CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22404Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	April 16, 2010
To:	Renata Albrecht, MD, Director Division of Special Pathogen and Transplant Products
Through:	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Kristina A. Toliver, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Oravig (Miconazole) Tablets, 50 mg
Application Type/Number:	NDA 022404
Applicant:	BioAlliance Pharma
OSE RCM #:	2009-1465

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Special Pathogen and Transplant Products for assessment of the Applicant's April 13, 2010 revisions to the container labels and carton labeling for Oravig Tablets to identify areas that could contribute to medication errors. These revisions were made in response to the Agency's label and labeling recommendations identified in OSE Labeling Review # 2009-1465, dated April 15, 2010.

2 MATERIAL REVIEWED

The Applicant provided revised label and labeling on April 13, 2010 (See Appendix A). We also evaluated the recommendations pertaining to the previous revisions in OSE review #2009-1465.

3 DISCUSSION

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2009-1465. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

3.1 CONCLUSION AND RECOMMENDATIONS

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective.

If you have further questions or need clarifications, please contact OSE Project Manager Karen Townsend, at 301-796-2311

1 page of draft labeling has been withheld as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	ORAVIG (miconazole) buccal tablets

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/s/

KRISTINA C ARNWINE
04/16/2010

CAROL A HOLQUIST
04/16/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	April 15, 2010
To:	Renata Albrecht, MD, Director Division of Special Pathogen and Transplant Products
Through:	Kristina A. Toliver, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Tselaine Jones Smith, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Oravig (Miconazole) Tablets, 50 mg
Application Type/Number:	NDA 022404
Applicant:	BioAlliance Pharma
OSE RCM #:	2009-1465

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from the Division of Special Pathogen and Transplant Products for assessment of the Applicant's January 22, 2010 revisions to the container labels and carton and insert labeling for Oravig Tablets to identify areas that could contribute to medication errors. These revisions were made in response to the Agency's label and labeling recommendations identified in OSE Labeling Review # 2009-1465, dated February 1, 2010.

1.2 REGULATORY HISTORY

The proprietary name, Oravig, was found acceptable in OSE Proprietary Name Reviews # 2009- 1462, dated January 27, 2010 and 2009-2209, dated November 10, 2009. The labels and labeling were previously reviewed in OSE Labeling Review #2009-1465, dated January 5, 2010.

On January 22, 2010, the Applicant submitted an Information Amendment (NDA 022404/SN0017) which included revised container labels, carton and insert labeling. We note the Applicant addressed most of DMEPA's container label and carton labeling recommendations from our January 5, 2010 review. During our review of the January 22, 2010 submission, we noted additional areas of concern. At the request of the Division of Special Pathogen and Transplant Products, our comments pertaining to the January 22, 2010 submission were forwarded to the Division in an e-mail dated March 30, 2010. These comments are contained in Appendix A. Subsequent to the Agency's communication; the Applicant e-mailed revised container labels, carton and insert labeling. The April 6, 2010 submission is the subject of this review.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the revised container labels and carton labeling by the Applicant via e-mail on April 6, 2010 (see Appendices B and C).

3 RECOMMENDATIONS

We note the Applicant addressed most of DMEPA's container label and carton labeling recommendations from the March 30, 2010 e-mail. However, DMEPA continues to note areas where the presentation of information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the container labels and carton labeling in Section 3.1. We request the recommendations be communicated to the Applicant, prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Karen Townsend, at 301-796-2311.

3.1 COMMENTS TO THE APPLICANT

3.1.1 General Comments

A. On the principal display panel, the dosage form is presented as 'tablet' rather than as 'tablets'. Revise to read as 'tablets' throughout the container labels and carton labeling.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1.2 Carton Labeling (2-count, Professional Sample)

A. Revise the statement of strength so that it is presented as 50 mg/tablet or 50 mg per tablet to ensure patients understand that each tablet contains 50 mg and will not administer the entire contents of the bottle.

Appendix A: Container labels, carton and insert labeling recommendations from the March 30, 2010 e-mail

1. Comments to the Division

   A. Package Insert Labeling (Full Prescribing -Dosage and Administration (Section 2.2)

      When compared to Section 17.1 (Patient Counseling Information), this section lacks important information with regards to instructions for proper use. For example,

      - If TRADENAME does not stick or falls off within the first 6 hours the same tablet should be repositioned immediately. If the tablet does not adhere, a new tablet should be placed.

      - If TRADENAME is swallowed within the first 6 hours it is recommended to drink a glass of water and a new tablet should be applied only once.

      - If TRADENAME falls off or is swallowed after it was in place for 6 hours or more a new tablet should not be applied until the next, regularly scheduled dose.

      Revise this section to include this important information as practitioners often rely on the Dosage and Administration section of the insert labeling for essential information with regards to the safe use of the product.

2. Comments to the Applicant

   A. General Comments

      As currently presented, the letter 'V' in the proprietary name has increased prominence, different font style and is presented in two different color fonts (e.g., blue and green) when compared to the other letters in the proprietary name on the container labels and carton labeling. In addition, the proprietary name 'Oravig' can be mistakenly read as two words, 'Ora' and 'Ig', since the letter 'V' resembles a checkmark that is placed between the two words. Revise the letter 'V' on the labels and labeling so that it is presented in the same format as the other letters in the proprietary name.

   B. Container Labels (2-count, Professional Sample)

      Present the entire '50 mg/tablet' statements in the same weight font in order to ensure that practitioner's patients understand that each tablet contains 50 mg.

3 pages of draft labeling has been withheld as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	ORAVIG (miconazole) buccal tablets

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/s/

KRISTINA C ARNWINE on behalf of TSELAINE E JONES SMITH
04/15/2010

KRISTINA C ARNWINE
04/15/2010

DENISE P TOYER
04/15/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-404	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: ORAVIG Established/Proper Name: Miconazole buccal tablet Dosage Form: buccal tablet Strengths: 50 mg		
Applicant: BioAlliance Pharma		
Date of Receipt: June 16, 2009		
PDUFA Goal Date: April 16, 2010	Action Goal Date (if different):	
Proposed Indication(s): treatment of oropharyngeal candidiasis		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 18-040 Monistat (miconazole) Injectable	Use in Specific Populations, Non-Clinical Toxicology
NDA 18-888 Monistat 3(miconazole nitrate) Vaginal Suppositories	Use in Specific Populations, Clinical Pharmacology, NonClinical Toxicology
Published Literature-	Clinical Pharmacology, Drug Interactions, Overdosage

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Applicant conducted 4 clinical studies and 3 non-clinical studies in support of their application. The three non-clinical studies, 31466TSH, 31370 TSH, and 31369 TSS provide the bridge from the approved product ([miconazole nitrate vaginal suppository and miconazole injectable]) and their product (50 mg buccal tablet). Both products are applied locally and exert their pharmacodynamic properties locally.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

All literature references list miconazole as the product used in their report

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Monistat (miconazole) Injectable	NDA 18-040	yes
Monistat 3 (miconazole nitrate) vaginal suppositories	NDA 18-888	yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

This is an NDA and not a supplement.

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

Approval letter for Monistat-3 indicates that this product was submitted under a 505(b) section of the FD&C act. As the applicant of record of all Monistat Products is Johnson & Johnson, it is to be assumed that all applications were 505(b).

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: NDA 18-040 for Monistat (miconazole), Injectable is a discontinued drug

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)
See reason for discontinuation on item d) above and reliance information on page 2

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form (buccal tablet), new dosing regimen, new route of administration, and a new indication (oropharyngeal candidiasis).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): Orange book lists numerous products (including generics) containing miconazole.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

There are no unexpired patents for miconazole products.

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

N/A YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): There are no unexpired patents for miconazole products

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole [redacted] tablet)

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/s/

JUDIT R MILSTEIN
04/15/2010
505(b)(2) Assessment Form

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: February 19, 2010

To: Judit Milstein, Chief Project Management Staff
Division of Special Pathogen and Transplant Products (DSPTP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Sharon Watson, Regulatory Review Officer
Marci Kiester, DTC Group Leader
Lisa Hubbard, Professional Group Leader
DDMAC

Subject: NDA 22-404
DDMAC labeling comments for ORAVIG (miconazole) Buccal Tablet

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DDMAC has reviewed the proposed product labeling (PI) for ORAVIG (miconazole) Buccal Tablet (Oravig) submitted for consult on January 15, 2010, and offers the following comments. DDMAC's comments on the proposed patient package insert (PPI) will follow under separate cover.

The version of the draft PI used in this review is titled, "Oravig Div Labeling 2-5-10.doc" and was emailed to DDMAC by DSPTP on February 5, 2010.

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the comments on the PI, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

20 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole (b) (4) (b) (4) tablet)

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/s/

KATHLEEN KLEMM
02/19/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 19, 2010
To:	Renata Albrecht, M.D., Director **Division of Special Pathogen and Transplant Products (DSPTP)**
Through:	Mary Willy, PhD, Deputy Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Barbara Fuller, RN, MSN, CWOCN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	ORAVIG (miconazole) Buccal Tablets
Application Type/Number:	NDA 22-404
Applicant/sponsor:	BioAlliance Pharma
OSE RCM #:	2009-1420

1 INTRODUCTION

This review is written in response to a request by the Division of Special Pathogen and Transplant Products (DSPTP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for ORAVIG (miconazole) Buccal Tablets. Please let us know if DSPTP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft ORAVIG (miconazole) Buccal Tablets Prescribing Information (PI) submitted June 16, 2009 and revised by the Review Division throughout the current review cycle.
- Draft ORAVIG (miconazole) Buccal Tablets Patient Package Insert (PPI) submitted on June 16, 2009 and revised by the Review Division throughout the current review cycle.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

14 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole (b) (4) (b) (4) tablet)

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/s/

BARBARA A FULLER
02/19/2010
DRISK Review of ORAVIG (miconazole) Buccal Tablets PPI

MARY E WILLY
02/19/2010

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

CLINICAL INSPECTION SUMMARY

DATE: February 16, 2010

TO: Judit Milstein, Supervisory Project Manager
Hala Shamsuddin, M.D., Medical Officer
Division of Special Pathogens and Transplant Products

FROM: Susan Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-404

APPLICANT: BioAlliance Pharma, Inc.
49 Boulevard du General Martial Valin
75015 Paris
France

REGULATORY CONTACT: Lavonne M. Patton, Ph.D.
Beckloff Associates
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

DRUG: Oravig (Lauriad (b) (4) miconazole buccal tablet)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Local treatment of oropharyngeal candidiasis

CONSULTATION REQUEST DATE: August 21, 2009

DIVISION ACTION GOAL DATE: April 11, 2010

PDUFA DATE: April 16, 2010

I. BACKGROUND:

Oropharyngeal candidiasis (OPC) is caused by *Candida spp*. fungi which are a commensal part of the normal flora in 20 to 60% of the population. However, fungal invasion of tissue may occur with resultant acute or chronic disease. Underlying host factors which may result in oropharyngeal candidiasis include human immunodeficiency virus (HIV) infection, hospitalization, diabetes mellitus, cancer chemotherapy, and denture use. The clinical presentation of OPC may include mouth soreness, burning, and/or altered taste. Clinical signs of OPC include white pseudomembranous plaques and patches (thrush), erythematous lesions, or angular chelitis. Untreated OPC may progress and invade the esophagus and the gastrointestinal tract or become more invasive, including fungemia or endocarditis. The options for treatment of OPC include topical delivery of antifungal therapy or systemic administration of antifungal agents. Topical agents are effective in the treatment of OPC, and due to their low systemic exposure, result in fewer adverse events and drug interactions than orally or intravenously administered antifungal agents. However, the most common causes of therapeutic failure using topical antifungal agents are noncompliance due to inconvenient formulation (e.g., mouthwash, gel, and troches), bad taste, and high levels of sugar to mask the unpleasant taste. In addition, the topical agents rapidly disappear from the oral cavity, requiring frequent daily dosing (three to five times a day) to maintain drug concentrations greater than the minimum inhibitory concentration (MIC). The goals in development of Lauriad® (b) (4) buccal tablets include broad antifungal spectrum of activity, improved salivary concentration, increased duration of miconazole exposure in the saliva with concentrations greater than the MIC, a convenient mode of administration, and once-daily application using an extended-release formulation.

The Lauriad® NDA was originally submitted on February 9, 2009 with an agency action of Refuse to File on April 3, 2009 due to the absence of code imprints on the Lauriad® tablets; in addition, amendments to the datasets were requested. The current Lauriad resubmission was received on June 15, 2009 (SN008). The proposed indication is local treatment of OPC using a Lauriad® dose of 50 mg daily. Miconazole was first approved in the U.S. in 1974 for topical treatment of fungal infections; it has been approved for use in numerous prescription and over the counter products and is marketed in over 100 countries. Significant adverse events after topical miconazole use have been uncommon.

Brief synopses of the protocols inspected are given below:

Protocol BA/2004/01/04: A comparative randomized, double-blind, double dummy, multicenter study of the efficacy and safety of miconazole Lauriad 50 mg administered once a day and Mycelex® Troches (clotrimazole 10 mg) administered five times a day in the treatment of oropharyngeal candidiasis in immunocompromised patients

This multicenter, Phase 3, randomized, double-blind, double-dummy study was conducted at 28 clinical sites in the U.S., Canada, and South Africa from July, 2006 to December, 2007; 30 sites screened patients. The primary objective of the study was to evaluate the clinical cure of miconazole Lauriad 50 mg (b) (4) buccal tablets once daily for 14 days compared with clotrimazole troches at Visit 5, the Test of Cure (TOC) visit (Days 17-22). This study enrolled adults with a clinical picture of oropharyngeal candidiasis; the patient was to be discontinued if the culture for *Candida spp*. was negative. Patients were to have documented HIV infection. Eligible patients were randomized to receive either Lauriad 50 mg (b) (4) buccal tablets once daily and placebo troches 5 times a day for 14 days or placebo buccal tablets once daily and clotrimazole troches 10 mg 5 times a day for 14 days. See the Table 3 from page 15 of the protocol for the Schedule of Study Procedures and Events. The primary efficacy measure was clinical cure at the TOC visit. Clinical cure was defined as a complete resolution of signs and symptoms.

Safety assessment included the rate and severity of adverse events (AEs) and serious adverse events (SAEs), local tolerability (gum irritation and application site inspection by the Investigator and oral discomfort rating by the patients), systemic exposure determined from plasma miconazole levels measured after 7 doses of miconazole Lauriad tablet (Day 7), adhesion time of buccal tablets and reasons for discontinued adhesion, number of (b) (4) buccal tablets detached and replaced, physical examination, and monitoring of hematology and biochemistry laboratory tests.

Brief Summary of Results

A total of 697 patients were screened, of which 578 were randomized (N = 291 in the miconazole group and N = 287 in the clotrimazole group). One patient randomized to the miconazole group lost all medications and was discontinued form the study, so that 290 patients were enrolled in the miconazole group and 287 in the clotrimazole group. Of the patients who received study drug, 23 patients in the miconazole group and 27 patients in the clotrimazole group withdrew from the study. In the miconazole group, the most common reasons for discontinuation included "other" (3.4%), noncompliance or protocol deviation (2.4%), lost to follow-up (1.0%), and Investigator decision (1.0%). In the clotrimazole group, the most common reasons for discontinuation were SAE (2.4%), lost to follow-up (2.4%), "other" (2.1%), death (1.7%), and noncompliance/protocol deviation (1.4%).

The predetermined noninferiority margin was 15%. For the ITT population, the clinical cure rates reported for the clotrimazole and miconazole groups were 65.2% and 60.7%, respectively. The treatment difference between the 2 groups was -0.045 with a 95% CI of (-0.124, 0.034). Similar findings were reported for the PP population. Lauriad miconazole was well tolerated and had good local tolerability. There were no clinically significant changes in laboratory test results, vital signs, or physical exam findings. Serum miconazole levels were undetectable following 7 days of therapy.

Protocol BA/2002/01/02: Comparison of the efficacy and safety of miconazole Lauriad tablets to those of miconazole gel in the treatment of oropharyngeal candidiasis: a multicenter randomized phase III trial in patients treated with radiotherapy for head and neck cancer

This multicenter Phase 3, randomized, parallel group, comparative trial with blind assessment of the primary endpoint at day 24 by a healthcare team member unaware of the treatment allocated to patients was conducted at 36 clinical sites in France and North Africa from May, 2002 to June 2004. The primary objective of the study was to compare the clinical efficacy of a 14 day miconazole Lauriad 50 mg bioadhesive buccal tablet treatment with that of miconazole gel 500 mg/day in 4 divided doses in the treatment of oropharyngeal candidiasis in head and neck cancer patients ≥ 18 years of age who have undergone radiotherapy. This study enrolled adults with oropharyngeal candidiasis (first episode or relapse) diagnosed on clinical criteria and mycological examination.

Eligible patients were randomized 1:1 to receive either miconazole Lauriad 50 mg bioadhesive buccal tablets, 50 mg/day in one topical administration (one bioadhesive tablet daily applied in the cuspid fossa in the morning after teeth brushing and remaining in the oral cavity until the tablet's complete erosion) or miconazole gel 125 mg 4 times daily (kept in the mouth as long as possible before swallowing). See the protocol pages 38-39 for the Investigation Schedule.

The primary endpoint was the success rate at day 14, based on oral examination, where success is defined as a complete or partial response. All other cases were considered as failure.

Safety assessment included the rate and severity of AEs and SAEs, local tolerability, physical examination, and monitoring of hematology and biochemistry laboratory tests.

Brief Summary of Results

There were 36 active centers which recruited 308 patients, 154 patients in each treatment group. Two randomized patients in the miconazole gel group were excluded (randomized after inclusion period, and one randomized before informed consent obtained). One patient was randomized in the miconazole Lauriad group, but took the miconazole gel and was therefore, considered in miconazole gel group in the safety population and in the mITT population. Six patients did not receive study drug, resulting in 354 subjects in the safety population, 147 in each arm. The mITT population consisted of all randomized patients with one efficacy evaluation after randomization having received at least one treatment dose (141 in the miconazole Lauriad group and 141 in the miconazole gel group). At Day 14, the success rate in the mITT population was higher in the miconazole Lauriad group (56.0%) than in the miconazole gel group (48.9%; 95% CI -19%, 4.8%). Success rates were similar in the PP population. The sponsor concludes that miconazole Lauriad was not inferior to miconazole gel in either the mITT or the PP populations, using a noninferiority margin of 20%. The study drugs were well tolerated, and there were no differences in the safety profile between miconazole Lauriad group and the miconazole gel group. Adverse events were rare, nonserious, and not unexpected. There were more reports of serious adverse events in the miconazole gel than in the miconazole Lauriad groups (7 versus 1 patient). The three deaths reported during the trial occurred in the miconazole gel group. None of the serious adverse events or deaths was considered treatment related.

Rationale for Site Selection

Only data from foreign sites is submitted with NDA 22-404 in support of Lauriad miconazole (b) (4) buccal tablets. The sites chosen for inspection were all relatively high enrollers in the two pivotal studies submitted with this NDA: Dr. Noveljic (Site 401); Dr. Ramlachan (Site 402); Dr. Ghaddari (Site 22); Dr. Daoud (Site 420). Of note, in Study BA2004/01/04, of the 101 subjects in the ITT population but not in the PP population, 25 (24.7%) and 17 (16.8%) were at Sites 405 and 402 respectively. The sponsor notified FDA on October 16, 2009 that the storage facility containing Dr. Ismael Mitha's (Site 405) study-related documentation for Study BA2004/01/04 in Benoni, South Africa was destroyed in a fire on August 28, 2009. As a result, source documents, medical records, and patient informed consent forms which were archived only at the storage facility were unavailable for inspection. After discussion with the review team, the decision was made to cancel the clinical investigator inspection of Dr. Mitha's site. Dr. Zoja Noveljic's site (Site 401) in South Africa which enrolled approximately 15% of the total subjects in study BA2004/01/04, was designated as a substitute.

II. RESULTS (by Site):

Name of CI, Location	Protocol #: and # of Subjects:	Inspection Date	Interim Classification	Final Classification
Dr. Zoja Noveljic Tiervlei Trial Centre Karl Bremmer Hospital Mike Pienaar Boulevard Bellville 7531 Capetown, South Africa Phone 021 945 9400 FAX 021 945 1836 Email: zoya@ttctrials.co.za	BA2004/01/04 Site 401 89 subjects	12/7/09 – 12/11/09	VAI	Pending
Padaruth Ramlachan Newlands West, 4037 Durban, South Africa Tel: +27 31 577 8932 Fax: +27 31 577 8757 Email: drprityh@medis.co.za	BA2004/01/04 Site 402 126 subjects	12/14/09 – 12/18/09	Pending	Pending
Dr.Brahim El-Ghaddari Institut National D'Oncologie Sidi Mohamed Ben Abdellah – Chu Rabatsale Chief de Service de Radiotherapie BP 6213 – Hay Ryad Rabat, Morocco Tel: 00.212.37.71.24.84 Fax: 00.212.37.71.24.68 Email: gued.io@sante.gov ma	BA2002/01/02 Site 22 40 subjects	12/7/09 – 12/11/09	Pending	Pending
Dr. Jamal Daoud UniversityHospital Center Habib Bourguiba Department of Radiotherapy Rue El Ferdaous Department of Carcinologic Radiotherapy 3029 SFAX Tunisia, Tunisia Tel: (216) 74 24 15 11 Fax: (216) 74 24 83 94 Email: jamel.daoud@rns.tn	BA2002/01/02 Site 42 52 subjects	12/14/09 – 12/17/09	Pending	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Dr. Zoja Noveljic**
   Tiervlei Trial Cenre
   Karl Bremmer Hospital, Mike Pienaar Blvd.
   Bellville 7531, Cape Town
   South Africa

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 104 subjects screened at this site, and 85 subjects were enrolled. During the inspection, sixteen subject records were reviewed to determine compliance with eligibility requirements, reconciliation of the investigational drug, and accuracy of the source documents in comparison to the case report forms and data listings provided by the sponsor. The observations noted are based on the EIR, communications with the field investigator, and a letter responding to the Form FDA 483 dated January 10, 2010 from Dr. Noveljic. There were no limitations to the inspection.

b. **General observations/commentary**: The inspection documented that the investigator did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration, did not adhere to the investigational plan in accordance with 21 CFR 312.60, did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation in accordance with 21 CFR 312.62(b), and failed to maintain adequate investigational drug disposition records with respect to quantity and use by subjects in accordance with 21 CFR 312.62(a).

Informed Consent Violations [21 CFR Part 50]

There were two subjects who signed Version 2.0 of the informed consent document, rather than the contemporaneous approved Version 2.1 of the informed consent document, which was approved on March 13, 2007 by the Ethics Committee and received by the site study coordinator on March 19, 2007. Subject 401023 signed Version 2.0 on April 23, 2007, was randomized, and completed the study on June 29, 2007 at which time she signed Version 2.1. Subject 401026 signed Version 2.0 of the informed consent document on April 23, 2007.

Medical Officer Comment: In Dr. Noveljic's written response of January 11, 2010, she notes that the only difference between Versions 2.0 and 2.1 was that the former describes obtaining 4 oral swabs during the study, while the latter describes obtaining 3. Although use of the incorrect version of the informed consent document represents a regulatory violation, it is doubtful that there was any significant impact on subject safety.

Protocol Violations 21 CFR 312.60

1. Six female subjects (401104, 401084, 401070, 401071, 401069, and 401064) were enrolled in the study using a double barrier method of contraception. The protocol specifies that female subjects must be using a "highly effective contraception method (i.e., hormonal or IUD) at least 1 month prior to study start and throughout the entire duration of the study". Permission for enrollment in the clinical trial was received after completion

of the trial. The Protocol Waiver Process documents located at the site state that the site will complete the Protocol Exception Form located in the Regulatory Binder. The form is then faxed to the Medical Monitor who grants or declines permission to enroll the subject. In Dr. Noveljic's written response letter of January 11, 2010, she states that double barrier contraception is "highly effective" and that some subjects were receiving treatment for tuberculosis which may render hormonal contraceptives less effective. She states that the Protocol Exception Forms were completed after the subjects were randomized at the project management team's request.

2. For the six subjects listed above, the date on which the waiver was granted should have been listed on page 14 of the CRF according to the CRF instructions; this date was omitted on all six CRFs, most likely due to absence of an area on the CRF to fill in the waiver date. The waiver date was also omitted for Subject 401030, who was granted a waiver for enrollment with a positive pregnancy test, which was thought to have been due to a recent stillborn pregnancy.

Medical Officer's Comment: Since the study protocol does not provide an exhaustive list of contraceptive methods which would be considered "highly effective', it is difficult to state definitively that failure to exclude subjects using double barrier contraception represents a protocol violation. Unintended pregnancy rates of male and female condoms used separately range from 15-21%, while hormonal contraception and IUD's have unintended pregnancy rates of less than 1%. However, according to the inspector, Dr. Noveljic and another South African clinical investigator were informed that the sponsor would not give "blanket approval' for inclusion in the trial while using double barrier contraception. Clearly, waivers should have been obtained for female subjects prior to enrollment in the study. There were no pregnancies reported during the trial; thus subject safety was not compromised.

Recordkeeping Violations [21 CFR 312.62]

1. Clinical observations were not always documented by the clinical investigator at the time of the subject visit. Specifically, an entry for Subject 401069 during Visit 3 indicates that there is "1-mild inflammation" at the LCF (left canine fossa). This entry was corrected on 10/16/07 by the investigator to read "IP attached".

Medical Officer's Comment: In Dr. Noveljic's written response of January 11, 2010, she notes that the sponsor project team requested the addition of "IP attached", as the troche (IP) would partially obscure the mucosa underneath the troche.

2. The time of application of clotrimazole troche/placebo and miconazole/placebo during Visit 2 for Subject 401069 were not documented in the statements written by the investigator.
3. Oral comfort status was graded at baseline as moderate in severity in the screening visit in the source document for Subject 40130, but graded as mild in the CRF.
4. The medical history in the source document for Subject 401049 indicates the subject was sterilized in 1994, but this information was not reported on the Medical and Surgical History case report form.

Inadequate Drug Disposition Records [21 CFR 312.62(a)]

The following subjects had discrepancies between the source record and the Drug Accountability Log/Master Investigational Product Log/Study Drug Destruction/Return Log (DAL):

1. The Visit 4 source record and CRF indicates that Subject 401030 returned 13 B(bis) tablets. The DAL states that 14 B(bis) tablets were returned.
2. The Visit 4 source record and DAL indicates that Subject 401049 returned 9 tablets in Bottle B (bis) Thirteen tablets in Bottle B(bis) are recorded on the Visit 4 CRF.
3. The Visit 4 source record and case report form for Subject 401069 state that 3 tablets from Bottle A were returned. The DAL states that four tablets from Bottle A were returned.

Medical Officer's Comment: These occurrences are considered isolated in occurrence, and are unlikely to impact data integrity. Furthermore, this finding represents more an issue with drug reconciliation, and not an issue with drug dispensation.

c. **Assessment of data integrity**: Although there were informed consent, protocol, recordkeeping, and drug dispensation violations reported from this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

2. Dr. Padaruth Ramlachan
Newlands West, 4037
Durban, South Africa

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 145 subjects screened at this site, 126 subjects were enrolled, and 114 completed the trial. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, the Form FDA 483, and a letter responding to the Form FDA 483 dated January 12, 2010 from Dr. Ramlachan. There were no limitations to the inspection.

b. **General observations/commentary**: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration, and did not adhere to the investigational plan, in accordance with 21 CFR 312.60.

Informed Consent Violations [21 CFR Part 50]

There were 71 subjects who signed Version 2.0 of the informed consent document, rather than the contemporaneously approved Version 2.1 of the informed consent document, which was approved on March 12, 2007 by the Ethics Committee and received by the investigator on March 16, 2007.

Medical Officer Comment: As noted in the discussion of the findings at Dr. Noveljic's site, the only difference between Versions 2.0 and 2.1 of the Informed Consent Document was that the former describes obtaining 4 oral swabs during the study, while the latter describes obtaining 3. Although failure to use the appropriate informed consent document is a

regulatory violation, it is doubtful that there was any significant impact on subject safety as a result.

Protocol Violations 21 CFR 312.60

1. Two SAEs were not reported to the sponsor within the required 24 hour time period. During Visit 4 on (b) (6) Subject 402039 was noted to be acutely ill and was transported by ambulance to a local hospital for treatment; it is not known if this subject remained hospitalized. This SAE was not reported to the sponsor until June 25, 2007. During Visit 3 on (b) (6) Subject 402065 was noted to unable to communicate or care for himself and was transferred from the clinical site to a local hospital. The SAE report was not reported to the CRO until July 27, 2007.
2. Two subjects were enrolled in the clinical trial despite not fulfilling the inclusion criteria. Subject 402001 was screened on 2/27/07; there was no neutrophil count recorded on the pathology report faxed to the site on 2/28/97. The subject was enrolled in the study on 3/1/07, despite the protocol requirement that that the neutrophil count be >750/mm^3. Subject 402035 was screened on 5/22/07; the pathology report faxed on 5/24/07 noted that the platelets were clumped, and accurate assessment of the platelet count was not possible. Despite lack of documentation that the subject's platelet count was > 100,000/mm^3, the subject was enrolled on 5/24/07.

   Medical Officer's Comment: Dr. Ramlachan stated in his written response of January 12, 2010 that the Pathologist was consulted in each case and provided verbal assurance that the laboratory value was in fact normal, based on the fact that the total WBC for Subject 402001 was normal and microscopic observation that the number of platelets present was normal, although not able to be quantified, for Subject 402035.

c. **Assessment of data integrity**: Although there were informed consent and protocol violations reported from this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

3. Brahim El Ghaddari, M.D.
Institut National D'Oncologie Sidi
Mohamed Ben Abdellah – Chu Rabatsale
Chief de Service de Radiotherapie
BP 6213-Hay Ryad
Rabat, Morocco

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 46 subjects screened at this site, 40 subjects were enrolled, and 40 completed the trial. The inspector reviewed 16 subject records during the inspection, and all informed consent documents were audited. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator and the Form FDA 483. There were no limitations to the

inspection.

b. **General observations/commentary**: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan in accordance with 21 CFR 312.60 and did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration.

Protocol Violations 21 CFR 312.60

1. Required photographs were not taken for any subject at this site, as required on Day 1, l4, 17, 30, and 60.
   Medical Officer's Comment: The primary efficacy endpoint was determined by physical examination, not photographs.
2. Subjects 1043, 3228, 3261, 3188, 3197, 3263, 3227, 3071, 3072, 3151, and 3152 were enrolled with a prothrombin time less than 80%, in violation of the Exclusion Criteria.
   Medical Officer's Comment: Since no invasive procedures were performed during this study and the study drugs have no effect on prothrombin time, this violation is unlikely to impact subject safety.

Informed Consent Violations [21 CFR Part 50]

Only copies of the informed consent documents were maintained at the site.

c. **Assessment of data integrity**: Although there were protocol, and informed consent violations reported from this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

4. Jamel Daoud, M.D.
University Hospital Center
Habib Bourguiba
Department of Radiotherapy
Rue El Ferdaous
Department of Carcinologic Radiotherapy
3029 SFAX
Tunis, Tunisia

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 58 subjects screened at this site, 53 subjects were enrolled, and 53 completed the trial. The inspector reviewed 19 subject records during the inspection, and all informed consent documents were audited. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator and the Form FDA 483. There were no limitations to the inspection.

b. **General observations/commentary**: Several deviations from FDA regulations

were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation in accordance with 21 CFR 312.62(b), did not adhere to the investigational plan in accordance with 21 CFR 312.60, and did not did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration.

Recordkeeping Violations [21 CFR 312.62(b)]

1. Of the 19 subjects audited, 9 did not have original source documents for fungal culture results from the contract laboratory: Subjects 2223, 2246, 1038, 2998, 2999, 3080, 3100, 3102, and 3120.
   Medical Officer's Comment: Copies of the fungal culture results were present at the site, and there were no discrepancies between these copies and the data listings/CRFs.
2. The source documents (hospital records) for Subject 3028 could not be located.
3. The source documents for Subjects 2997 and 2223 on Day 60 were dated one year after the date of the scheduled visit. The source documents contained an obliterated entry on October 31, 2003 for Subject 2244 and the date November 5, 2003 was added.
   Medical Officer's Comment: The inspector's opinion was that the added date of November 5, 2003 was to correct a transcriptional error, rather than fraudulent activity.
4. The inclusion visit of October 23, 2003 physician's notes are obliterated with white-out for Subject 2223.

Protocol Violations 21 CFR 312.60

Required photographs were not taken for any subject at this site, as required on Day 1, l7, 14, 30, and 60.

Medical Officer's Comment: The primary efficacy endpoint was determined by physical examination, not photographs.

Informed Consent Violations [21 CFR Part 50]

The informed consent form for Subject 2223 was initially dated October 27, 2003; this date was crossed out and a date of October 23, 2003 was added with a different pen, but without initials. The subject's pre-inclusion visit occurred on October 23, 2003.

c. **Assessment of data integrity**: Although there were recordkeeping, protocol, and informed consent violations reported from this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the inspections demonstrated that the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations.

The violations identified at these four sites should have any significant impact on data integrity or subject safety. The data submitted by BioAlliance Pharma Inc. may be used in support of the indication.

Follow-Up Actions: The observations noted above for Drs. Ramlachan, El-Ghaddari, and Daoud are based on preliminary communications with the field investigators and the Form FDA 483's issues at the three sites, as well as Dr. Ramlachan's written response dated January 10, 2010 to the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole [redacted] tablet)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN D THOMPSON
02/19/2010

TEJASHRI S PUROHIT-SHETH
02/19/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 5, 2010
To:	Renata Albrecht, MD, Director Division of Pathogen and Transplant Products
Through:	Kristina C. Arnwine, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Tselaine Jones Smith, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Oravig (Miconazole) Tablets, 50 mg
Application Type/Number:	NDA 22-404
Applicant:	BioAlliance Pharma
OSE RCM #:	2009-1461

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Special Pathogen and Transplant Products for a review of the container label, carton, insert and patient instructions for use labeling for Oravig from a medication error perspective.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the container label, carton, insert and patient instructions for use labeling that were submitted on June 15, 2009 (see Appendices A and B).

3 RECOMMENDATIONS

We noted areas where information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert and patient instructions for use labeling in Section 3.1, *Comments to the Division*. Section 3.2, *Comments to the Applicant,* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant, prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Catherine Carr, at 301-796-2311.

3.1 COMMENTS TO THE DIVISION

A. General Comments

DMEPA notes the dosage form is presented as '(b) (4) buccal tablets'. During the October 19, 2009 monthly review progress meeting (GAM) the Division noted that this dosage form was unacceptable and recommended 'buccal tablet' as the correct dosage form. Thus, the dosage form should be changed in all labels and labeling to reflect 'buccal tablets' rather than '(b) (4) buccal tablets'.

B. Package Insert Labeling (Full Prescribing

1. Dosage and Administration (Section 2)

A. Section 2.2

When compared to Section 17.1 (Patient Counseling Information), this section lacks important information with regards to instructions for proper use. For example,

- If TRADENAME does not stick or falls off within the first 6 hours the same tablet should be repositioned immediately. If the tablet does not adhere, a new tablet should be placed.
- If TRADENAME is swallowed within the first 6 hours it is recommended to drink a glass of water and a new tablet should be applied only once.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- If TRADENAME falls off or is swallowed after it was in place for 6 hours or more a new tablet should not be applied until the next, regularly scheduled dose.

Revise this section to include this important information as practitioners often rely on the Dosage and Administration section of the insert labeling for essential information with regards to the safe use of the product.

3.2 COMMENTS TO THE APPLICANT

1. General Comments

a. The proprietary name is not included on the proposed labels and labeling. Revise the labels and labeling to include the proprietary name and resubmit the labels and labeling to the Division of Medication Error Prevention and Analysis so that we can evaluate the appearance of the proprietary name on the labels and labeling from a safety perspective.

b. Ensure that the established name is at least one-half the size of the proprietary name and has a prominence commensurate with the prominence of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

c. The dosage form is presented as '(b) (4) buccal tablets'. The use of the term '(b) (4) as part of the dosage form in unacceptable. The preferred term for the dosage form is 'buccal tablets'. Thus, the dosage form should be changed in all labels and labeling to reflect 'buccal tablets' rather than '(b) (4) buccal tablets

2. Container Labels (Trade -14 count)

a. As currently presented, the strength appears on the side panel. Relocate the strength to the principal display panel so that the presentation of the proprietary name, established name, dosage form and strength is consistent with the format of this information on the carton labeling.

b. Relocate the 'Rx only' statement to the side panel to allow room on the principal display panel for the proprietary name, established name, dosage form and strength.

c. If space permits, include the statement 'Do not chew, crush or swallow tablets' on the side panel.

d. Remove the statement (b) (4) that is located on the side panel as it does not include the complete dosing instructions.

3. Container Labels (Professional Sample-2 count)

a. See Comments 2a through 2d

b. Postmarketing evidence has shown that patients may mistake the entire contents of the container as one dose if a 'per tablet' statement is not included in conjunction with the strength. Revise the presentation of the strength to read '50 mg per tablet' or '50 mg/tablet'.

4. Carton Labeling (Professional Sample-2 count, Trade-14 count)

a. Increase the prominence of the statement 'Each (b) (4) tablet contains 50 mg of miconazole.'

b. Revise the statement (b) (4) to read as 'Do not chew, crush or swallow tablets' in order to maintain consistency with the insert labeling. Increase the prominence of this statement.

c. Remove the statement (b) (4) that is located on the side panel as it does not include the complete dosing instructions.

3 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole [redacted] tablet)

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/s/

TSELAINE E JONES SMITH
01/05/2010

KRISTINA C ARNWINE
01/05/2010

DENISE P TOYER
01/05/2010

DSI CONSULT: Request for Clinical Inspections

Date: August 21, 2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan D. Thompson, M.D. Medical Officer
Division of Scientific Investigations
Office of Compliance/CDER

Through: Renata Albrecht, M.D., Division Director Division of Special Pathogen and Transplant Products (DSPTP)
Yuliya Yasinskaya, MD, Acting Team Leader, DSPTP
Hala Shamsuddin, M.D., Medical Reviewer, DSPTP

From: Christina H. Chi, Ph.D., Regulatory Health Project Manager, DSPTP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-404/S-000 (original)
Applicant: BioAlliance Pharma, Inc.
Applicant representative: Beckloff Associates, Inc.
Contact information: Lavonne M. Patton, Ph.D.
LPatton@beckloff.com
7400 West 110th Street, Suite 300
Overland Park, Kansas 66210
913-451-3955 (phone)
913-661-3814 (direct)
913-451-3846 (fax)

Drug Proprietary Name: Lauriad miconazole (b) (4) buccal tablet, 50 mg.
NME (Yes/No): No
Review Priority (Standard or Priority): S
Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity (Yes/No): No
Proposed New Indication: For Local Treatment of Oropharyngeal Candidiasis (OPC)

PDUFA: April 16, 2010
Action Goal Date: April 11, 2010
Inspection Summary Goal Date: February 16, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 405 Ismael Mitha Benmed Park Clinic 1 Mowbay Avenue Benoni 1507, South Africa Phone: +27 (0) 11 422 1928 Fax: +27 (0) 86 672 8441 Site 402 Padaruth Ramlachan Newlands West, 4037 Durban, South Africa Phone: +27 31 577 8932 Fax: +27 31 577 8757	BA2004/01/04	113/577 subjects (19.6%) 126/577 (21.8%)	Oropharyngeal Candidiasis (OPC)

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 22 Dr. Lamya Kanouni Dr. Brahim El-Ghaddari Dr. H. El-Omari Alaoui Dr. Aziz Mansouri National Institute of oncology Department of radiotherapy BP 6213 Agdal Rabat, Morocco Tel : not listed Fax : 212 377 124 69	BA2002/01/02	40/282 (14.2%)	Oropharyngeal Candidiasis (OPC)
Site 42 Dr. Jamal Daoud University Hospital center Habib Bourguiba Department of radiotherapy Rue El Ferdaous Department of carcinologic radiotherapy 3029 SFAX Tunisia, Tunisia Tel : (216) 74 24 15 11 Fax : (216) 74 24 83 94		52/282 (18.4%)	

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

BA2004/01/04

Site 405 randomized 113/577 (19.6%) patients, response rate (ITT) was numerically lower than other sites, though equal in both treatment arms.

Site 402 randomized 126/577 patients (21.8%).

The study as a whole randomized 577 patients that constituted the ITT population, and 476 patients constituted the PP population. The PP population included patients who received at least 10 days of therapy, had an efficacy evaluation at test of cure visit, were compliant within 71.4% and 120%, and

did not have a major protocol violation. Of the 101 patients in the ITT but not in PP, 25 (24.7%) and 17 (16.8%) were at sites 405 and 402 respectively.

BA2002/01/02
Efficacy rate at Site 22 was numerically lower for the study's drug than for the comparator drug (25% vs. 60%, compared to 56% vs. 49% for the study as a whole). It also reported almost all the "bad taste" reported in the adverse events (9/10).

Efficacy rate at Site 42 was numerically higher than the efficacy rates at other sites, though equal in both arms. (85.1% for sponsor's drug, vs. 88% for comparator, compared to 56% and 49% respectively for the study as a whole)

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
x Only foreign data are submitted to support an application (for study BA2002/01/02
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
x Other (specify)

Enrollment of large number of patients for study BA2004/01/04

For study BA2004/01/04 the sponsor contracted an independent auditor, (b) (4), to audit centers 101, 105, 401, 402, 405 and 413. Audit certificates were included in the submission.

For study BA2002/01/02, the sponsor contracted an independent auditor, (b) (4), to audit centers 17, 22, 42 and 60. Audit certificates were included in the submission.

IV. **Tables of Specific Data to be Verified**

Should you require any additional information, please contact Christina H. Chi, Ph.D., Regulatory Health Project Manager, at 301-796-0695 or Hala Shamsuddin, M.D., Medical Reviewer, at 301-796-1600.

Concurrence: (as needed)

Yuliya Yasinskaya, M.D., Acting Medical Team Leader (Concurrence: 8-14-09)
Hala Shamsuddin, M.D., Medical Reviewer
Renata Albrecht, M.D., Division Director (Concurrence: 8-18-09)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22404	ORIG 1	BIOALLIANCE PHARMA	Lauriad (miconazole (b) (4) (b) (4) tablet)

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/s/

CHRISTINA H CHI
08/21/2009

RENATA ALBRECHT
08/21/2009

MEMORANDUM

To: **Judit Milstein**
Division of Special Pathogen and Transplant Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **March 2, 2010**

Re: **Comments on draft labeling for Oravig (miconazole) buccal tablets**
NDA 22-404

We have reviewed the proposed label for Oravig (FDA version dated 2/23/10 and received by SEALD 2/25/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

17 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole [redacted] tablet)

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/s/

IRIS P MASUCCI
03/11/2010

LAURIE B BURKE
03/16/2010