Maintenance Organization.

3) Why is the proposed four (4) arm treatment study being proposed in patients more than 12 years of age? Dr. Lehrman responded that she could not think of a prospective design for an exposure study.

BW concluded the conversation by offering to re-work the draft label again. They stated that the new draft would be arriving soon.

The conversation was cordial throughout.

cc: NDA ORIG. 19,909/S-003 & S-004; 18-828/S-010 & S-012; 20-089/S-001

HFD-530
HFD-530/ADMA/DMurphy
HFD-530/SMO/DFreeman/2-10-92
HFD-530/ASCSO/TDeCicco

HFD-530/CSO/CBroadnax/DRAFTED 2-6-92/EDIT 2-10-92

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APPLICATION NUMBER: NDA 18828/S010

CORRESPONDENCE

DF
2/11/92

Wellcome

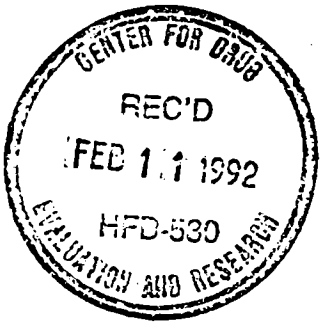
Burroughs Wellcome Co.

Donald A. Knight
Vice President
Drug Regulatory Affairs and
Scientific Administration

CR16

NDA NO. 20-089 REF. NO. 332
NDA SUPPL FOR SEI DRAFT

SEI 002



February 11, 1992

David W. Feigal, Jr., M.D., Director
Division of Antiviral Drug Products, HFD-530
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: SUPPLEMENTAL NEW DRUG APPLICATION
NDA 20-089
ZOVIRAX® (Acyclovir) Tablets

Dear Dr. Feigal:

We are submitting herewith a Supplemental New Drug Application to provide for the use of ZOVIRAX Tablets in the treatment of primary varicella infections.

For safety and efficacy data in support of this supplemental application, reference is made to our supplemental NDA for ZOVIRAX Suspension (NDA 19-909/S-003) submitted October 18, 1990.

A copy of the proposed package insert, identical to that submitted on this date to the ZOVIRAX Capsules and Suspension Supplemental NDAs, is attached. This package insert reflects changes discussed in the February 4, 1992, discussions between members of your division and B.W. Co.

If you have any questions concerning this application, please contact Dr. Beverly Atwood at (919) 248-8076.

Sincerely,

Donald A. Knight

TRZO/92/0073
DAK/cp(pr)*
Enclosure