CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-478

CORRESPONDENCE

Document Information Page

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Application #(s):	NDA 21-478
Document Type:	NDA Telecon
COMIS Decision:	
Drafted by:	HFD-530/RPM/Belouin-12/17/02
Revised by:	
Concurrence by:	HFD-530/MOTL/Laessig- HFD-530/MO/Wu-
Finaled:	HFD-530/RPM/Belouin-
Filename:	V:\DAVDP\CSO\ONeill\NDA\21-478 Zovirax Cream\Faxes\021217fx.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this document to the incoming document the telecon concerns. If there is no such document, then link the document to the initial submission of the NDA or supplement, as appropriate.

END OF DOCUMENT INFORMATION PAGE

The Fax begins on the next page.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 17, 2002

To: Grace Pagano	**From:** Sean J. Belouin, R.Ph
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: 919-483-5756	**Fax number:** 301-827-2523
Phone number: 919-483-5127	**Phone number:** 301-827-2481

Subject: Labeling changes regarding NDA 21-478

Total no. of pages including cover: 2

Comments: The following labeling changes for NDA 21-478 are on behalf of the review team:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 17, 2002

To: Grace Pagano, GlaxoSmithKline

Through: Katherine Laessig, M.D., Medical Team Leader, HFD-530
Teresa Wu, M.D., Medical Reviewer, HFD-530

NDA: 21-478 Zovirax® (acyclovir) Cream 5%

Subject: Labeling changes regarding NDA 21-478

The following labeling changes for NDA 21-478 are on behalf of the review team:

1. Replace all 'Use only for cold sores' with "[redacted]." (PI, package box, 2g tube)

2. Line 144-145, please delete "[redacted]" Since this paragraph focuses on 'local site events' for which the event rates were 5% and 4% for the Cream and vehicle, respectively, as described in the preceding paragraph.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

151

Sean J. Belouin, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

Document Information Page

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Application #(s):	NDA 21-478
Document Type:	NDA Telecon
COMIS Decision:	
Drafted by:	HFD-530/RPM/Belouin-12/04/02
Revised by:	
Concurrence by:	HFD-530/MOTL/Laessig- 1/5/ HFD-530/MO/Wu- 1/5/
Finaled:	HFD-530/RPM/Belouin- 1/5/
Filename:	V:\DAVDP\CSO\ONeill\NDA\21-478 Zovirax Cream\Faxes\021204fx.doc
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Linking Instructions:	Link this document to the incoming document the telecon concerns. If there is no such document, then link the document to the initial submission of the NDA or supplement, as appropriate.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2002

To: Grace Pagano	**From:** Sean J. Belouin, R.Ph
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: 919-483-5756	**Fax number:** 301-827-2523
Phone number: 919-483-5127	**Phone number:** 301-827-2481

Subject: Labeling changes regarding NDA 21-478

Total no. of pages including cover: 3

Comments: The following labeling changes for NDA 21-478 are on behalf of the review team:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 4, 2002

To: Grace Pagano, GlaxoSmithKline

Through: Katherine Laessig, M.D., Medical Team Leader, HFD-530
Teresa Wu, M.D., Medical Reviewer, HFD-530

NDA: 21-478 Zovirax ® (acyclovir) Cream 5%

Subject: Labeling changes regarding NDA 21-478

The following labeling changes for NDA 21-478 are on behalf of the review team:

10 pages redacted from this section of the approval package consisted of draft labeling

Document Information Page

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Application #(s):	NDA 21-~~380~~ 478
Document Type:	NDA Telecon
COMIS Decision:	
Drafted by:	HFD-530/RPM/Belouin-10/01/2002
Revised by:	
Concurrence by:	HFD-530/ChemTL/Miller- /S/ HFD-530/Chem/Gu- /S/
Finaled:	HFD-530/RPM/Belouin- /S/
Filename:	V:\DAVDP\CSO\ONeill\NDA\21-478 Zovirax Cream\Faxes\020827fx.doc 1001
DFS Key Words:	
Notes:	
Linking Instructions:	Link this document to the incoming document the telecon concerns. If there is no such document, then link the document to the initial submission of the NDA or supplement, as appropriate.

END OF DOCUMENT INFORMATION PAGE

The Fax begins on the next page.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2002

To: James A. Zisek, Project Director/CMC Submissions	**From:** Sean J. Belouin, R.Ph
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-2523
Phone number: 919-483-4423	**Phone number:** 301-827-2481

Subject: Chemistry comments regarding NDA 21-478, submission dated March 15, 2002

Total no. of pages including cover: 3

Comments: The following chemistry comments for NDA 21-478, submission dated March 15, 2002 are on behalf of Zi Qiang Gu, Ph.D and Steve Miller, Ph.D:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 1, 2002

To: James A. Zisek, Project Director/CMC Submissions, GlaxoSmithKline

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
Zi Qiang Gu, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-478 Zovirax ® (acyclovir) Cream 5%

Subject: Chemistry comments regarding NDA 21-478, submission dated March 15, 2002

The following chemistry comments for NDA 21-478, submission dated March 15, 2002 are on behalf of Zi Qiang Gu, Ph.D and Steve Miller, Ph.D:

CHEMISTRY

Questions and Response:

For —— Sample Pack for Zovirax Cream, 5%

1. Will the Division agree to accept an Amendment to the NDA (no late than November 2002) in order to provide a Sample Pack Update?

   Yes, an update prior to (date) would be acceptable.

2. If an Amendment is agreeable and it is limited to the sample pack data, will the Division conduct the review under the original review clock or is the Amendment likely to trigger an extension to the review clock?

   This would not trigger an extension to the review clock.

3. In view of the satisfactory — stability data on the trade pack, which is of same type and product contact materials to the tube proposed for the sample pack, does the Division agree that a — shelf-life may be assigned to the sample pack?

   We would recommend — , shelf-life for the sample pack initially assuming satisfactory batch analysis data. The shelf-life may be extended through annual report filings as real-time stability data on commercial-scale product becomes available (see recommendations in the Draft Stability Guidance at: http://www.fda.gov/cder/guidance/1707dft.pdf).

   We recommend that a commitment statement be provided in the amendment that the stability data for the sample pack will be monitored and analyzed, and any results not consistent with the trade pack will be reported to the Agency.

4. Does the Division agree that stability data on the sample pack may be submitted in future Annual Reports?

   The stability data on the sample pack may be submitted in future Annual Reports if the data show results consistent with stability data from the trade pack.

For an Alternate 2 g Trade Pack for Zovirax Cream, 5%

5. In view of the satisfactory — stability data on the original trade pack, which is of same type and product contact materials to the proposed alternate pack, does the Division agree that a — shelf-life may be assigned to the sample pack?

   We agree.

6. Does the Division agree that stability data on the alternative trade pack may be submitted in future Annual Reports?

   We agree.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Belouin, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

10/01/02 14:49
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
10/01	01'14"	919 990 5381	CALLING	03	OK	0000

10/01/02 14:48 DAVDP → 919194835381 NO.762 P01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2002

To: James A. Zisek, Project Director/CMC Submissions	**From:** Sean J. Belouin, R.Ph
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: 919-483-5381	**Fax number:** 301-827-2523
Phone number: 919-483-4423	**Phone number:** 301-827-2481

Subject: Chemistry comments regarding NDA 21-478, submission dated March 15, 2002

Total no. of pages including cover: 3

Comments: The following chemistry comments for NDA 21-478, submission dated March 15, 2002 are an behalf of Zl Qiang Gu, Ph.D and Steve Miller, Ph.D:

DOCUMENT INFORMATION PAGE

For internal use only.

Application #(s):	NDA 21-478
Document Type:	Meeting Minutes
COMIS Decision:	
Drafted by:	NP
Revised by:	
Initialed by:	~~HFD-530/Dir Birnkrant~~ HFD-530/Dep Dir/Murray- LSI HFD-530/CPM/DeCicco- LSI HFD-530/Acting MTL/Toerner- LSI HFD-530/Chem TL/Miller- LSI HFD-530/Chem/Gu- LSI HFD-530/RPM/Patel- LSI HFD-530/RPM/Young- LSI
Finalized:	
Filename:	V: \DAVDP\CSO\Young\NDA\nda 21478\meeting\02FEB22prendamm.doc
DFS Key Words:	Pre-NDA Teleconference
Notes:	DFSd on 3/25/02 NP
Linking Instructions:	

- Nisha - you can make these changes and keep the minutes moving forward. i.e. LSI

END OF DOCUMENT INFORMATION PAGE

The Meeting Minutes begin on the next page

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-478

GlaxoSmithKline
Attention: David M. Cocchetto, Ph.D.
Vice President, AV/AB Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Cocchetto:

Please refer to the teleconference between representatives of your firm and the FDA on February 22, 2002. The purpose of this Pre-NDA teleconference was to discuss the format and content of your pending New Drug Application for Zovirax® (acyclovir) Cream.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Nitin Patel, R.Ph., Regulatory Project Manager at (301) 827-2335.

Sincerely yours,

/S/

Anthony W. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment

Background
On July 30, 1999, Glaxo Wellcome (GW) submitted the original NDA 21-122 for Zovirax CS Cream 5% for the treatment of recurrent herpes labialis. The NDA was filed and given a standard 10-month review clock. However, on April 28, 2000, the Sponsor chose to withdraw the NDA.

In October 2001, the Sponsor expressed interest in reactivating the NDA and obtained a new NDA number, 21-478. On January 30, 2002, GSK submitted a briefing package and requested a pre-NDA meeting or teleconference to discuss the format and content of the re-submission of the NDA. Due to the Division's familiarity with this application, a teleconference was granted.

GSK plans to submit the NDA in late March 2002.

Discussion
In order to facilitate the discussion, the Sponsor submitted 11 questions in the briefing document. (Please note the Sponsor's question is in bold font and the Division's response is in regular font.)

1. **Is this use of paper and electronic components acceptable to the Division?**

   Yes, the Division finds both paper and electronic formats acceptable for an NDA submission.

2. **Does the Division accept this approach to the Table of Contents for NDA 21-478, including the method of distinguishing the new components of NDA 21-478?**

   The Division finds the Sponsor's proposed Table of Contents acceptable, however, the Division requested clarification on the intended patient population (Over-the Counter (OTC) use versus prescription only), since [redacted] are included in the proposed Table of Contents. The Sponsor intends Zovirax Cream to be available by a prescription only. As a result, the Division would be interested in reviewing only the safety information in these studies. The Division suggests this safety data be included in the Safety Update Report. (Please see Question 9 below).

3. **Is this updated content of Item 2 (Labeling) acceptable to the Division?**

   Without reviewing the proposed draft labeling, comments cannot be provided at this time. However, the Division approves of a patient package insert to help assure proper use of Zovirax Cream.

4. **Is provision of this Stability Update as a separate component in Item 4 acceptable?**

   Yes, the Division accepts the proposal to include the Stability Update, based on data collected since submission of the original NDA, as a separate component in Item 4.

5. **Is provision of GSK's responses as a separate component in Item 4 acceptable?**

   Yes, the Division finds it acceptable to include the responses to the Division's April 6, 2000 request to Glaxo Wellcome for additional information on specific CMC issues as a separate component in Item 4.

6. **Will the Division agree to accept an Amendment to the NDA (no later than September 2002) in order to provide stability data on the sample pack?**

   Yes, the Division agrees to accept an Amendment to the NDA (no later than September 2002) in order to provide stability data on the sample pack.

   In addition to the [redacted] sample pack mentioned in the briefing document, the Sponsor is considering using a [redacted] tube as a sample pack. The Division is unable to comment on this proposal because data have not been submitted on the [redacted] tube. The Sponsor will submit information for the Division's review.

7. **If an Amendment is agreeable and it is limited solely to this stability data, will the Division conduct the review under the original review clock or is the Amendment likely to trigger an extension to the review clock?**

   At this time, the Division does not anticipate that this Amendment would require an extension of the review clock, if it is limited solely to stability data and is received no later than September 2002.

8. **In view of the satisfactory 3-year stability data on the trade pack, will satisfactory 3 months stability data on the sample pack (at controlled room temperature and accelerated conditions) support a [redacted] shelf-life for the sample pack?**

   The Division is unable to answer this question prior to reviewing the data.

9. **Does the Division accept GSK's proposal to provide a Safety Update Report as part of the original submission of NDA 21-478?**

   Yes, the Division accepts the proposal to provide a Safety Update Report as part of the original submission of NDA 21-478.

10. **Does the Division agree that no further Safety Update Report should be planned by GSK, unless specifically requested by the Division during the review period?**

    The Division would like to review all post-marketing serious adverse events reported in other countries where Zovirax Cream is approved.
    An additional 120 day Safety Report to include all post-marketing adverse events data after December 31, 2001, should be provided for review.

11. **We welcome the Division's feedback on this proprietary name, as well as information on the likely timeline for formal acceptance of this name.**

    Once the label is received, a consult will be sent to the Office of Drug Safety (ODS) to review the Sponsor's proposed trade name, Zovirax Cream. However, the Division reminded the Sponsor that previous reviews for NDA 21-122 expressed concern over the tradename Zovirax [redacted] cream since [redacted] might be confused with corticosteriods. In addition, the review team identified that the proposed trade name, Zovirax Cream, may result in an inadvertent use for genital herpes. As a result, the Division recommended that '[redacted]' would provide clarity for the intended indication.

Summary/Action Items

1. The Sponsor will provide additional information on their proposal to use a [redacted] tube as a sample pack. The Division agrees to have further discussion after the review of this proposal.
2. Due to the review team's concerns that Zovirax Cream may result in its inadvertent use for genital herpes, the Sponsor will submit the carton labeling and commercial package for both Zovirax Cream and Zovirax [redacted] These labels will aid in the Office of Drug Safety's review.
3. The Division provided additional comments about potential post-marketing commitments that arose during the review of NDA 21-122:
   a. [redacted]
   b. [redacted]