

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22404Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED UPON AND
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation or
Composition) and/or Method of Use**

NDA NUMBER

22-404

NAME OF APPLICANT/NDA HOLDER

BioAlliance Pharma

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME

ORAVIG

ACTIVE INGREDIENT(S)

Miconazole

STRENGTH(S)

50 mg

DOSAGE FORM

Buccal Tablet

APPROVAL DATE OF NDA OR SUPPLEMENT

April 16, 2010

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,916,485

b. Issue Date of Patent

07/12/2005

c. Expiration Date of Patent

09/11/2022

d. Name of Patent Owner

BioAlliance Pharma

Address (of Patent Owner)

49 boulevard du Général Martial Valin

City/State

Paris

ZIP Code

75015 PARIS - FRANCE

FAX Number (if available)

+33 1 45 58 08 81

Telephone Number

+33 1 45 58 76 00

E-Mail Address (if available)

aude.michel@bioalliancepharma.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Ms Mary Anne Armstrong, PhD

Address (of agent or representative named in 1.e.)

P.O. Box 747

City/State

Falls Church, Virginia

ZIP Code

22040-6747

FAX Number (if available)

(703) 205-8050

Telephone Number

(703) 205-8000

E-Mail Address (if available)

mailroom@bskb.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

| | | |
|--|------------------------------|--|
| 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |
| 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |
| 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. | | |
| 2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.) | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |
| 2.6 Does the patent claim only an intermediate? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |
| 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

| | | |
|---|---|--|
| 3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |
| 3.2 Does the patent claim only an intermediate? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |
| 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

| | | |
|---|---|---|
| 4.1 Does the patent claim one or more approved methods of using the approved drug product? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |
| 4.2 Patent Claim Number(s) (as listed in the patent) 48 | Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |

| | |
|--|---|
| 4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. | Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Method of use for treating oropharyngeal candidiasis with a (b) (4) buccal tablet applied to the gum and containing 50 mg per tablet. |
|--|---|

| | |
|--|--|
| 4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description. | Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.) Treatment of oropharyngeal candidiasis |
|--|--|

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

| | |
|--|-------------------------------|
| 6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) | Date Signed 05/26/2010 |
|--|-------------------------------|

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

| | |
|--|---|
| <input checked="" type="checkbox"/> NDA Applicant/Holder | <input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| <input checked="" type="checkbox"/> Patent Owner | <input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |
| Name BioAlliance Pharma | |
| Address 49 boulevard du Général Martial Valin | City/State Paris |
| ZIP Code 75015 PARIS - FRANCE | Telephone Number +33 145 58 76 01 |
| FAX Number (if available) +33 145 58 08 81 | E-Mail Address (if available) dominique.costantini@bioalliancepharma.com |

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 Office of Chief Information Officer (HFA-710)
 5600 Fishers Lane
 Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED UPON AND
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

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1. GENERAL

a. United States Patent Number

17,651,698

b. Issue Date of Patent

01/26/2010

c. Expiration Date of Patent

01/08/2026

d. Name of Patent Owner

BioAlliance Pharma

Address (of Patent Owner)

49 boulevard du Général Martial Valin

City/State

Paris

ZIP Code

75015 PARIS - FRANCE

FAX Number (if available)

+33 1 45 58 08 81

Telephone Number

+33 1 45 58 76 00

E-Mail Address (if available)

aude.michel@bioalliancepharma.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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Falls Church, Virginia

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| 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> No |
| 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
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FDA will not list the patent in the Orange Book as claiming the drug product if:

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4. Method of Use

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| | | |
|--|---|-----------------------------|
| 4.1 Does the patent claim one or more approved methods of using the approved drug product? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |
| 4.2 Patent Claim Number(s) (as listed in the patent) 1 to 17 | Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | |

| | |
|---|---|
| 4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. | Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Method of use for treating oropharyngeal candidiasis with a (b) (4) buccal tablet applied to the gum and containing 50 mg per tablet. |
|---|---|

| | |
|--|--|
| 4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description. | Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.) Treatment of oropharyngeal candidiasis |
|--|--|

FDA will not list the patent in the Orange Book as claiming the method of use if:

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- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

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Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

| | |
|--|-------------------------------|
| 6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) | Date Signed 05/26/2010 |
|--|-------------------------------|

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Check applicable box and provide information below.

| | |
|--|---|
| <input checked="" type="checkbox"/> NDA Applicant/Holder | <input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| <input checked="" type="checkbox"/> Patent Owner | <input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |
| Name BioAlliance Pharma | |
| Address 49 boulevard du Général Martial Valin | City/State Paris |
| ZIP Code 75015 PARIS - FRANCE | Telephone Number +33 145 58 76 01 |
| FAX Number (if available) +33 145 58 08 81 | E-Mail Address (if available) dominique.costantini@bioalliancepharma.com |

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 Office of Chief Information Officer (HFA-710)
 5600 Fishers Lane
 Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-404

Division of Special Pathogen and Transplant Products

Trade Name ORAVIG

Generic Name miconazole buccal tablets

Applicant Name BioAlliance Pharma

Approval Date, If Known April 16, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA# 18-888 Monistat 3 (Miconazole suppositories)

NDA# 18-040 Monistat (miconazole) Injectable

There are 3 Rx products and more than 15 OTC products listed in the Orange Book for miconazole

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation 1- Study BA2004/01/04 – 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.

Investigation 2- Study BA2002/01/02-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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study BA2004/01/04 – 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

Study BA2002/01/02-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

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Judit Milstein
Title: Chief, Project Management Staff
Date: 4/5/10

Name of Office/Division Director signing form: Renata Albrecht, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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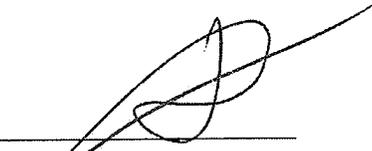
/s/

JUDIT R MILSTEIN
04/15/2010

RENATA ALBRECHT
04/16/2010

1.3.3 Debarment Certification

BioAlliance Pharma hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this NDA for miconazole Lauriad® 50 mg Mucoadhesive Buccal Tablet.

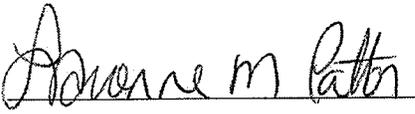


Dominique Costantini, M.D.
CEO
BioAlliance Pharma
49 Boulevard du Général Martial Valin
75015 PARIS



Date

Countersigned by:



Lavonne M. Patton, Ph.D.
Director, Managing Consultant
Beckloff Associates, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210
U.S. Agent for BioAlliance Pharma



Date

MEMORANDUM

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

DATE: April 23, 2010

FROM: Judit Milstein, Chief Project Management Staff

SUBJECT: Pre-Approval Safety Conference

APPLICATION/DRUG: NDA 22-404/ORAVIG/Miconazole buccal tablets

On March 23, 2010, a pre-approval safety conference was held simultaneously with the wrap-up meeting

Attendees

Renata Albrecht, MD, Division Director, DSPTP
Ozlem Belen, MD, MPH, Deputy Director for Safety, DSPTP
Hala Shamsuddin, MD, Medical Officer, DSPTP
Yuliya Yasinskaya, MD, Acting Medical Team Leader, DSPTP
Yoriko Harigaya, PhD, Clinical Pharmacology Reviewer, OCP, DCP4
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader, OCP, DCP4
Xianbin Li, PhD, Statistical Reviewer, OB, DBIV
Karen Higgins, PhD, Statistical Team Leader and CDTL, OB, DBIV
Owen McMaster, PhD, Pharmacology/Toxicology Reviewer, DSPTP
William Taylor, PhD, Pharmacology/Toxicology Team Leader, DSPTP
Lynette Berkeley, PhD, Clinical Microbiology Reviewer, DSPTP
Shukal Bala, PhD, Clinical Microbiology Team Leader, DSPTP
Andrew Yu, PhD, Chemistry Reviewer, ONDQA, DNDQA II
Rapti Madurawe, PhD, Pharmaceutical Assessment Lead, ONDQA, DNDQA II
Alfred Sorbello, DO, MPH, Medical Officer, OSE, DVP II
S. Christopher Jones, PharmD, MS, Safety Evaluator, OSE, DPV II
Judit Milstein, Chief Project Management Staff, DSPTP

The Review Division indicated that there are no major concerns about this product. They indicated that they have seen non-permanent cases of dysgeusia and some cases of hypersensitivity. The Review Division also indicated that also unusual, there have been some cases of choking, as the product can remain attached to the buccal mucosa for 6-24 hours.

It was also explained that the product will be approved for adults, that pediatric studies have been waived for patients 0 to less than ≤ 5 years of age due to the risk of choking and that pediatric studies are deferred for patients >5 to <17 years of age to verify safety, efficacy and compliance with use instructions.

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

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/s/

JUDIT R MILSTEIN

04/14/2010

Minutes of the Pre-approval Safety Conference

| | | | | |
|--|--|---|--|---------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Judit Milstein Chief, Project Management Staff OND/OAP/DSPTP | | FROM(Division/Office) Sharon Watson, Pharm.D. Kathleen Klemm, Pharm.D. Regulatory Review Officers Division of Drug Marketing, Advertising, and Communications (DDMAC) | | |
| DATE: 4/23/2010 | IND NO. | NDA NO. 022404 | TYPE OF DOCUMENT: Promotional Materials | DATE OF DOCUMENTS: 4/19/2010 |
| NAME OF DRUG ORAVIG (miconazole) buccal tablets | PRIORITY CONSIDERATION YES – Launch advisory | CLASSIFICATION OF DRUG: Antifungal (Candidiasis) | DESIRED COMPLETION DATE: 5/7/2010 | |
| NAME OF FIRM: Strativa Pharmaceuticals | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input checked="" type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| COMMENTS/SPECIAL INSTRUCTIONS: | | | | |
| <p>DDMAC has received proposed professional and direct to consumer promotional materials for Oravig for launch advisory comments and would appreciate the Review Division's feedback on the questions below. This consult request will be entered into DARRTS, and copies of the proposed promotional materials and pertinent references will be delivered electronically. Hard copies can be hand-delivered upon request. Please let us know if there is any additional information you need to assist you during your review. If you have any questions, please feel free to contact us.</p> <p>Thank you, Sharon 301-796-3991</p> <p>Katie 301-796-3946</p> | | | | |
| SIGNATURE OF REQUESTER Sharon Watson, Pharm.D. Kathleen Klemm, Pharm.D. | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL (DARRTS and email) <input type="checkbox"/> FACSIMILE | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Date: April 23, 2010

From: Sharon Watson, Pharm.D, Regulatory Review Officer
Kathleen Klemm, Pharm.D, Regulatory Review Officer
DDMAC

To: Judit Milstein, Chief, Project Management Staff
OND/OAP/DSPTP

Re: Consult for DDMAC on ORAVIG (miconazole) buccal tablets Launch Promotional Materials
NDA 022404

DDMAC is reviewing proposed launch promotional materials from Strativa Pharmaceuticals for ORAVIG (miconazole) buccal tablets (Oravig) and would appreciate your feedback on the questions below. The proposed materials include a direct-to-consumer (DTC) Patient Brochure and a healthcare professional Visual Aid and Journal Ad. (Please note that the Journal Ad contains claims that are derived from the Visual Aid, and as such, our questions focus on the Visual Aid.) Please feel free to comment on any other concerns you may have with the proposed materials. Thank you in advance for your time.

1. The proposed Patient Brochure claims that Oravig is indicated for (b) (4). Similar claims are included in the proposed healthcare professional Visual Aid. However, we note that page 9 of the April 12, 2010, Medical Officer's Clinical Review indicates that there are two main types of oropharyngeal candidiasis (OPC), pseudomembranous (or thrush) and erythematous (or atrophic, which includes denture stomatitis). In addition, we note that Oravig has an indication only for localized treatment.

DDMAC is concerned that this presentation is misleading, and fails to adequately communicate the approved indication of Oravig. Is it clinically accurate to describe the indication of Oravig as "fo (b) (4) in adults? If not, why not?

(b) (4)

References

1. Oravig [package insert]. Spring Valley, NY: Par Pharmaceutical, Inc.; April 2010.
2. Epstein JB. Diagnosis and treatment of oropharyngeal candidiasis. *Oral Maxillofacil Surg Clin N Am.* 2003;15:91-102.
3. Appleton ST. Candidiasis: Pathogenesis, Clinical Characteristics, and Treatment. *CDA Journal.* 2000;28:942-948.
4. Data on file. BA-OVG-001. Strativa Pharmaceuticals.
5. Murray PA, Koletar SL, Mallegol I, et al. Itraconazole oral solution versus clotrimazole troches for the treatment of oropharyngeal candidiasis in immunocompromised patients. *Clin Ther.* 1997;19:471-480.
6. Bensadoun R-J, Daoud J, El Gueddari B, et al. Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500-mg gel in the treatment of oropharyngeal candidiasis. *Cancer.* 2007;112:204-211.
7. Data on file. BA-OVG-002. Strativa Pharmaceuticals.
8. Dupont B, Attali P. Evaluation of miconazole mucoadhesive buccal tablet: a novel, once-daily, antifungal treatment for oropharyngeal candidiasis. Poster presented at: 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) September 12-15, 2009; San Francisco, CA.
9. Data on file. BA-OVG-004. Strativa Pharmaceuticals.
10. Data on file. BA-OVG-003. Strativa Pharmaceuticals.
11. Barasch A, Attali P. Efficacy of miconazole mucoadhesive buccal tablets compared to clotrimazole troches for the treatment of oropharyngeal candidiasis: SMILES. Poster presented at: 44th American Society of Health-System Pharmacists (ASHP) Mid-Year Clinical Meeting; December 6-10, 2009; Las Vegas, NV.

| 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/

KATHLEEN KLEMM
04/23/2010

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|---|-------------------------------|---|
| NDA # 22-404 | NDA Supplement # BLA STN # | If NDA, Efficacy Supplement Type: |
| Proprietary Name: ORAVIG Established/Proper Name: miconazole buccal tablets Dosage Form: buccal tablets | | Applicant: BiAlliance, Pharma Agent for Applicant (if applicable): Beckloff and Associates, Inc. |
| RPM: Judit Milstein | | Division: DSPTP |
| <p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> | | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #s) and drug name(s):</p> <p>NDA 18-040-Monistat (miconazole) for Injection</p> <p>NDA 18-888-Monistat 3 (miconazole nitrate) vaginal suppositories</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product provides for the localized oral delivery of miconazole to the buccal mucosa. No other product has been approved for this dosage form/route of administration for this indication.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p>Two months prior to reach action, review the information in the 505(b)(2) Assessment and submit the draft to CDER-OND-IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 16, 2010</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

| | |
|--|---|
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | Original submission dated February 5, 2009, received February 6, 2009 RTF on April 3, 2009 Resubmission dated June 15, 2009 Received on June 16, 2009 |
| ❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | <input type="checkbox"/> Received |
| ❖ Application Characteristics ² | |
| <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p> | |
| ❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>) | <input type="checkbox"/> Yes, date |
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Public communications (<i>approvals only</i>) | |
| <ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • Press Office notified of action (by OEP) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| | |
|--|---|
| <p>❖ Exclusivity</p> | |
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires: |
| <p>❖ Patent Information (NDAs only)</p> | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. <i>Applicant provided Paragraph II certification for both listed drugs described above.</i> | 21 CFR 314.50(i)(1)(i)(A)(2) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input type="checkbox"/> No paragraph III certification Date patent will expire |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee

Yes No

| | |
|--|---|
| <p>bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner’s receipt of the applicant’s notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | |
| CONTENTS OF ACTION PACKAGE | |
| ❖ Copy of this Action Package Checklist ³ | Yes |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Approval: April 16, 2010 Refuse to file- April 3, 2009 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | April 13, 2010 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | June 15, 2009 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

| | |
|---|---|
| ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | June 13, 2010 |
| ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) | Proprietary Name Granted on 11/10/09 Reviews dated 2/1/10 and 11/10/09 |
| ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA Carton and Container-4/16/10 Carton and Container-4/15/10 PI and Carton and Container 1/5/10 <input checked="" type="checkbox"/> DRISK Content of labeling 2/19/10 <input checked="" type="checkbox"/> DDMAC Package Insert – 2/19/10 Patient Labeling- 2/19/10 Consult-1/15/10 <input checked="" type="checkbox"/> SEALD 3/16/10 <input type="checkbox"/> Other reviews |
| Administrative / Regulatory Documents | |
| ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ 505(b)(2) Assessment (<i>indicate date</i>) | Filing review-9/16/09 Filing Review- 4/7/09 4/15/10 |
| ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input checked="" type="checkbox"/> Included 4/16/10 |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant in on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 3/17/10 If PeRC review not necessary, explain: _____ • Pediatric Record created in DARRTS | <input checked="" type="checkbox"/> Yes |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) | Letters: 74 day letter-8/26/09 ACK of resubmission-6/26/09 ACK letter-2/18/09 |

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
 Version: 12/4/09

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| | <p>Faxes-e-mails-telecons 2/20/10-Clinical Micro info req 1/11/10-Comments on labeling 12/23/09-CMC-microbial limits 12/7/09-CMC dissolution info 9/26/09-Request for DSI site info 9/16/09-CMC request-dissolution 9/9/09-Request for DSI sites (duplicate of document 9/11/09) 6/4/09-Stats info request 5/28/09-Minutes of telecon 5/6/09-CMC info request 4/28/09-Comments on debossing 4/22/09-Meeting granted 4/10/09-ISS datasets 3/26/09-Clinical info request 3/17/09-Micro request 2/25/09-Stats request 2/20/09-CMC request for info</p> |
| ❖ Internal memoranda, telecons, etc. Pre-Approval Safety Conference minutes | 4/14/10 |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A or no mtg |
| • Pre-NDA meeting (<i>indicate date of mtg</i>) | 9/11/2008 |
| • EOP2 meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | 5/6/09-MMA telecon 3/16/09-Minutes of tcon (stats) |
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available (<i>do not include transcript</i>) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | 4/16/10 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical Information⁵ | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | 4/12/2010 |
| • Clinical review(s) (<i>indicate date for each review</i>) | NDA review 4/12/2010 Filing review 8/18/09 Filing review 3/24/09 |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |

⁵ Filing reviews should be filed with the discipline reviews.

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|---|---|
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | 4/13/10 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Not applicable |
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input checked="" type="checkbox"/> None |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | 2/19/10 Consult Request: 8/21/09 |
| Clinical Microbiology <input type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | NDA Review 4/5/10 NDA review 2/22/10 Filing Review 7/28/09 Filing Review 3/27/09 |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Review(s) (<i>indicate date for each review</i>) | NDA review 3/26/10 Filing Review 8/18/09 Filing Review 4/7/09 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | NDA review 4/13/10 Filing Review 8/18/09 Filing Review 4/6/09 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) | <input checked="" type="checkbox"/> None |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| <ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| <ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) | 4/16/10 |
| <ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | NDA Review 4/15/10 Filing Review 8/19/09 Filing Review 4/10/09 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No carc |

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|---|--|
| ❖ ECAC/CAC report/memo of meeting | <input checked="" type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>) | <input checked="" type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>) | NDA Review: 3/23/10 NDA Review 2/23/10 Filing Review 7/27/09 Filing Review 5/1/09 Filing Review 3/23/09 (duplicate of review dated 3/26/09) |
| ❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>) | 1/25/10 12/7/09 Consult 8/11/09 Consult 3/10/09 |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>) | Consult to DMEPA on debossing 4/21/09 |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | See CMC review 3/23/10, page 6 |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | |
| <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | |
| ❖ Facilities Review/Inspection | |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) | Date completed: 3/10/10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| <input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>) | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed |

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

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

/s/

JUDIT R MILSTEIN
04/19/2010
Action Package Checklist



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 69,578

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Lavonne M. Patton, Ph.D.
Director, Managing Consultant
7400 West 110th Street, Suite 300
Overland Park, Kansas 66210

Dear Dr. Patton:

Please refer to your Investigational New Drug Application (IND) for Lauriad[®] (miconazole) Buccal Tablet, 50 mg.

We also refer to the meeting held on August 12, 2008, between representatives of your firm and this agency to discuss the NDA submission plan for Lauriad[®] (miconazole) Buccal Tablet. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 796-0695.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Division Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Minutes of the Meeting.
BioAlliance Pharma's handouts.

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 12, 2008

TIME: 11:00 AM – 12:00 PM

LOCATION: Food and Drug Administration
Building 22, Conference Room # 1415
10903 New Hampshire Ave., Silver Spring, MD. 20903

APPLICATION: IND 69,578

PRODUCT NAME: Lauriad[®] (miconazole) Buccal Tablet, 50 mg

INDICATION: Local treatment of oropharyngeal candidiasis (OPC)

SPONSOR: BioAlliance Pharma, France.

TYPE OF MEETING: B (pre-NDA meeting)

MEETING CHAIR: Eileen Navarro, M.D.

MEETING RECORDER: Christina H. Chi, Ph.D.

FDA ATTENDEES:

**Center for Drug Evaluation and Research, Office of Antimicrobial Products,
Division of Special Pathogen and Transplant Products (DSPTP):**

| | |
|------------------------------------|-----------------------------------|
| Renata Albrecht, M.D. | Division Director |
| Shukal Bala, Ph.D. | Microbiology Team Leader |
| Lynette Y. Berkeley, Ph.D. | Microbiology Reviewer |
| Christina H. Chi, Ph.D. | Regulatory Health Project Manager |
| Dakshina Chilukuri, Ph.D. | Clinical Pharmacology Reviewer |
| Phillip Colangelo, Pharm.D., Ph.D. | Clinical Pharmacology Team Leader |
| June Germain, M.S. | Regulatory Health Project Manager |
| Karen M. Higgins, Sc.D. | Biostatistics Team Leader |
| XianBin Li, Ph.D. | Biostatistics Reviewer |
| Dorota Matecka, Ph.D. | Chemistry Reviewer |
| Owen McMaster, Ph.D. | Pharmacology/Toxicology Reviewer |
| Judit Milstein | Chief, Project Management Staff |
| Eileen Navarro, M.D. | Medical Team Leader |

EXTERNAL CONSTITUENT ATTENDEES:

Sponsor: BioAlliance Pharma, France.

Consultants:

Beckloff Associates, Inc., Kansas, USA.

Pierre Attali, M.D. Chief Medical Officer, BioAlliance Pharma
Caroline Lemarchand, Pharm.D., Ph.D. Chemistry, Manufacturing and Controls Director,
BioAlliance Pharma
Delphine Lucas, Pharm.D. Regulatory Affairs Director, BioAlliance Pharma



Lavonne Patton, Ph.D. Director (Regulatory Consultant), Beckloff Associates, Inc.

BACKGROUND:

- April 17, 2008: BioAlliance Pharma requested a meeting to discuss the adequacy of the clinical program as well as the presentation of data for an upcoming NDA submission for Lauriad. This NDA will be submitted under Section 505(b)(2).
- May 12, 2008: A briefing package containing 12 questions was submitted.
- July 23, 2008: The Division sent a fax with preliminary responses and comments in preparation for the August 12, 2008 meeting.
- August 1, 2008: BioAlliance Pharma submitted a response to the Divisions preliminary comments. In this response, the sponsor seeks additional clarification on question 1, 12, 5, and 7, and requests comments on two new CMC questions.

MEETING OBJECTIVES:

- To discuss the adequacy of the CMC, nonclinical as well as the clinical program in support of the proposed indication.
- To reach an agreement on the appropriate format and content of the NDA.
- To discuss the presentation of data and data analyses of the studies.
- To review the proposed clinical development plan of the Pediatric use.

DISCUSSION POINTS:

For the purposes of these minutes, the following format is used:

- BioAlliance Pharma's original questions are in normal font.
- FDA's responses sent per facsimile to the sponsor on July 23, 2008 are in italics.
- BioAlliance Pharma's August 1, 2008, response and clarification to the Division's fax of July 23, 2008 are in normal font, immediately following the FDA's fax response (in italics).
- The meeting discussion is in bold font.
- Pertinent miscellaneous issues or items discussed during the meeting were recorded under "closing discussions" section.

The meeting started with a reiteration by the sponsor that they wish to obtain clarification specifically on Questions 1, 12, 5, and 7, in that same order.

Q1: BioAlliance intends to submit data from four completed clinical studies—one pharmacokinetic study (Study BA2000/01/01) and three clinical studies (Study BA2002/01/02, Study BA2002/01/03, and Study BA2004/01/04) with Lauriad[®] (miconazole) Mucoadhesive Buccal Tablets in relevant patient populations as support for the NDA. Details of each of these studies re provided in Section 5 and Appendices 3, 4, 5, and 6 of this briefing package. In addition, a literature review will be conducted to provide any relevant clinical safety information for miconazole and Milk Protein Concentration (MPC) in the NDA.

Does the Agency agree that these clinical data support filing of the 505(b)(2) NDA?

FDA's Response: Yes. Preliminary review of the information you submitted seems to indicate that these clinical data will support filing of the NDA. However, you will need to provide justification for the proposed non-inferiority margins, as this information is needed for proof of efficacy in non-inferiority studies. Non-inferiority studies need to rely on some amount of historical evidence of the effect of the active control in order to reliably make any conclusions regarding the effect of the test drug: discussion of the issue can be found in the ICH guidance documents "E9 Statistical Principles for Clinical Trials" and "E10 Choice of Control Group and Related Issues in Clinical Trials" (located www.fda.gov/cder/guidance/index.htm), as well as 21CFR314.126(b)(2)(iv).

BioAlliance's August 1, 2008 response:

A detailed justification document for the proposed noninferiority margins for both studies BA2002/01/02 and BA2004/01/04 is being drafted and will be submitted to the Division prior to the NDA submission. The justification will be based on the principles addressed in the ICH guidance documents "E9 Statistical Principles for Clinical Trials" and "E10 Choice of Control Group and Related Issues in Clinical Trials."

The justification of the noninferiority margin that is being prepared takes into consideration that the indication is for a non-life threatening condition for which alternative therapies are available. Examples of the types of information that will be summarized to support the noninferiority margin include:

1. For the pivotal trial BA2004/01/04 (in HIV positive patients):
 - There are very few placebo-controlled trials reported in the literature; however, clotrimazole efficacy in OPC has been demonstrated versus placebo in clinical trials.
 - There is significant variability across OPC studies and populations as there are many variables, such as the patients immune status, that can affect the efficacy of antifungal agents in the treatment of OPC in HIV patients.
 - The efficacy of clotrimazole in HIV positive patients is consistently reported at an efficacy rate around 70%.
 - HIV positive patients suffering from OPC are markedly immunocompromised, so that spontaneous resolution of OPC is infrequent.
 - The efficacy of placebo in OPC is reported at rates below 20% in immunocompromised patients.
 - The efficacy of topical antifungal agents is demonstrated and highly variable across studies and drugs.
2. For the supportive study BA2002/01/02 (in head and neck cancer patients):
 - Only small-sized placebo controlled trials have evaluated the efficacy of either ketoconazole or clotrimazole versus placebo in cancer patients. The efficacy rate of placebo was below 20%.
 - Superiority of antifungal agents over placebo has been shown with only a small number of patients demonstrating the clinical relevance of the difference.
 - Miconazole oral gel was chosen as the comparator as it contains the same active principle as that in Lauriad[®] (miconazole) and is also administered for local oral effects on OPC in Europe.
 - When the BA2002/01/02 trial was designed there was only one trial that evaluated the efficacy of antifungal agents in patients suffering from head and neck cancer. The efficacy rate of the 2 antifungals tested was around 50%.
 - Variables such as concomitant oral diseases related to cancer treatments can affect the efficacy of antifungal agents in the treatment of OPC in patients with cancer, leading to large variability across studies and populations.

Does the Agency have additional comments regarding the strategy for justification of the noninferiority margins?

Meeting Discussion:

BioAlliance presented slide # 1 as the basis for further discussion.

BioAlliance stated that they intend to market the product in the United States and describe its benefits as ease of use and improved compliance due to the once a day dosing.

The Division responded that the direction BioAlliance has taken is quite sensible. However, reiterating the Agency's comments of April 2008, the following will be taken into consideration during the review:

1. **Data driven estimate of the treatment effect of the control over no treatment to ensure that the treatment effect is great than the margin. A non-inferiority margin should be no larger than a conservative estimate of the treatment effect. To determine an estimate of the treatment effect (the difference between a control treatment over placebo), BioAlliance should conduct a systematic literature search. Discussion of the justification should include an outline of the criteria used for the literature search, databases searched, key words, etc. The highest level of evidence to estimate a treatment effect would be from superiority trials over placebo, the next would be superiority trials over another treatment, and the lowest level, but potentially adequate if necessary, would be estimates of no treatment rates compared to estimates of treated rates. The variability of the treatment effect estimated should be taken into account. Typically, a 95% confidence interval of the treatment effect (difference between treatment and placebo) would be calculated from historical studies, and the lower bound of the confidence interval would be the conservative estimate of the treatment effect. Where estimates of a no-treatment rate and a treated rate are calculated from separate sources, often 95% confidence intervals are calculated for each rate and the smallest difference between these intervals is determined to be the conservative estimate of the treatment effect. If this method cannot be used, please address that in the discussion. BioAlliance should submit any applicable references.**
2. **Discussion as to how the studies used to estimate the treatment effect (of the control over placebo or no treatment) would be comparable to the current study. BioAlliance should consider the patient population studied, the study region, concomitant medication that might confound the results, the definition of disease, definition of endpoints, and the timing of endpoints.**
3. **Discussion of the clinical relevance of the margin chosen. Consider if a loss of efficacy in an amount as large as the margin chosen make sense from a clinical standpoint.**

BioAlliance asked if they can send samples of the justification in advance and inquired when comments will be received.

The Division explained that the response will be sent out as soon as possible based on the Division's workload at that time and on the quality of the response. The Division requested that the response clearly address all the points mentioned above. The Division also noted that noninferiority issues have been the subject of recent advisory committee discussions and advised the company to consult the transcripts of these advisory committee deliberations as part of their preparation. The Division stressed the importance of submitting as complete a document as possible. Relevant background information such as the natural history of the disease in the patient population of interest, evolution in patient treatment standards, other relevant epidemiological background data, efficacy data from ineffective therapies or efficacy data from superiority studies may all be useful to assess in proposing a margin and should be included in the NDA.

BioAlliance responded that they were not able to find any placebo controlled studies in literature and all of the studies that they found had small sample sizes. BioAlliance indicated that they were not sure that they would be able to justify a margin using the conservative methods just outlined.

The Division stated that they should address the points above as well as the drawbacks with the data that are available, and reiterated that BioAlliance should make as strong a scientific case as possible.

Q12: It is planned that the following information would be summarized in the nonclinical section of the NDA.

- A detailed summary of the nonclinical studies conducted with Lauriad[®] (miconazole) will be included in the nonclinical overview (local lymph node assay in mice and local tolerance study in hamsters) and the corresponding reports provided in Module 4
- A detailed summary of the available nonclinical literature studies describing the toxicity of miconazole
- A review of available safety literature on mucoadhesive buccal tablets
- Literature describing the available nonclinical toxicologic profile of the milk protein concentrate component of Lauriad[®] (miconazole)

Does the Agency agree that a summary of the nonclinical safety information described above will adequately support the 505(b)(2) NDA submission?

FDA Response: This proposal is acceptable.

Additional FDA comments:

- a. As we indicated in our comments sent to you on July 27, 2004, it is important to characterize the PK of miconazole from the buccal tablet in the event of accidental ingestion (i.e., swallowing) of the buccal tablet. Please provide clarification if you have performed either non-clinical or other clinical studies to evaluate the PK of Lauriad when administered orally.*

- b. *In the proposed package insert included in the meeting package, you have indicated that Lauriad can be administered with food and drinks. Please provide clarification if there is evidence to support the above-mentioned statement.*

BioAlliance's August 1, 2008 response (to additional FDA comments to Q12 item a):

Nonclinical or clinical studies have not been performed to evaluate the PK of Lauriad[®] (miconazole) when ingested orally. However, information from the clinical pharmacokinetics/pharmacodynamics and efficacy studies will be included in the NDA. These studies demonstrate that:

- If the tablet is swallowed:
 - Miconazole will be released slowly from the tablet (80% in 8 hours). Hypromellose is one of the main excipients of the formulation. As hypromellose is not pH sensitive, if a tablet is swallowed the drug substance release profile would not be modified.
 - Only 50 mg at most will be available for absorption, which is 2.5-fold less than the amount of miconazole oral gel (125 mg), which is recommended to be kept in the mouth for 2–3 minutes and then swallowed.
 - Absorption of miconazole through the intestine is known to be low (20%).
 - Consequently, miconazole plasma concentrations are unlikely to be detected, or should be low if detected as confirmed in the PK/PD and Phase III clinical trials.
- Plasma miconazole concentrations were not detected in any of the 40 patients that were measured in the clinical studies (Studies BA2002/01/02 and BA2004/01/04). These patients applied Lauriad[®] (miconazole) buccally—none of these patients swallowed the tablet.
- Plasma miconazole concentrations have been detected in 5/162 samples in the PK/PD clinical trial in healthy volunteers (Study BA2000/01/01). The plasma concentrations were all below 0.83 µg/mL. These patients applied Lauriad[®] (miconazole) buccally—none of these patients swallowed the tablet.
- Less than 2% of tablets are swallowed within the first 6 hours and most of them are swallowed after 12 hours of adhesion to the gum. After 12 hours, the majority of the active substance has been released from the tablet. Therefore, what is being swallowed is the remainder of the matrix.

These clinical data demonstrate that swallowing a tablet fully loaded with miconazole is likely to occur infrequently. Even so, due to the low strength (50 mg) and the slow release mechanism, plasma concentrations are likely to be low even if the tablet was swallowed in the first 12 hours after adhesion to the gum.

Meeting Discussion:

BioAlliance presented slide # 2 as the basis for further discussion.

BioAlliance stated that Lauriad is registered and marketed widely in Europe and to date, a number of patients has been treated with it.

The Division requested that information and justification be provided in the upcoming NDA submission supporting their assertion that no safety issues have emerged when the buccal tablet is accidentally dislodged.

BioAlliance indicated that in the clinical trials, eating and drinking were allowed. It was only recommended that patients place the tablet on the gum after brushing their teeth. However, in order to evaluate whether the tablet could be dislodged, subanalyses were carried out in which the effects of mouthwashes, meals, and drinks on tablet dislodgement were evaluated, and there was no difference in dislodgement. Therefore, no special recommendation is required for the use of the tablet other than the placement of the tablet on the gum after meals or tooth brushing activities.

The Division requested that BioAlliance provide data on the duration of the tablet's adhesion to the gum under conditions of anticipated clinical use (without any restriction on eating, drinking, or mouthwash) and the relationship of the duration of adherence to plasma concentration of miconazole.

BioAlliance responded that they will consider the Division's suggestions and explained that there are some instructions, with some pictogram, in the Lauriad packet for patients and health care providers to comprehend where to place the 50 mg, once a day for 14 days tablets.

The Division inquired how BioAlliance determined the placement of the tablet. BioAlliance responded that the location chosen is where salivary flow is constant and intended to facilitate distribution into the mouth and pharynx.

Q5: As might be expected in a global trial for oral candidiasis, the majority of the 577 patients randomized in Study BA2004/01/04 were enrolled at centers in South Africa (442 patients). Other patients were included in the United States and in Canada. Any differences in patient populations based on the geographical differences will be analyzed and discussed in the NDA. Preliminary data describing the patient demographics in Study BA2004/01/04 are provided in Section 5.2.3.

Does the Agency agree with this approach and/or have any recommendation for analysis?

FDA's Response: Any differences in patient populations based on the geographical differences could help us to understand possible differences in treatment effects. To show consistency of the treatment effect across geographic regions, subgroup efficacy analyses by geographic regions may be considered as secondary analyses.

BioAlliance's August 1, 2008 response:

Results from the analysis based on geographic regions indicate that there are no significant differences between regions. In order to evaluate whether treatment efficacy may be influenced by the geographical origin of patients, a univariate and multivariate analysis of factors influencing the clinical cure was carried out. These factors included, among others: prognostic variables, the geographical origin of patients, and treatment groups. The univariate analysis showed that patients in the United States were not significantly more likely to be cured than patients in the Republic of South Africa (RSA) ($p = 0.1533$). In the multivariate analysis, the geographical origin was not an explicative factor of the cure. Likewise, the univariate and multivariate analysis of factors influencing relapse tested the geographical origin of patients. In the univariate analysis, the origin of patients was an explicative factor of relapse ($p = 0.0257$). In the multivariate analysis, antifungal drugs ($p < 0.0001$), viral load below the median (0.0004), extensive signs of OPC ($p = 0.0018$), and the absence of mycological cure ($p = 0.0372$) were the only factors found statistically significantly related to relapse. These data demonstrate that clinical cure and relapse are related to the severity of OPC and the HIV disease and not to the geographical origin of patients.

These data will be included in the NDA.

Meeting Discussion:

BioAlliance expressed concern about the acceptability of the clinical data generated in South Africa. Therefore, BioAlliance performed a logistic regression analysis based on the efficacy in terms of relapse, extent and severity of the disease to arrive at the clinical cure.

The Division explained that although the Agency has generally accepted data from studies conducted outside the United States, there are important aspects to consider in evaluating the relevance of foreign safety and efficacy data. At a minimum, BioAlliance would need to conduct a sensitivity analysis by-center for efficacy. Other aspects to describe in the NDA would be whether there were any relevant differences in the standards of care and in reporting adverse events in the foreign sites and the US. Bioalliance should similarly describe access to care for both HIV and OPC between the populations in the different geographical locations of the trial sites. A description of the distribution and susceptibility of the OPC isolates in the foreign sites would also be relevant, compared to the anticipated pathogens in the analogous population in the US. Furthermore, to the extent that clinical trial sites may account for genomic differences in populations exposed to the drug compared to those anticipated to use the drug in the US, Bioalliance may have to explain why these differences may be relevant or not, based on the extent of miconazole's absorption and metabolic fate. Therefore, the NDA package should describe why the study outcomes are expected to predict the safety and efficacy of patients treated in the United States, by describing the populations adequately, the local standards of care, the pathogens and their resistance patterns.

BioAlliance stated that they will provide all the requested medical information.

The Division requested that data from CD4 cell counts, the Candida species identified by a laboratory in the US, as well as methodology and results of susceptibility testing for miconazole, clotrimazole, etc., for microorganisms be provided.

BioAlliance responded that they have collected the information and that this will be provided in the NDA submission. BioAlliance stated that samples for mycological testing were sent to the Center for Medical Mycology, University Hospitals of Cleveland, Ohio.

The Division inquired as to whether the history of previous antifungal treatment was obtained.

BioAlliance responded that the information has been collected and only 10 to 15 % of the enrolled patients have received previous treatment for Candida.

Q7: During the pre-IND meeting, BioAlliance requested deferral of the pediatric requirement until Phase IV, after Lauriad[®] (miconazole) has been approved as safe and effective for adults. Prior to filing the NDA, BioAlliance will submit a request for a waiver of pediatric studies in younger children and a deferral of pediatric studies in older children (research for age cut-off ongoing). With these requests, BioAlliance will submit a pediatric plan as a Proposed Pediatric Study Request in expectation that the proposed study will comply with requirements of the Pediatric Research Equity Act and also result in the Agency's issuance of a Written Request per the Best Pharmaceuticals for Children Act.

Does the Agency have any comments on this plan?

FDA's response: Yes. We concur with your plan. We also recommend that you take into consideration issues such as how long the tablet remains in the mouth and ease of swallowing if requesting partial waiver for different age groups. We would also recommend you evaluate if a different formulation might be needed for younger age pediatric patients.

BioAlliance's August 1, 2008 response:

As part of the request for a pediatric partial waiver for a certain age group, we have taken the following approach:

1. A review of pediatric developmental, cognitive, and social milestones to assess the most appropriate and responsible age level for which to study Lauriad[®] (miconazole), given the level of motor, verbal, and cooperative skills needed for application and vigilance with a parent or guardian.
2. An assessment of the anatomical area where Lauriad[®] (miconazole) has been studied in adults (the canine eminence), to determine if there are limiting anatomical factors for children of a certain age group. Currently, we are measuring the vestibular depth in children, determined by our consulting pediatric oral surgeon to be sufficient.

3. A review and summary of the literature on salivary flow rate data in children and adults to evaluate differences that could affect the release and delivery of Lauriad® (miconazole) in children.

The potential for aspiration, as well as adhesion to the esophagus or trachea is a safety concern in children, a risk that can not be assumed through study without careful evaluation. We will include the data from the adult study on the length of time that the tablet remains in the mouth. However, because the tablet is not meant to be swallowed, but accidental ingestion is a concern, a study participant must be at the age level to understand the risks of dislodgement, be capable of reinserting or repositioning the tablet, and be able to communicate a dislodgement or accidental ingestion to a parent or guardian. For these reasons, we believe it is not appropriate to study the use of Lauriad® (miconazole) in very young children. We are not considering the development of a different formulation for younger pediatric patients.

Does the agency agree with this approach?

Meeting Discussion:

BioAlliance explained that they are currently mapping pediatric development skills in cognitive, verbal, cooperative, which are necessary for a pediatric patient to notify or communicate to their parent or care-giver. They stated that a letter requesting a waiver for pediatric studies is being formulated and currently they are waiting for some feedback from Center for Disease Control and Prevention and the American Pediatric Association. They also indicated that they will appreciate receiving further guidance, especially on the recommended dosage.

The Division responded that the safety of the formulation, such as the size of the capsules and its characteristics, would be the foremost consideration in the age-appropriate studies, should the product be proven efficacious in adults. The sponsor will have to present evidence regarding the maturational skill in the ability of a pediatric patient to swallow a tablet that is accidentally dislodged and a discussion of risk benefit, incorporating the severity of the disease and the availability of alternative therapies into account in requesting a waiver.

BioAlliance was requested to consult the newly passed FDAAA legislation regulations regarding the requirement for a pediatric development plan for new drugs, including the development of a pediatric formulation. In formulating the pediatric plan, and in requesting waiver in certain pediatric age groups, BioAlliance was advised to consider currently available treatments for OPC, include discussion of the epidemiology and frequency of the disease in pediatric patients, the similarity of the disease between adults and pediatric patients, and maturation of swallowing and cognitive skills.

The Division explained that there is a continued focus on making products available to treat pediatric patients and development of appropriate pediatric formulations is part of that process. The Division suggested that BioAlliance consider and address all these issues in their waiver request.

Additionally, BioAlliance has the following CMC questions for the Division (submitted in the August 1, 2008 response):

Q13: Lauriad (miconazole) was originally developed for the European market where imprint codes on solid oral dosage forms are not required. The product is currently marketed in France, Germany, Denmark, and the United Kingdom. BioAlliance would now like to bring this product to the US market as it provides a once daily, local treatment option for OPC. Local treatment is recommended by the Infectious Disease Society of America as first line therapy for the treatment of OPC.

BioAlliance is aware of the FDA requirements for imprinting all solid oral dosage form human drug products as defined in 21 CFR 206.10.

21 CFR 206.7(b)(1) states, "For a drug subject to premarket approval, FDA may provide an exemption from the requirements of 206.10 upon a showing that the product's size, shape, texture, or other physical characteristics make imprinting technologically infeasible or impossible."

BioAlliance plans to request an exemption in writing from the imprint requirement based upon the texture and other physical characteristics of the dosage form, which make it difficult to provide an imprint for this buccal tablet.

This exemption is based upon the following experience with the product:

-
-

(b) (4)

Furthermore, the shape of the Lauriad[®] tablet is unique from other round, white tablets in that one side of the tablet is flat and the other side is concave, which will help identify it.

For these reasons, BioAlliance plans to file the NDA without the imprint code.

Does the Agency agree with the BioAlliance approach for the tablet imprinting requirements?

Meeting Discussion:

BioAlliance stated that they will provide a request for an exemption, in writing, from the imprint requirement for their proposed product, miconazole buccal tablet.

The Division responded that a consult will be submitted to the Division of Medical Error Prevention and Analysis (DMEPA) upon receipt of their written request for a waiver.

Q14: The proposed commercial container closure for Lauriad[®] (miconazole) Mucoadhesive Buccal Tablet, 50 mg is a white round high density polyethylene (HDPE) bottle (15 mL) with a (b) (4) screw cap closure (b) (4)

(b) (4) No cotton or rayon filler is used in the bottle. Each bottle contains 14 tablets.

BioAlliance plans to use the same container closure configuration for packaging of physician samples but with a single tablet per bottle. Stability data are not available on the proposed packaging configuration for physician samples.

Meeting Discussion:

BioAlliance stated that stability data are not available on the proposed packaging configuration for physician samples.

The Division responded that, based on the information provided, it is acceptable to use the stability data obtained for the product packaged in the proposed commercial packaging configuration to support the stability of physician samples packaged in the same container/closure system. However, the expiration dating will be determined based on the review of the overall stability information provided in the NDA submission including the available stability data for the physician samples.

Closing Discussion:

BioAlliance stated that most likely they will submit the NDA in November or early December 2008.

The Division requested that sham data sets be sent prior to the NDA submission, to allow the Division to determine whether the data is optimally organized for review.

AGREEMENTS REACHED:

BioAlliance will:

- submit for feedback a written justification of their proposed noninferiority margin and well as their proposed efficacy analyses plan. The Division will provide comments on this proposal at the earliest possible time. Additionally, they noted that as requested by the Division, some sham data sets will be submitted as soon as possible.
- submit a request for an exemption from the imprint requirement for the proposed drug product.
- submit with the NDA a Pediatric Study Plan with full justification for the request to waive Pediatric studies for certain pediatric age groups.

ATTACHMENTS (HANDOUTS): BioAlliance's 2 slides.

Linked Applications

Sponsor Name

Drug Name

IND 69578

BIOALLIANCE PHARMA

MICONAZOLE LAURIAD 50MG
BIOADHESIVE BUCC

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/s/

RENATA ALBRECHT

09/11/2008

meeting minutes



NDA 22-404

BioAlliance Pharma
c/o Beckloff Associates
Attention: Lavonne Patton, Ph.D.
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Dr. Patton:

Please refer to your new drug application (NDA) submitted on February 5, 2009 and received on February 6, 2009, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lauriad[®] (miconazole) Mucoadhesive Buccal Tablet, 50 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d)(3) for the following reason:

Refuse to File Issue: 21 CFR 206.10 Code imprint required

Your tablet does not contain a code imprint as required under 21 CFR 206.10 for a solid oral dosage form and no exemption to this requirement under 21 CFR 206.7 was granted. We note that on August 18, 2008, you requested an exemption of the imprinting requirement under 21 CFR 206.7(b)(1). The Division responded to your request on November 3, 2008, and requested you demonstrate that tablet imprinting is not feasible and provide samples that demonstrate failed attempts to imprint the proposed tablet.

A user fee refund is not applicable for this application because you were granted a small business waiver.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference.

Additional Issues Not Related to the Refuse to File Decision

The following deficiencies are not issues pertaining to our refusal to file the application. However, these issues need to be addressed before we can perform a substantive review of the application.

1. Submit a justification for concluding that the results from foreign trials BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04 are applicable to the US population.
2. Adverse events (AE) for studies BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04 were coded using different versions of MedDRA. If feasible, provide coding using a unified version.
3. Include all data on the 18 subjects enrolled in study BA 2000/01/01 in the ISS dataset. Because the AE for these 18 subjects were coded using WHOART, translate the AE data into MedDRA terms and provide verbatim investigator terms mapped to MedDRA preferred terms when adding AE data for this study into ISS.
4. For the two controlled clinical trials, BA2002/01/02 and BA2004/01/04, submit efficacy and safety analyses by gender, race, and age.

If you have any questions, call Ms. Sherry Spriggs, Regulatory Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
4/3/2009 03:59:58 PM

From: Spriggs, Sherry
To: "Patton, Lavonne";
cc: Milstein, Judit; Higgins, Karen M;
Subject: NDA 22-404; Lauriad; BioAlliance - Microbiology Request
Date: Tuesday, March 17, 2009 4:03:38 PM

Hi Lavonne,

The clinical microbiology review team has the following request in reference to NDA 22-404 for Lauriad (miconazole):

- 1) Template for the clinical microbiology datasets and summary tables were shared with you sometimes in August/September, 2008 (see attachment). However, we are unable to locate the datasets or the summary tables. It will be helpful for our review if you could specify the file name and the path for the micro datasets for the 3 clinical studies.

2. It appears that the references lists in Modules 4 and 5 include all studies supporting the respective sections of the NDA. It will be helpful for our review if you could add titles to the list or give us a list of all microbiology studies (mechanism of action, activity in vitro and in vivo) with titles.

Would you be able to provide the information as soon as possible?

Thank you so much.

Sherry

Sherry Spriggs
Regulatory Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
FDA/CDER/OND
Building 22, Room 6135
Silver Spring, MD 20993
Phone: 301-796-4018
Fax: 301-796-9881
Email: Sherry.Spriggs@fda.hhs.gov

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/s/

Sherry Spriggs
3/17/2009 04:27:31 PM
CSO

| | |
|------------|--------------------------|
| NDA | 22404 SN 000 |
| Product | Miconazole buccal tablet |
| Trade Name | Oravig |
| Submitted | June 16, 2009 |
| Reviewed | March 1, 2010 |
| Reviewer | Hala Shamsuddin MD |

Addendum

The financial disclosure form was reviewed. The clinical investigators who participated in the studies submitted in NDA 22404 had not entered into financial arrangement with the sponsor.

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

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/s/

HALA H SHAMSUDDIN
04/13/2010

YULIYA I YASINSKAYA
04/13/2010



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: February 20, 2010

| | |
|---|---|
| To: Lavonee M. Patton, Ph.D. | From: Judit Milstein, Chief Project Management Staff |
| Company: Beckloff Associates, Inc, on behalf of BioAlliance Pharma | Division of Special Pathogen and Transplant Products |
| Fax Number: 913 451-3846 | Fax Number: 301-796-9881 |
| Phone Number: 913 451-3955 | Phone Number: 301-796-0763 |

Subject: Information request on clinical microbiology data

Total no. of pages including cover: 3

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-0763.

Judit Milstein
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 22-404
Oravig (miconazole) buccal tablets
Beckloff Associates, Inc. on behalf of BioAlliance Pharma

RE: Request for additional information on clinical microbiology data

Dear Dr. Patton,

We refer to your NDA submission dated June 15, 2009, received June 16, 2009 for your Oravig (miconazole) buccal tablets.

In order to continue with the timely review of your submission we ask that you respond to the following information request by no later than March 1, 2010.

We are having some difficulty assessing your data for microbiological outcome for Study 02. To help us understand the data

- a. Please provide a definition for eradp14 in the data set d_me (eradication at day 14 by patient).
- b. Please explain the difference between eradp14 and the fungal culture results shown in Table 34 in the study report.
- c. In the data set oe, when oecat="FUNGIC CULTURE", there is a value of "D" in the numerical variable OEORRESN (Numeric Result/Finding in Original Units). Please explain what "D" represents.

Please, contact me at 301-796-0763 if you have any questions regarding this request.

Judit Milstein
Chief, Project Management Staff
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

JUDIT R MILSTEIN

02/20/2010

Information request on clinical microbiology data

**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, Supervisory Consumer Safety Officer
Division of Special Pathogen and Transplant Products (DSPTP)

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

CC: Katie Klemm, Regulatory Review Officer, DDMAC
Marci Kiester, DTC Group Leader, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC

Subject: **NDA 022404**

DDMAC labeling comments for Oravig (miconazole) Buccal Tablet

DDMAC has reviewed the proposed patient labeling (PPI) for Oravig (miconazole) Buccal Tablet use submitted for consult on January 15, 2010.

The version of the patient labeling used in this review is the OSE marked up copy from February 18, 2010.

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

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

If you have any questions on the comments for the patient labeling, please contact Sharon Watson at 301.796.3991 or Sharon.Watson@fda.hhs.gov.

8 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)
tablet)

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/s/

SHARON M WATSON
02/19/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Judit Milstein, Chief Project Management Staff

Division of Special Pathogen and Transplant Products (DSPTP)

REQUEST DATE
January 15, 2010

IND NO.

NDA/BLA NO.
22404

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

ORAVIG (miconazole)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)

February 23, 2010

NAME OF FIRM:

Beckloff and Associates

PDUFA Date: April 16, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
 PATIENT PACKAGE INSERT (PPI)
 CARTON/CONTAINER LABELING
 MEDICATION GUIDE
 INSTRUCTIONS FOR USE (IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
 IND
 EFFICACY SUPPLEMENT
 SAFETY SUPPLEMENT
 LABELING SUPPLEMENT
 PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
 LABELING REVISION

EDR link to submission:

http://edr.fda.gov:7777/edr/EDR_Main.jsp

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: January 20, 26, February 9, 23, March 10, 23

Wrap-Up Meeting: February 23, 2010

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

JUDIT R MILSTEIN

01/15/2010

Consult to DDMAC-Labeling



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2010

| | |
|---|---|
| To: Lavonee M. Patton, Ph.D. | From: Judit Milstein, Chief Project Management Staff |
| Company: Beckloff Associates, Inc, on behalf of BioAlliance Pharma | Division of Special Pathogen and Transplant Products |
| Fax Number: 913 451-3846 | Fax Number: 301-796-9881 |
| Phone Number: 913 451-3955 | Phone Number: 301-796-0763 |

Subject: Preliminary recommendations for the labeling, carton and container labels of Oravig

Total no. of pages including cover: 4

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-0763.

Judit Milstein
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 22-404
Oravig (miconazole) buccal tablets
Beckloff Associates, Inc. on behalf of BioAlliance Pharma

RE: Recommendations for revisions to the labeling, carton and container labels

Dear Dr. Patton,

We refer to your NDA submission dated June 15, 2009, received June 16, 2009 for your Oravig (miconazole) buccal tablets.

Find enclosed the Division's preliminary recommendations for the labeling of Oravig.

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 they 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). The use of the term (b) (4) as part of the dosage form is 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). This request was previously conveyed to you in a fax dated December 9, 2009
- d. Revise the storage statement in the carton and other labeling to read as follows:

“Store at 20-25°C (77- 86 °F) See USP controlled room temperature, excursions between 15 to 30 °C permitted.”

This statement may be abbreviated in the carton label if the complete text does not fit in the label

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 [REDACTED] ^{(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 tablet contains 50 mg of miconazole.’
- b. Revise the statement ‘Do not suck, chew or swallow tablets’ 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 [REDACTED] ^{(b) (4)} that is located on the side panel as it does not include the complete dosing instructions.

In order to proceed with the timely review of your submission, we request that you provide this information no later than January 25, 2010.

Thank you

Judit Milstein
Chief Project Management Staff

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

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/s/

JUDIT R MILSTEIN

01/11/2010

Comments on labeling, carton and container labels



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2009

| | |
|---|---|
| To: Lavonee M. Patton, Ph.D. | From: Judit Milstein, Chief Project Management Staff |
| Company: Beckloff Associates, Inc, on behalf of BioAlliance Pharma | Division of Special Pathogen and Transplant Products |
| Fax Number: 913 451-3846 | Fax Number: 301-796-9881 |
| Phone Number: 913 451-3955 | Phone Number: 301-796-0763 |

Subject: Information request on microbial limits testing

Total no. of pages including cover: 3

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-0763.

Judit Milstein
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 22-404
Oravig (miconazole) buccal tablets
Beckloff Associates, Inc. on behalf of BioAlliance Pharma

RE: Request for additional information on microbial limits testing

Dear Dr. Patton,

We refer to your NDA submission dated June 15, 2009, received June 16, 2009 for your Oravig (miconazole) buccal tablets.

In order to continue with the timely review of your submission we ask that you respond to the following information request by no later than January 15, 2010.

The drug product release testing should include microbial limits testing for each commercial batch. After additional acceptable microbial limits testing data for the product has been collected, you may submit a prior approval supplement to request reduction or elimination of microbial limits testing at release. For guidance related to elimination or reduction in microbial limits testing refer to “Q6A International Conference on Harmonization; Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances”.

Please, contact Judit Milstein, Chief Project Management Staff at 301-796-0763 if you have any questions regarding this request.

Rapti Madurawe, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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

/s/

RAPTI D MADURawe
12/23/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2009

| | |
|---|---|
| To: Lavonee M. Patton, Ph.D. | From: Judit Milstein, Chief Project Management Staff |
| Company: Beckloff Associates, Inc, on behalf of BioAlliance Pharma | Division of Special Pathogen and Transplant Products |
| Fax Number: 913 451-3846 | Fax Number: 301-796-9881 |
| Phone Number: 913 451-3955 | Phone Number: 301-796-0763 |

Subject: Information request on dissolution acceptance criteria and labeling

Total no. of pages including cover: 3

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0763.

Judit Milstein
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 22-404
Oravig (miconazole) buccal tablets
Beckloff Associates, Inc. on behalf of BioAlliance Pharma

RE: Request for additional information on dissolution acceptance criteria

Dear Dr. Patton,

We refer to your NDA submission dated June 15, 2009, received June 16, 2009 for your Oravig (miconazole) buccal tablets.

In order to continue with the timely review of your submission we ask that you respond to the following information request by no later than January 4, 2010.

1. The dissolution acceptance criteria (AC) of the product at 8 hours proposed in the NDA is: (b) (4) at 8 hours. Please consider setting an upper limit or a Q value.
2. Please provide a release specification with acceptance criteria for all the impurities in miconazole drug substance.
3. Please link all miconazole drug substance batches used to manufacture clinical batches and indicate:
 - i) The level of (b) (4) present in the drug substance and
 - ii) The level of (b) (4) in the final product if any.
4. What is your proposed regulatory release specification in the drug substance for impurity (b) (4) which is of genotoxic safety concern?

In addition, we request you delete reference to (b) (4) from the carton and container labels as well as from the Package Insert.

Please, contact Judit Milstein, Chief Project Management Staff at 301-796-0763 if you have any questions regarding this request.

Stephen Miller, Ph.D.
Acting Chief, Branch IV
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

STEPHEN P MILLER
12/07/2009



NDA 022404

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

BioAlliance Pharma
c/o Beckloff Associates
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, Kansas 66210

Attention: Lavonne Patton, Ph.D.
Director, Managing Consultant, Beckloff Associates, Inc.

Dear Dr. Patton:

Please refer to your New Drug Application (NDA) dated February 5, 2009, received February 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Miconazole Tablet, 50 mg.

We also refer to your August 11, 2009, correspondence, received August 12, 2009, requesting review of your proposed proprietary name, Oravig. We have completed our review of the proposed proprietary name, Oravig and have concluded that it is acceptable.

The proposed proprietary name, Oravig, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 11, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Judit Milstein at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

CAROL A HOLQUIST
11/10/2009



Memorandum

TELEPHONE FACSIMILE

Date: September 26, 2009

From: Christina H. Chi, Ph.D., Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products

To: Lavonne M. Patton, Ph.D.

NDA: 22-404

Drug: Lauriad[®] miconazole (b) (4) Buccal Tablet

Indication: Local treatment of Oropharyngeal Candidiasis

Subject: Information Request for NDA 22-404.

In order to continue with the timely review of your NDA, the Division of Scientific Investigation team requests the following information to be submitted by October 2, 2009:

For the Study BA2002/01/02, please list the patient numbers (by treatment arm) randomized at the following two clinical sites:

- Brahim El-Ghaddari, Morocco
- Jamal Daoud, Tunisia

Please call Judit Milstein at 301-796-1600 if you need additional information.

Sincerely,

Christina H. Chi, Ph.D.
Regulatory Health Project Manager

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

CHRISTINA H CHI
09/26/2009

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

| Application Information | | |
|--|--|--|
| NDA # 22-404 | NDA Supplement #: | Efficacy Supplement Type SE |
| Proprietary Name: Lauriad Established/Proper Name: miconazole Dosage Form: (b) (4) Buccal Tablet Strengths: 50mg | | |
| Applicant: BioAlliance Pharma, Inc. Agent for Applicant (if applicable): Beckloff Associates, Inc | | |
| Date of Application: June 15, 2009 Date of Receipt: June 16, 2009 Date clock started after UN: | | |
| PDUFA Goal Date: April 16, 2010 | | Action Goal Date (if different): Target date: |
| Filing Date: August 14, 2009 Date of Filing Meeting: July 27, 2009 | | |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 3 | | |
| Proposed Indication(s): local treatment of oropharyngeal candidiasis | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: Refer to Appendix A for further information. | | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) |
| Review Classification: If the application includes a complete response to pediatric WR, review classification is Priority. If a tropical disease Priority review voucher was submitted, review classification defaults to Priority. | | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted |
| Resubmission after withdrawal? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO Resubmission after refuse to file? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO | | |
| Part 3 Combination Product? | N/A <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device | |
| <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: None of the above | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | |

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| Collaborative Review Division (if OTC product): N/A | |
| List referenced IND Number(s): IND 69,578 | |
| PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Application Integrity Policy | |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aip.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments: | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| User Fees | |
| Form 3397 (User Fee Cover Sheet) submitted | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| User Fee Status Comments: | <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required |
| <i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i> | |
| Exclusivity | |
| Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |

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| <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p> | |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO</p> |
| <p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | <p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | |
| <p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p> | <p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> |

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| <p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> | | | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p>If yes, please list below:</p> | | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration |
| | | | |
| | | | |
| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> | | | |
| Format and Content | | | |
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p> | | | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | |
| <p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p> | | | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p> | | | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

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| <p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p> | <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| Patent Information (NDAs/NDA efficacy supplements only) | |
| <p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| Debarment Certification | |
| <p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |

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| <p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | |
| <p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | <p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| Financial Disclosure | |
| <p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| Pediatrics | |
| <p>PREA</p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>COMMENT: The Sponsor is requesting: a pediatric waiver for children under the age of 3 years old because of the choking hazard from the product and a pediatric deferral for children ages 3 years and older.</p> | <p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |

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| BPCA (NDAs/NDA efficacy supplements only): | |
| Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| Comments: | |
| Prescription Labeling | |
| Check all types of labeling submitted. Comments: | <input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) |
| Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Comments: | |
| Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Comments: | |
| All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO DDMAC advise me to send them later. |
| Comments: | |
| MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| Comments: MedGuide is not needed | |
| REMS consulted to OSE/DRISK? | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Comments: | |
| Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| Comments: On August 11, 2009 the sponsor submitted 2 proposed proprietary names (Oravig or (b)(4)) and they | |

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| are currently under being evaluated by OSE. | |
|---|--|

| OTC Labeling | |
|--------------|--|
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| | |
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| <p>Check all types of labeling submitted.</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) |
| <p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |

| Meeting Minutes/SPA Agreements | |
|--------------------------------|--|
|--------------------------------|--|

| | |
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| <p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO |
| <p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES Date(s): P-IND meeting: 5-18-07 Pre-NDA meeting: 8-12-08 <input type="checkbox"/> NO |
| <p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO |

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 27, 2009

NDA #: 22-404

PROPRIETARY/ESTABLISHED NAMES: Lauriad® (miconazole),
(b) (4) Buccal Tablet, 50 mg

APPLICANT: BioAlliance Pharma

BACKGROUND:

- On February 5, 2009 Beckloff Associates submitted a 505(b)(2) New Drug Application for miconazole Lauriad® 50 mg (b) (4) buccal tablet on behalf of BioAlliance Pharma, for the treatment of oropharyngeal candidiasis.
- On April 3, 2009, the FDA issued a refuse-to-file (RTF) letter because of the absence of code imprints on the tablet (21 CFR 206.10).
- On April 29, the sponsor held a teleconference to discuss the plan to address the RTF letter.
- On May 1, 2009, the Division called to respond to the sponsor's questions regarding the appropriate reference listed drugs (RLD) and patent certification. The Division explained that:
 1. NDA 20-968 is not listed in the Orange book because it was switched from Rx to OTC and became NDA 21-308; therefore NDA 20-968 cannot be the RLD of this application.
 2. The Medicare Modernization Act (MMA) indicates that if the incorrect certification is submitted, no amendments can be submitted to provide a correction. Also, a correct patent certification is required.
- On June 15, 2009, the sponsor resubmitted the NDA, which included information to address the deficiency listed in the RTF letter. The RLD on form 356(h) is for NDA 21-261, Monistat 3 Combination Pack.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|----------------------|-------------------------|--|
| Regulatory Project Management | RPM: | Christina H. Chi, Ph.D. | Y |
| | CPMS/TL: | Judit Milstein | Y |
| Cross-Discipline Team Leader (CDTL) | Karen Higgins, Sc.D. | | Y |
| Clinical | Reviewer: | Hala Shamsuddin, M.D. | Y |
| | TL: | Yulia Yasinskaya, M.D. | Y |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |

| | | | |
|--|-----------|-------------------------------------|---|
| | | | |
| Labeling Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |
| | TL: | | |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | Lynette Berkeley, Ph.D. | Y |
| | TL: | Shukal Bala, Ph.D. | Y |
| Clinical Pharmacology | Reviewer: | Yoriko Harigaya, Ph.D. | Y |
| | TL: | Philip Colangelo, Pharm.D, Ph.D. | Y |
| Biostatistics | Reviewer: | XianBin Li, Ph.D. | Y |
| | TL: | Karen Higgins, Sc.D. | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Owen McMaster, Ph.D. | Y |
| | TL: | William Taylor, Ph.D. | Y |
| Statistics, carcinogenicity | Reviewer: | | |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | Andrew Yu, Ph.D. | Y |
| | TL: | Rapti Madurawe, Ph.D. | Y |
| Facility (<i>for BLAs/BLA supplements</i>) | Reviewer: | | |
| | TL: | | |
| Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>) | Reviewer: | Bryan Riley | N |
| | TL: | Jim McVey | N |
| Bioresearch Monitoring (DSI) | Reviewer: | Susan Thompson.MD | Y |
| | TL: | Jean Mulinde, MD | N |
| Other reviewers | | | Y |

OTHER ATTENDEES: Renata Albrecht, David Roeder, Daphne Lin, Kathleen Klemm, Paul Loebach, Darrell Jenkins, Mohammed Huque, Ozlem Belen, Kennerly Chapman, John Lazor, Melissa Truffa, Sharon Watson

| | |
|--|--|
| <p>505(b)(2) filing issues?</p> <p>If yes, list issues:</p> | <p><input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> |
| <p>Per reviewers, are all parts in English or English translation?</p> <p>If no, explain:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |

| | |
|--|---|
| <p>Electronic Submission comments</p> <p>List comments:</p> | <p><input checked="" type="checkbox"/> Not Applicable</p> |
| <p>CLINICAL</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>• Clinical study site(s) inspections(s) needed?</p> <p>If no, explain:</p> | <p><input checked="" type="checkbox"/> YES; Consult sent on 8/21/09 <input type="checkbox"/> NO</p> |
| <p>• Advisory Committee Meeting needed?</p> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason: N/A</p> |
| <p>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p> |

| | |
|---|--|
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>• Clinical pharmacology study site(s) inspections(s) needed?</p> | <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p>• Establishment(s) ready for inspection?</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |

| | |
|-------------------------------------|--|
| <input checked="" type="checkbox"/> | Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system. |
| <input type="checkbox"/> | If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER. |
| <input type="checkbox"/> | If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | If BLA or priority review NDA, send 60-day letter. |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 on August 26, 2009 |
| <input type="checkbox"/> | Other |

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/s/

CHRISTINA H CHI
09/16/2009

JUDIT R MILSTEIN
09/16/2009
CSO Filing Review



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

Date: September 16, 2009

| | |
|---|---|
| To: Lavonne M. Patton, Ph.D. | From: Christina H. Chi, Ph.D. Regulatory Health Project Manager |
| Company: Beckloff Associates, Inc., for BioAlliance Pharma | Division of Special Pathogen and Transplant Products |
| Fax number: (913) 451- 3846 | Fax number: (301) 796-9881 |
| Phone number: (913) 451- 3955 | Phone number: (301) 796-0695 |

Subject: Information Request on dissolution acceptance criteria.

Total no. of pages including cover: 4

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-9881. Thank you.



Memorandum

TELEPHONE FACSIMILE

Date: September 16, 2009

From: Christina H. Chi, Ph.D., Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products

To: Lavonne M. Patton, Ph.D.

NDA: 22-404

Drug: Lauriad[®] miconazole (b) (4) Buccal Tablet

Indication: Local treatment of Oropharyngeal Candidiasis

Subject: Information Request for NDA 22-404.

In order to continue with the timely review of your NDA, the Chemistry review team requests the following information to be submitted by September 30, 2009:

1. The dissolution acceptance criteria of the drug product in the NDA was revised as follows:
 - a. (b) (4) at 4 hours
 - b. (b) (4) at 8 hours

We noted that data from the clinical batch show a dissolution rate of about (b) (4) at 8 hours after 2 years; faster than the revised acceptance criterion of (b) (4)

Please provide the following information to justify the revised dissolution acceptance criteria and demonstrate tablet dissolution is not compromised at the end of the proposed shelf life.

- (i) All available dissolution data that you have generated beyond 4 hours of dissolution
- (ii) Explain why the dissolution rates at 4 and 8 hours generally slow down during storage when compared to initial dissolution rate. For example, Batch E213X012 slows from (b) (4) and (b) (4) at 4 and 8 hours respectively after 36 months of storage during long-term stability study.

- (iii) Dissolution profile comparisons of the clinical batch with stability batches stored for over a year or more.
 - (iv) During the clinical study, did tablets breakup during use, dissolve completely, or were left over tablets removed before the next dose?
 - (v) Data to show that the entire dose in the tablet is released when used as recommended. If the entire dose is not released, indicate the delivered dose and the consistency of the delivered dose.
2. Please provide an update on when you will submit the stability data (debossed 14-tablet and 2-tablet configurations) that you intend to provide during the review cycle.

Please call me at 301-796-0695 if you need additional information.

Sincerely,

Christina H. Chi, Ph.D.
Regulatory Health Project Manager

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

CHRISTINA H CHI
09/16/2009

From: Chi, Christina H
Sent: Tuesday, September 01, 2009 4:00 PM
To: 'Patton, Lavonne'
Cc: Thompson, Susan (CDER)
Subject: Request for information - Lauriad miconazole (b) (4) buccal tablets

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Lavonne:

Please send me the following information as soon as possible:

1. A telephone number to contact Dr. Kanouni, Site 22 of Protocol BA2002/01/02
2. E-mail addresses for the following four clinical investigators:
 - a. Dr. Kanouni (Site 22, Protocol BA2002/01/02)
 - b. Dr. Daoud (Site 42, Protocol BA2002/01/02)
 - c. Dr. Mitha (Site 405, Protocol BA2004/01/04)
 - d. Dr. Ramlachan (Site 402, Protocol BA2002/01/04).

Thank you,
Christina Chi, Ph.D.

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

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/s/

CHRISTINA H CHI
09/11/2009

From: Chi, Christina H
Sent: Tuesday, September 01, 2009 4:00 PM
To: 'Patton, Lavonne'
Cc: Thompson, Susan (CDER)
Subject: Request for information - Lauriad miconazole (b) (4) buccal tablets

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Lavonne:

Please send me the following information as soon as possible:

1. A telephone number to contact Dr. Kanouni, Site 22 of Protocol BA2002/01/02
2. E-mail addresses for the following four clinical investigators:
 - a. Dr. Kanouni (Site 22, Protocol BA2002/01/02)
 - b. Dr. Daoud (Site 42, Protocol BA2002/01/02)
 - c. Dr. Mitha (Site 405, Protocol BA2004/01/04)
 - d. Dr. Ramlachan (Site 402, Protocol BA2002/01/04).

Thank you,
Christina Chi, Ph.D.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22404

ORIG-1

BIOALLIANCE
PHARMA

Lauriad (miconazole (b) (4)
tablet)

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/s/

CHRISTINA H CHI
09/09/2009



NDA 22-404

FILING COMMUNICATION

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Lavonne M. Patton, Ph.D.
Director
7400 West 110th Street, Suite 300
Overland Park, Kansas 66210

Dear Dr. Patton:

Please refer to your new drug application (NDA) dated June 15, 2009, received June 16, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Lauriad (miconazole (b)(4) buccal tablet), 50 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is April 16, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which include the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 1, 2009.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a partial waiver of

pediatric studies for this application, for pediatric patients younger than 3 years old. Once we have reviewed your request, we will notify you if the partial waiver request is granted or denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies for this application, for pediatric patients older than 3 years. Once we have reviewed your request, we will notify you if the partial deferral request is granted or denied.

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 796-0695.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Division Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
08/26/2009

| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
|--|---|--|---|-----------------------------|
| TO (Division/Office): Quality Microbiology Office of Pharmaceutical Sciences, Quality Microbiology (Attn: Sylvia Gant) | | FROM: Andrew Yu, Ph.D./ Rapti Madurawe, Ph.D. (Chemistry Reviewer/Chemistry Team Leader) Via: Christina H. Chi, Ph.D. | | |
| DATE 8/11/09 | IND NO. N/A | NDA NO. 22-404 | TYPE OF DOCUMENT Electronic NDA - module 3 | DATE OF DOCUMENT 6/15/09 |
| NAME OF DRUG : Miconazole (b) (4) Buccal tablets | PRIORITY CONSIDERATION S | CLASSIFICATION OF DRUG Antifungal | DESIRED COMPLETION DATE 11/16/09 | |
| NAME OF FIRM: BioAlliance Pharma, Inc. (US rep.: Beckloff Associates, Inc.) | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY | PRE--NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT | RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW): XX | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW): | | CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW): New Drug Microbiology | | |
| III. BIOPHARMACEUTICS | | | | |
| DISSOLUTION BIOAVAILABILTY STUDIES PHASE IV STUDIES | | DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RICK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| CLINICAL | | PRECLINICAL | | |

COMMENTS/SPECIAL INSTRUCTIONS:

The final dosage form contains MPC (milk protein concentrate), a (b) (4) agent derived from milk by sterilization. The applicant describes in their submission various special microbial tests

Coliform Count

Bile Tolerant Gram Negative Bacteria

Salmonella

Escherichia coli

Staphylococcus aureus

Listeria

Thermophilic bacteria

Bacillus cereus

(Acceptance criteria for Listeria, thermophilic bacteria, and Bacillus cereus have been established by (b) (4) as the manufacturer of MPC.)

Please determine if the validation method and tests for the product are acceptable.

Supporting information can be found in the EDR, NDA 22-404, original application dated February 5, 2009 under Quality section 3.2.P.4 titled Control of Excipient/Milk Protein Concentrate.

Note: The original NDA submission was dated February 5, 2009. This submission was refused to file on April 3, 2009. The resubmission is dated June 15, 2009.

SIGNATURE OF REQUESTER Andrew Yu, Ph.D.,
Via: Christina H. Chi, Ph.D.

METHOD OF DELIVERY (Check one)
 E-MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

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/s/

CHRISTINA H CHI

08/11/2009

Please let me know who the assign reviewer will be.



NDA 22-404

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Dr. Lavonne M. Patton
Director
Commerce Plaza II, Ste. 300
7400 West 110 St.
Overland Park, KS 66210

Dear Dr. Patton:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our April 3, 2009, refusal to file letter for the following:

Name of Drug Product: Miconazole Lauriad (b) (4) (b) (4) Tablet, 50 mg

Review Priority Classification: Standard (S)

Date of Application: June 15, 2009

Date of Receipt: June 16, 2009

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 14, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 16, 2010.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request, for this application, for a waiver of pediatric studies in children less than three years of age and a deferral of pediatric studies in children between ages 4 to 16. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Dr. Christina Chi, Regulatory Project Manager, at (301) 796-0695.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Judith Milstein
6/26/2009 10:37:00 AM
Acknowledgment of resubmission of NDA



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: June 4, 2009

| | |
|---|---|
| To: Lavonne Patton, Ph.D. | From: Sherry Spriggs |
| Company: BioAlliance Pharma | Division of Special Pathogens and Transplant Products |
| Fax number: 913-451-3846 | Fax number: 301-796-9881 |
| Phone number: 913-451-3955 | Phone number: 301-796-4018 |
| Subject: Clinical Information Requested With Re-submission | |

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-4018.

Sherry Spriggs
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 22-404

Lauriad (miconazole) 50mg (b) (4)

Dear Dr. Patton,

To expedite the review of your application, please add a USUBJID (unique subject ID) column to every dataset included in your resubmission. If possible, provide the datasets in a format that can be loaded into I-review.

Thank you,

Sherry Spriggs
Regulatory Project Manager

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/s/

Sherry Spriggs
6/4/2009 03:23:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-404

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Lavonne Patton, Ph.D.
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Dr. Patton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50 mg.

We also refer to the teleconference between representatives of your firm and the FDA on April 29, 2009. The purpose of the meeting was to discuss the information on the debossing of the tablet that will be submitted with the NDA.

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, call Sherry Spriggs, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Product Quality Acting Branch Chief
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosures: Meeting Minutes

TELECONFERENCE MINUTES

MEETING DATE: April 29, 2009
TIME: 10:00 am – 10:25 am
APPLICATION: NDA 22-404
DRUG NAME: Lauriad[®]
TYPE OF MEETING: TYPE A

MEETING CHAIR: Norman Schmuff, Ph.D.

MEETING RECORDER: Sherry Spriggs, M.P.H.

FDA ATTENDEES: (Title and Office/Division)

| | |
|-------------------------|--|
| Norman Schmuff, Ph.D. | Product Quality Branch Chief |
| Rapti Madurawe, Ph.D. | Product Quality Team Leader |
| Andrew Yu, Ph.D. | Product Quality Reviewer |
| Xuhong Li, Ph.D. | Product Quality Reviewer |
| Yuliya Yasinskaya, M.D. | Clinical Team Leader |
| Shukal Bala, Ph.D. | Clinical Microbiology Team Leader |
| Lynette Berkeley, Ph.D. | Clinical Microbiology Reviewer |
| Judit Milstein, B.S. | Chief, Project Management Staff -- call-in |
| Sherry Spriggs, M.P.H. | Regulatory Project Manager |

EXTERNAL CONSTITUENT ATTENDEES:

| | |
|--------------------------------------|---|
| Caroline Lemarchand, Pharm.D., Ph.D. | Chemistry, Manufacturing, and Controls Director; BioAlliance Pharma |
| Delphine Lucas, Pharm.D. | Regulatory Affairs Director; BioAlliance Pharma |
| Michel Forest, Pharm.D. | Regulatory Compliance; BioAlliance Pharma |
| Michael Day, B.S. | Chemistry, Manufacturing, and Controls Consultant; Beckloff Associates, Inc. |
| Cheryl Elder, Pharm.D. | Regulatory Affairs; Strativa Pharmaceuticals |
| Lavonne Patton, Ph.D. | Regulatory Consultant; Beckloff Associates, Inc. |

BACKGROUND:

NDA 22-404 for Lauriad[®] (miconazole) 50 mg (b) (4) buccal tablet was submitted on February 5, 2009. On April 3, 2009 a Refusal to File action letter was sent to the applicant citing non-compliance with 21 CFR 206.10 Code Imprint Requirement.

On April 17, 2009, BioAlliance submitted a Type A meeting request and briefing package which includes information on the successful manufacturing of debossed tablets. On April 22, 2009 BioAlliance Pharma submitted samples of debossed tablets.

The Division provided preliminary comments on the briefing package on April 27, 2009. In response to these comments, the sponsor indicated that during the teleconference, they would like to focus on questions 3a and 3b.

On April 28, 2009, the sponsor submitted via e-mail a timetable for the submission of the stability samples.

MEETING OBJECTIVES:

1. To confirm that the CMC information to be presented in the 505(b)(2) NDA is sufficient to support the filability of the NDA.

DISCUSSION POINTS:

The discussion focused on questions 3a and 3b posted by the applicant in the briefing package. For the purposes of these minutes, the questions posted by the applicant are in *italics* font, responses sent by the Agency on April 27, 2009 are in normal font, and discussions during the teleconference are in **bold** font.

1. Does FDA agree that the proposed tablet debossing with the letter "L" on the flat side in combination with the tablet shape and color represents a unique identifier for the U.S. market and will satisfy the requirements of 21 CFR 206.10?

Agency response: The Agency agrees that the proposed tablet debossing will satisfy the requirements of 21 CFR 206.10 for filing purpose.

2. BioAlliance Pharma considers the planned updates to the CMC information in the NDA, as described below, to show sameness of the non-debossed and debossed tablets. These updates, in combination with the data already included in the original file, are considered satisfactory to support filability of the NDA. Does the Division agree?

BioAlliance Pharma plans to update the NDA with development data on tablet debossing that shows the commercial tablets can be debossed. The following Sections will be updated :

- *All sections of the NDA that mention the debossing code or tablet appearance will be updated appropriately to reflect that the commercial tablet will be debossed (i.e., Sections 1.14.1.2, 1.14.1.3, 2.3.P, 2.3.R, 3.2.P.1, 3.2.P.2, 3.2.P.3, 3.2.P.5, 3.2.P.8, and 3.2.R).*
- *Section 3.2.P.1 will be updated to reflect the debossed appearance of the tablets.*
- *Section 3.2.P.2 will be updated to include the process development data and In Process Control (IPC) results that support debossing the tablets; specifically, the following information will be provided that demonstrates equivalence of debossed and nondebossed tablets:*
 - *experimental results for different debossing options (flat vs rounded face) that were explored;*
 - *data to support comparability of the non-debossed and debossed tablets; especially dissolution profile with f2 similarity analysis comparisons that support similarity of the debossed and non-debossed tablets.*

- Section 3.2.P.3 will be updated with a drawing of the embossed punch with the proposed letter “L”. A blank master batch record will also be referenced that reflects addition of the embossed punch.
- Section 3.2.P.5 will be updated to include the revised release specifications to reflect the change in appearance and batch analysis results that include the dissolution and adhesion results that support equivalence of the debossed and non-debossed tablets.
- Section 3.2.P.8 will be updated with a post-approval commitment to put the first three commercial batches of debossed miconazole Lauriad® 50 mg (b) (4) on stability.
- Section 3.2.R will be updated to include a blank master batch record for the commercial production of debossed tablets.
- Patient Information Leaflet will be updated to include the description of the debossed

Given the results presented in Section 4 below, BioAlliance Pharma considers that equivalence of the non-debossed and debossed tablets has been demonstrated; debossing does not impact the drug product quality or performance.

Agency response: The Agency agrees that the proposed update in the above sections with the debossed tablet will support filability of the NDA. The adequacy of the information contained in the updated sections will be a review issue.

3. Thirty-six (36)-month room temperature and 6 months accelerated stability data for primary stability batches of the non-debossed tablet (commercial scale of (b) (4)) will be presented when the NDA is resubmitted. Based on the physical and chemical results on debossed tablets, which indicate that debossing does not have a detectable impact on the formulation quality and performance of the tablet, BioAlliance Pharma believes that the data supporting the non-debossed tablet can also support the debossed tablet and will therefore propose a shelf-life of 36 months for the trade product.

a) To further support the debossed tablet, BioAlliance Pharma will commit in the NDA to put the first three commercial batches of debossed Miconazole Lauriad® 50 mg (b) (4) on stability. When available, stability results will be provided in the Annual Report.
Does the Division agree with this assessment and plan?

b) BioAlliance Pharma has also presented physician samples (bottles of 2 non-debossed tablets) in the NDA. The container closure for the physician samples is the same as for the proposed commercial container closure containing 14 tablets and was used in the primary stability batches. In addition to the data included in the NDA on the primary stability batches, BioAlliance Pharma proposes to submit, at the request of the Agency an update to the NDA to provide accelerated and long-term stability data on the 2-count bottle of nondebossed tablets. With the combined data, BioAlliance Pharma plans to propose a shelf life of 36 months for physician sample containers of the debossed tablets.

Is this approach acceptable to the Division?

Agency responses:

a) Yes, the Agency agrees with the assessment and plan for stability report in a) above with the demonstration of nondebossed and debossed tablet comparability as described in question 2. Please provide available stability data for a batch of the debossed tablet within the review cycle.

DISCUSSION:

BioAlliance summarized the stability submission plan for the 14-count package in the table given below. Bioalliance asked if the stability data submission plan for debossed tablets batch # 812021 would meet FDA's requirement.

The Agency stated it would but BioAlliance would also need to submit release data for debossed tablet comparability. BioAlliance stated the information will be provided in the NDA re-submission. Bioalliance also confirmed the F2 dissolution comparison data was generated from the debossed tablet batch #812021.

BioAlliance asked how the Agency plans to use the data submitted for the debossed and non-debossed data to establish the shelf-life for the debossed tablets. The Agency responded that the data in the NDA will be looked as a whole in order to establish the shelf-life. The Agency also indicated that although debossing is not expected to affect the stability outcome, both the chemical stability and dissolution comparability data will be taken into account for the final determination. The Division also indicated that any information the applicant can supply to show that dissolution remains unchanged over time would be helpful.

b) The Agency agrees the shelf-life of the debossed 2-count physician samples can be supported by the stability data presented for the nondebossed 2-count physician samples with additional data from the nondebossed 14-count configuration. It may not be possible to extrapolate the shelf-life of the 2-count configuration using stability data from the 14-count configuration due to the increased air space and drug product sensitivity to oxidation. Please submit sufficient stability data for the 2-count configuration within the review cycle. The acceptability of the proposed shelf-life will be a review issue.

The stability data tables currently provided do not identify the number of tablets in the container. Please distinguish the 14-count stability data sets from that of the 2-count.

DISCUSSION:

BioAlliance clarified that all stability data in the current NDA submission is for the 14-count package. Bioalliance stated that stability data for the 2-count package will be submitted during the review cycle as described in the table (see below).

The Agency stated that it is in agreement with the timetable presented by the applicant.

In response to BioAlliance's question, the Agency confirmed that it will look at the "whole picture" of the 2-count stability data the same as the 14-count stability data.

The Agency asked if data is available on bioadhesive properties of debossed versus non-debossed? BioAlliance responded the data is available and referenced table 5 in the meeting package (see below).

4. Milk Protein Concentrate (MPC) has been used as an ingredient in dairy products and medical nutrition products for many years in both the US and in Europe. In 2002, (b) (4) supplied about 55% of the MPC for the United States market. MPC is used in several food applications, especially as an ingredient in processed cheese products (22%), while 77% of the MPC is used in specialty nutritional products including infant formula, medical nutrition, sports bars, and beverages (USITC Publication 3692, 2004). As discussed at the pre-NDA meeting, BioAlliance Pharma has included the following information in the NDA: MPC specifications, analytical methods, and a manufacturing flow chart. BioAlliance Pharma has also included information in Module 2.4 on a literature review on MPC. Based on your filing determination review, does the Agency consider that the information provided for MPC is sufficient to permit a substantive review?

Agency response: The Agency agrees the information will be sufficient to permit the review for MPC.

ATTACHMENT: Availability of Stability Data Table

Miconazole Lauriad® 50 mg (b) (4) Buccal Tablets

**Availability of Stability Data to support discussion during April 29th, 2009 Teleconference
(Question 3a and 3b, Briefing Package submitted April 13th, 2009 - NDA 22,404;
Amendment SN0006)**

| No. of Batches | Scale | Code | Package | Stability Data to be Submitted | | |
|---|---------------------------------|--------------|----------|--|--|------------------------------------|
| | | | | NDA re-submission targeted June 1st, 2009 | August 09 (1) | December 09 (2) |
| 3 (primary stability ; batch No.E213X011, E213X012, and E213X013) | Commercial | Non-debossed | 14-count | 36 months long-term and 6 months accelerated | - | - |
| 1 (biobatch ; batch No.E213X021) | Commercial | Non-debossed | 14-count | 24 months long-term and 6 months accelerated | 36 months long-term and 6 months accelerated | - |
| 1 (batch No. 812021) | Commercial (sub-batch debossed) | Debossed | 14-count | - | 3 months long-term and accelerated | 6 months long-term and accelerated |
| 1 (batch No. 810020) | Commercial | Non-debossed | 2-count | - | 3 months long-term and accelerated | 6 months long-term and accelerated |
| 1 (to be manufactured) | Commercial | Debossed | 14-count | - | - | 3 months long-term and accelerated |
| | | | 2-count | | | |

(1) within approximately 3 months of re-submission of the NDA

(2) within approximately 6 months of re-submission of the NDA

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/s/

Rapti Madurawe
5/28/2009 09:46:55 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 06, 2009

| | |
|---|---|
| To: Lavonne Patton, PhD | From: Sherry Spriggs |
| Company: BioAlliance Pharmaceuticals | Division of Special Pathogens and Transplant Products |
| Fax number: (913) 451-3846 | Fax number: 301-796-9881 |
| Phone number: (913) 451-3955 | Phone number: 301-796-4018 |
| Subject: Chemistry Comments For NDA NDA 22-404 | |

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-4018.

Sherry Spriggs
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Sherry Spriggs
5/6/2009 03:10:44 PM

MEMORANDUM OF TELECON

DATE: May 1, 2009

APPLICATION NUMBER: NDA 22-404, Lauriad[®]

BETWEEN:

Name: Lavonne Patton, Ph.D., Executive Director, Pharmaceutical Development
David Rosen, Patent Attorney
Phone: 913-451-3955
Representing: BioAlliance Pharma

AND

Name: Sherry Spriggs, Regulatory Project Manager
Judith Milstein, Chief Project Management Staff
David Roeder, Associate Director for Regulatory Affairs
Division of Special Pathogen and Transplant Products

SUBJECT: Patent Certification

BACKGROUND:

- February 5, 2009: BioAlliance Pharma submitted a 505(b)(2) application, where they list NDA 20-968 as a reference listed drug. This NDA is not listed in the Orange Book as it has been the subject of an Rx to OTC switch to NDA 21-083.
- April 30, 2009: BioAlliance Pharma requested a teleconference to discuss comments relayed in regards to reference listed drugs and patent certification

For the purposes of these minutes, questions by BioAlliance are in normal font and Division responses are in **bolded** font.

Question 1:

In our 505(b)(2) NDA, BioAlliance is seeking to rely on FDA's determination that Miconazole is safe and effective as an anti-fungal agent. Based upon our review of publicly available information, we believe that the appropriate approved reference listed drugs to support this determination is both NDA 20-968 Monistat Dual-Pak (Miconazole Nitrate Insert and Cream) and NDA 18-888 Monistat 3 (Miconazole Nitrate 200mg Vaginal Suppository).

If FDA believes that other products are more appropriate to be cited as the reference products, we would like to discuss those reference listed products.

FDA's Response: The Division indicated that 505(b)(2) applications cannot rely on a drug not listed in the Orange Book. The Division also clarified that NDA 20-968

has been the subject of an Rx to an Over-the-counter (OTC) switch, and is now listed as NDA 21-308.

BioAlliance indicated there are 2 unexpired patents listed for NDA 21-308 and they understand that they will need to search for another application to rely on for the resubmission of their NDA.

Question 2:

We would also request that FDA clarify the relationship and impact of the Medicare Modernization Act on the reference listed drugs cited in our 505(b)(2) NDA submission.

FDA's Response: The Medicare Modernization Act indicates that if the incorrect certification is submitted, no amendments can be submitted to provide a correction; Instead, the applicant needs to withdraw the application and re-submit it with the correct patent certification.

Sherry Spriggs, M.P.H.
Regulatory Health Project Manager

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/s/

Sherry Spriggs
5/6/2009 02:58:32 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: April 28, 2009

| | |
|---|---|
| To: Lavonne Patton, PhD | From: Sherry Spriggs |
| Company: BioAlliance Pharmaceuticals | Division of Special Pathogens and Transplant Products |
| Fax number: (913) 451-3846 | Fax number: 301-796-9881 |
| Phone number: (913) 451-3955 | Phone number: 301-796-4018 |
| Subject: Chemistry Comments on Meeting Information Packet submitted on April 17, 2009. | |

Total no. of pages including cover: 6

Comments:

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-4018.

Sherry Spriggs
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 22-404

Miconazole Lauriad (b) (4) buccal Tablet

Submission date: April 17, 2009

Dear Dr. Patton:

The following are the Division's responses to the questions provided in your briefing package dated April 17, 2008, with regard to the CMC issue described in the Refusal to File letter dated April 3, 2009. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference, scheduled for Wednesday, April 29, 2009 by contacting me.

Your original questions are in *italics* followed by the Division's responses in **bold** type.

- 1. Does FDA agree that the proposed tablet debossing with the letter "L" on the flat side in combination with the tablet shape and color represents a unique identifier for the U.S. market and will satisfy the requirements of 21 CFR 206.10?*

Agency response:

The Agency agrees that the proposed tablet debossing will satisfy the requirements of 21 CFR 206.10 for filing purpose.

- 2. BioAlliance Pharma considers the planned updates to the CMC information in the NDA, as described below, to show sameness of the non-debossed and debossed tablets. These updates, in combination with the data already included in the original file, are considered satisfactory to support filability of the NDA. Does the Division agree?*

BioAlliance Pharma plans to update the NDA with development data on tablet debossing that shows the commercial tablets can be debossed. The following Sections will be updated:

- All sections of the NDA that mention the debossing code or tablet appearance will be updated appropriately to reflect that the commercial tablet will be debossed (i.e., Sections 1.14.1.2, 1.14.1.3, 2.3.P, 2.3.R, 3.2.P.1, 3.2.P.2, 3.2.P.3, 3.2.P.5, 3.2.P.8, and 3.2.R).*
- Section 3.2.P.1 will be updated to reflect the debossed appearance of the tablets.*
- Section 3.2.P.2 will be updated to include the process development data and In Process Control (IPC) results that support debossing the tablets; specifically, the following information will be provided that demonstrates equivalence of debossed and nondebossed tablets:*
 - experimental results for different debossing options (flat vs rounded face) that were explored;*

- *data to support comparability of the non-debossed and debossed tablets; especially dissolution profile with f2 similarity analysis comparisons that support similarity of the debossed and non-debossed tablets.*
- *Section 3.2.P.3 will be updated with a drawing of the embossed punch with the proposed letter “L”. A blank master batch record will also be referenced that reflects addition of the embossed punch.*
- *Section 3.2.P.5 will be updated to include the revised release specifications to reflect the change in appearance and batch analysis results that include the dissolution and adhesion results that support equivalence of the debossed and non-debossed tablets.*
- *Section 3.2.P.8 will be updated with a post-approval commitment to put the first three commercial batches of debossed miconazole Lauriad® 50 mg (b) (4) on stability.*
- *Section 3.2.R will be updated to include a blank master batch record for the commercial production of debossed tablets.*
- *Patient Information Leaflet will be updated to include the description of the debossed*

Given the results presented in Section 4 below, BioAlliance Pharma considers that equivalence of the non-debossed and debossed tablets has been demonstrated; debossing does not impact the drug product quality or performance.

Agency response:

The Agency agrees that the proposed update in the above sections with the debossed tablet will support filability of the NDA. The adequacy of the information contained in the updated sections will be a review issue.

3. *Thirty-six (36)-month room temperature and 6 months accelerated stability data for primary stability batches of the non-debossed tablet (commercial scale of (b) (4)) will be presented when the NDA is resubmitted. Based on the physical and chemical results on debossed tablets, which indicate that debossing does not have a detectable impact on the formulation quality and performance of the tablet, BioAlliance Pharma believes that the data supporting the non-debossed tablet can also support the debossed tablet and will therefore propose a shelf-life of 36 months for the trade product.*
 - a) *To further support the debossed tablet, BioAlliance Pharma will commit in the NDA to put the first three commercial batches of debossed Miconazole Lauriad® 50 mg (b) (4) on stability. When available, stability results will be provided in the Annual Report.*

Does the Division agree with this assessment and plan?

- b) *BioAlliance Pharma has also presented physician samples (bottles of 2 non-debossed tablets) in the NDA. The container closure for the physician samples is the same as for the proposed commercial container closure containing 14 tablets and was used in the*

primary stability batches. In addition to the data included in the NDA on the primary stability batches, BioAlliance Pharma proposes to submit, at the request of the Agency an update to the NDA to provide accelerated and long-term stability data on the 2-count bottle of nondebossed tablets. With the combined data, BioAlliance Pharma plans to propose a shelf life of 36 months for physician sample containers of the debossed tablets.

Is this approach acceptable to the Division?

Agency responses:

- a) **Yes, the Agency agrees with the assessment and plan for stability report in a) above with the demonstration of nondebossed and debossed tablet comparability as described in question 2. Please provide available stability data for a batch of the debossed tablet within the review cycle.**
- b) **The Agency agrees the shelf-life of the debossed 2-count physician samples can be supported by the stability data presented for the nondebossed 2-count physician samples with additional data from the nondebossed 14-count configuration. It may not be possible to extrapolate the shelf-life of the 2-count configuration using stability data from the 14-count configuration due to the increased air space and drug product sensitivity to oxidation. Please submit sufficient stability data for the 2-count configuration within the review cycle. The acceptability of the proposed shelf-life will be a review issue.**

The stability data tables currently provided do not identify the number of tablets in the container. Please distinguish the 14-count stability data sets from that of the 2-count.

4. *Milk Protein Concentrate (MPC) has been used as an ingredient in dairy products and medical nutrition products for many years in both the US and in Europe. In 2002, (b) (4) supplied about 55% of the MPC for the United States market. MPC is used in several food applications, especially as an ingredient in processed cheese products (22%), while 77% of the MPC is used in specialty nutritional products including infant formula, medical nutrition, sports bars, and beverages (USITC Publication 3692, 2004). As discussed at the pre-NDA meeting, BioAlliance Pharma has included the following information in the NDA: MPC specifications, analytical methods, and a manufacturing flow chart. BioAlliance Pharma has also included information in Module 2.4 on a literature review on MPC. Based on your filing determination review, does the Agency consider that the information provided for MPC is sufficient to permit a substantive review?*

Agency response:

The Agency agrees the information will be sufficient to permit the review for MPC.

If you have any questions regarding the contents of this transmission, please contact me at 301-796-4018.

Sherry Spriggs
Regulatory Project Manager

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/s/

Sherry Spriggs
4/28/2009 04:52:03 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-404

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Lavonne Patton, Ph.D.
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Dear Dr. Patton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50 mg.

We also refer to your April 17, 2009, correspondence, received April 20, 2009, requesting a meeting to discuss the CMC issue relayed in the April 3, 2009 Refusal to File action letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: April 29, 2009

Time: 10:00 a.m. – 11:00 a.m.

Phone Arrangements: CALL-IN NUMBER: 1-866-738-5057

PASSCODE: 1923635

CDER Participants:

Renata Albrecht, M.D., Division Director
Norman Schmuff, Ph.D., Product Quality Branch Chief
Rapti Madurawe, Ph.D., Product Quality Team Leader
Andrew Yu, Ph.D., Product Quality Reviewer
Karen Higgins, Sc.D., Statistical Team Leader
Yuliya Yasinskaya, M.D., Clinical Team Leader
Judit Milstein, B.S., Chief Project Management Staff
Sherry Spriggs, M.P.H., Regulatory Project Manager

We have received 12 desk copies of the background information for this meeting, on April 20, 2009. If the materials presented in the information package are inadequate to justify holding a meeting, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Sherry Spriggs, M.P.H.
Regulatory Project Manager
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products

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/s/

Sherry Spriggs
4/21/2009 04:09:07 PM

Phone number: 913-451-3955

Phone number: 301-796-4018

Subject: NDA 22-404 Comments on Clinical Dataset

Total no. of pages including cover: 3

Document to be mailed:

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Dear Ms. Patton,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50mg.

We also refer to the fax sent to you on March 26, 2009, requesting additional information on the datasets submitted with your NDA. We also refer to your request for clarification dated April 8, 2009.

We have reviewed your request and have the following comments:

ISS datasets should include information on all subjects in your NDA submission, including those from Phase I studies. Please integrate data on all 18 subjects from Study BA2000/01/01 into the ISS datasets and provide a unique subject identification number and applicable demographic information for each subject.

We are providing the above information by email for your convenience. Please, contact me at 301-796-4018 if you have any questions regarding the contents of this transmission.

Thank you.

Sherry Spriggs, M.P.H.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

| Application Information | | |
|--|--|----------------------------------|
| NDA # 22-404 Type: 505(b)(2) | NDA Supplement # N-000 | Efficacy Supplement Type SE- N/A |
| Proprietary Name: (b) (4) Established/Proper Name: miconazole lauriad Dosage Form: (b) (4) Buccal Tablet Strengths: 50mg | | |
| Applicant: BioAlliance Pharma Agent for Applicant (if applicable): Beckloff Associates | | |
| Date of Application: February 5, 2009 Date of Receipt: February 6, 2009 Date clock started after UN: | | |
| PDUFA Goal Date: December 6, 2009 | Action Goal Date (if different): December 4, 2009 | |
| Filing Date: April 7, 2009 Date of Filing Meeting: March 24, 2009 | | |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 3 | | |
| Proposed Indication(s): local treatment of oropharyngeal candidiasis | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| Refer to Appendix A for further information. | | |
| Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i> | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted | |
| Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/> | | |
| Part 3 Combination Product? <input type="checkbox"/> | <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device | |
| <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | |

| | |
|--|--|
| Collaborative Review Division (if OTC product): | |
| List referenced IND Number(s): 69,578 | |
| PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Application Integrity Policy | |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments: | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| User Fees | |
| Form 3397 (User Fee Cover Sheet) submitted | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| User Fee Status Comments: | <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required |
| <i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i> | |
| Exclusivity | |
| Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II,</i> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |

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| Office of Regulatory Policy (HFD-007) | |
| Comments: | |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO |
| <p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | <input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| 505(b)(2) (NDA/NDA Efficacy Supplements only) | |
| <p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p> | <input type="checkbox"/> Not applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |

| <p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> | | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO | | | | | | | | | | | | |
|---|-----------|---|------------------------|-----------|------------------|------------------------|--|--|--|--|--|--|--|--|
| <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> | | | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
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| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | |
| <p>Format and Content</p> | | | | | | | | | | | | | | |
| <p>Do not check mixed submission if the only electronic component is the content of labeling (COL).</p> <p>Comments:</p> | | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | | | | | | | | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | | | | | | | | | | | |
| <p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p> | | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO | | | | | | | | | | | | |
| <p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p> | | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO | | | | | | | | | | | | |

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| <p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Patent Information (NDAs/NDA efficacy supplements only) | |
| <p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Debarment Certification | |
| <p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

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| <p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | |
| <p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | <p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| Financial Disclosure | |
| <p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| Pediatrics | |
| PREA | |
| <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | |
| <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> | <p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> |
| <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> | <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) | <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| Comments: | |

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| <u>BPCA (NDAs/NDA efficacy supplements only):</u> | |
| Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments: | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| Prescription Labeling | |
| Check all types of labeling submitted. Comments: | <input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) |
| Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments: | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments: | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments: NDA is RTF | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments: | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| REMS consulted to OSE/DRISK? Comments: | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments: Application is RTF | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |

| OTC Labeling | |
|---|---|
| <p>Check all types of labeling submitted.</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) |
| <p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Meeting Minutes/SPA Agreements | |
| <p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO |
| <p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: A pre-IND meeting to discuss the submission of the NDA was held on May 18, 2007</p> | <input checked="" type="checkbox"/> YES Date(s): Pre-IND Meeting – May 18, 2007; Pre-NDA Meeting - August 12, 2008 <input type="checkbox"/> NO |
| <p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO |

MEMO OF FILING MEETING

DATE: March 24, 2009

NDA #: 22-404

PROPRIETARY/ESTABLISHED NAMES: Lauriad[®] (miconazole), (b) (4) Buccal Tablet, 50 mg

APPLICANT: BioAlliance Pharma

BACKGROUND: On February 5, 2009 Beckloff Associates submitted a 505(b)(2) New Drug Application for miconazole Lauriad[®] 50 mg (b) (4) buccal tablet on behalf of BioAlliance Pharma. The proposed indication is treatment of oropharyngeal candidiasis. BioAlliance has developed a (b) (4) buccal delivery system that allows the slow release of an active drug in the mouth.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|----------------------|---------------------------------|--|
| Regulatory Project Management | RPM: | Sherry Spriggs | Y |
| | CPMS/TL: | Judit Milstein | Y |
| Cross-Discipline Team Leader (CDTL) | Karen Higgins, Sc.D. | | Y |
| Clinical | Reviewer: | Hala Shamsuddin, M.D. | Y |
| | TL: | Yulia Yasinskaya, M.D. | Y |
| OSE RPM: Marlene Hammer | Reviewer: | Raichell Brown | N |
| | TL: RPM | Laura Pincock Marlene Hammer | N Y |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | Lynette Berkeley, Ph.D. | Y |
| | TL: | Shukal Bala, Ph.D. | Y |
| Clinical Pharmacology | Reviewer: | Dakshina Chilukuri, Ph.D. | Y |
| | TL: | Philip Colangelo, Ph.D. | Y |
| Biostatistics | Reviewer: | Xianbin Li, Ph.D. | Y |
| | TL: | Karen Higgins, Sc.D. | Y |

| | | | |
|--|-----------|-----------------------|---|
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Owen McMaster, Ph.D. | Y |
| | TL: | William Taylor, Ph.D. | Y |
| Product Quality (CMC) | Reviewer: | Andrew Yu, Ph.D. | Y |
| | TL: | Rapti Madurawe, Ph.D. | Y |
| Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>) | Reviewer: | Vinayak Pawar | N |
| | TL: | Jim McVey | N |
| Bioresearch Monitoring (DSI) | Reviewer: | Susan Thompson.MD | N |
| | TL: | Jean Mulinde, MD | N |
| Other reviewers | | | |

OTHER ATTENDEES: Renata Albrecht (Division Director), Dave Roeder (ADRA), Yoriko Harigaya (OCP/DCP4), Jeannie David (ONDQA), Ozlem Belen (DSPTP, Deputy Director for Safety), Diana Willard (Chief Project Management), Norman Schmuft (ONDQA)

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| 505(b)(2) filing issues? If yes, list issues: | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| Per reviewers, are all parts in English or English translation? If no, explain: | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
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| Electronic Submission comments List comments: | <input type="checkbox"/> Not Applicable |
| CLINICAL Comments: Reviewer request for additional information was faxed to the sponsor on March 26, 2009 and included in the RTF letter. | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: Application is RTF | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO |

| | |
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| <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> To be determined Reason: this drug/biologic is not the first in its class |
| <ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>PRODUCT QUALITY (CMC)</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE |

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| <p>Comments: Tablet is missing imprinting as requested in 21 CFR 206. Although the sponsor requested a waiver, the Division did not grant it. In a letter dated November 3, 2008, the Division requested the sponsor to demonstrate that the imprinting of the proposed name on your product (tablet) is not feasible, that is, provide samples that demonstrate failed attempts to imprint the proposed drug product.</p> | <input checked="" type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <ul style="list-style-type: none"> ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Sterile product? <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Although this is not a sterile formulation, a consult was sent to the Quality microbiology to determine if the validation method and test for microbiological contamination are acceptable, as the product contains milk protein concentrate</p> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>FACILITY (BLAs only)</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| REGULATORY PROJECT MANAGEMENT | |
| <p>Signatory Authority: Renata Albrecht, M.D.</p> | |

| | |
|---|--|
| GRMP Timeline Milestones: No planning meeting was held as the application is RTF | |
| Comments: | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input checked="" type="checkbox"/> | The application is unsuitable for filing. Explain why: Application is not sufficiently complete to permit a substantive review. Refuse to File Issue: 21 CFR 206.10 Code imprint required. The tablet does not contain a code imprint as required under 21 CFR 206.10 for a solid oral dosage form and no exemption to this requirement under 21 CFR 206.7 was granted. On August 18, 2008, the applicant requested an exemption of the imprinting requirement under 21 CFR 206.7(b)(1). The Division responded on November 3, 2008, requesting that the applicant demonstrate that tablet imprinting is not feasible and to provide samples that demonstrate failed attempts to imprint the proposed tablet. |
| <input type="checkbox"/> | The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review |
| ACTIONS ITEMS | |
| <input checked="" type="checkbox"/> | Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system. |
| <input checked="" type="checkbox"/> | If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER. |
| <input type="checkbox"/> | If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | If BLA or Priority Review NDA, send 60-day letter. |
| <input type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input type="checkbox"/> | Other |

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

/s/

Sherry Spriggs
4/7/2009 04:34:02 PM
CSO

Judit Milstein
4/7/2009 05:02:39 PM
CSO
NDA 22-404 CSO Filing Review

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference.

Additional Issues Not Related to the Refuse to File Decision

The following deficiencies are not issues pertaining to our refusal to file the application. However, these issues need to be addressed before we can perform a substantive review of the application.

1. Submit a justification for concluding that the results from foreign trials BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04 are applicable to the US population.
2. Adverse events (AE) for studies BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04 were coded using different versions of MedDRA. If feasible, provide coding using a unified version.
3. Include all data on the 18 subjects enrolled in study BA 2000/01/01 in the ISS dataset. Because the AE for these 18 subjects were coded using WHOART, translate the AE data into MedDRA terms and provide verbatim investigator terms mapped to MedDRA preferred terms when adding AE data for this study into ISS.
4. For the two controlled clinical trials, BA2002/01/02 and BA2004/01/04, submit efficacy and safety analyses by gender, race, and age.

If you have any questions, call Ms. Sherry Spriggs, Regulatory Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Renata Albrecht
4/3/2009 03:59:58 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: March 25, 2009

| | |
|---|---|
| To: Lavonne Patton, PhD | From: Sherry Spriggs |
| Company: BioAlliance Pharmaceuticals | Division of Special Pathogens and Transplant Products |
| Fax number: (913) 451-3846 | Fax number: 301-796-9881 |
| Phone number: (913) 451-3955 | Phone number: 301-796-4018 |
| Subject: Clinical Information Request for data sets for 505(b)(2) NDA 22-404; Submission Number 0001; Dated February 5, 2009 | |

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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If you have any questions regarding the contents of this transmission, please contact me at 301-796-4018.

Sherry Spriggs
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

505(b)(2) NDA 22-404
Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50mg
Submission date: February 5, 2009

Dear Dr. Patton:

In order to continue with the timely review of your NDA, we request you provide the following clinical information:

1. Please submit a rationale for assuming the applicability of foreign data to US population for studies BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04.
2. Please submit the coding dictionary used for mapping investigator verbatim terms to preferred terms for studies BA 2000/01/01, BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04.
3. Please include the data of the 18 subjects enrolled in study BA 2000/01/01 in the ISS dataset. As the adverse events for these 18 subjects were coded using WHOART, please translate the adverse event data into MedDRA terms.
4. AE for studies 02, 03 and 04 were coded using different versions of MedDRA. If feasible, please provide coding using a unified version.

We request you provide the above mentioned information by **April 3, 2009**.

If you have any questions, please call me at (301) 796-4018.

Sherry Spriggs
Regulatory Project Manager

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/s/

Sherry Spriggs
3/26/2009 01:25:46 PM

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/s/

Sherry Spriggs
3/17/2009 04:27:31 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-404

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Lavonne Patton, Ph.D.
Director, Managing Consultant, Scientific Consulting
7400 West 110th Street
Overland Park, KS 66210

Dear Dr. Patton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50 mg.

We also refer to the teleconference between representatives of your firm and the FDA on February 27, 2009. The purpose of the meeting was to provide clarification on the fax sent to you on February 25, 2009.

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

If you have any questions, call me at (301) 796-4018.

Sincerely,

{See appended electronic signature page}

Sherry Spriggs, M.P.H.
Regulatory Project Manager
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 27, 2009
TIME: 11:00am – 11:15am
APPLICATION: NDA 22-404
DRUG NAME: Lauriad[®](miconazole) (b) (4) 50mg
TYPE OF MEETING: Teleconference

MEETING CHAIR: Karen Higgins, Sc.D.

MEETING RECORDER: Sherry Spriggs, M.P.H.

FDA ATTENDEES: Division of Special Pathogen and Transplant Products

| | |
|------------------------|---|
| Karen Higgins, Sc.D. | Cross Discipline Team Leader, Statistical Team Leader |
| Xianbin Li, Ph.D. | Statistical Reviewer |
| Hala Shamsuddin, M.D. | Clinical Reviewer |
| Sherry Spriggs, M.P.H. | Regulatory Health Project Manager |

EXTERNAL CONSTITUENT ATTENDEES: Beckloff Associates, Inc. (US Agent for BioAlliance Pharma)

Lavonne Patton, Ph.D. Director, Managing Consultant, Scientific Consulting

BACKGROUND:

NDA 22-404 was submitted on February 5, 2009. On February 25, 2009 the Division sent a fax to the applicant indicating that for Study BA2004/01/04, the reviewers could not find in the submission the randomized treatment indicator variable, nor any derived variables such as ITT population (yes/no), mITT population (yes/no), PP population (yes/no), LOCF ITT (yes/no) and partial LOCF ITT (yes/no) with variables created based on the LOCF method. In addition, for Study BA2002/01/02, the reviewers were not able to replicate the primary efficacy results, and requested the sponsor explain where in the submitted data sets the information for the primary efficacy analyses (PP and MITT) are contained. In the same fax, the Division requested the applicant send analysis data sets for both studies. On February 26, 2009 BioAlliance Pharma requested clarification on the contents of the facsimile sent on February 25, 2009.

DISCUSSION:

The sponsor indicated that they plan on sending the information for Study BA2004/01/04 by March 6, 2009 and for Study BA2002/01/02 by March 9, 2009. As the information requested for Study BA2002/01/02 will be sent outside of the requested date of March 6, 2009, the sponsor wanted to know if this is a fileability issue.

The Division indicated that these are fileability issues, and that they can not guarantee a review of the information submitted at the later time; however, it will do its best to review the information received from the sponsor in time for filing.

The sponsor also asked if Study BA2004/01/04 was the more important of the two studies and therefore they should submit this information first?

The Division stressed the importance of receiving information on both studies since both would be important in the review of the application.

In addition, the sponsor stated they plan to respond to the Agency's request for analysis data sets of Study BA2004/01/04 and Study BA2002/01/2, and that it is their goal to provide the analysis data sets for Study BA2004/01/04 the second week in March 2009.

The Division stated that the variables listed in number 1 and 2 of the fax appear to be the most important variables for review of the studies. However, this might not be an exhaustive list and once the additional information is received and reviewed it is possible that additional information would be needed.

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/s/

Sherry Spriggs
3/16/2009 04:14:49 PM

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/s/

Andy Yu
3/10/2009 11:14:05 AM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

FACSIMILE TRANSMITTAL SHEET

DATE: February 25, 2009

| | |
|--|---|
| To: Lavonne Patton | From: Sherry Spriggs |
| Company: BioAlliance Pharma | Division of Special Pathogens and Transplant Products |
| Fax number: 913-451-3846 | Fax number: 301-796-9882 |
| Phone number: 913-451-3955 | Phone number: 301-796-4018 |
| Subject: Comments on NDA 22-404, Data Set | |

Total no. of pages including cover: 3

Comments: Concurrence

Karen Higgins, Sc.D.

CDTL and Statistical Team Leader

Document to be mailed: YES NO

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Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50mg.

We also refer to your submission dated February 5, 2009, which contain original NDA submission. We have reviewed the submission and have the following comments:

After reviewing your study reports and submitted data sets, we found the following problems:

1. For **Study BA2004/01/04**, we could not find a randomized treatment indicator variable. Additionally we could not find any derived variables such as actual treatment group, ITT population (yes/no), mITT population (yes/no), PP population (yes/no), LOCF ITT (yes/no) and partial LOCF ITT (yes/no) with variables created based on the LOCF method.
2. For **Study BA2002/01/02**, we were not able to replicate your primary efficacy results. Please explain where in your submitted data sets the information for the primary efficacy analyses (PP and MITT) are contained.

We recommend you send analysis data sets for both studies. Analysis data sets contain raw and derived variables that represent the analyses performed by the sponsor and can be used by the FDA reviewers to replicate and validate those analyses.

If this information is contained in the submission, please direct us to the location of this information. Please note that this information is essential for our review of this NDA. If it is not currently contained within your submitted NDA, we would need this information by **March 6, 2009** in order for us to be able to review it prior to filing of this NDA. Note that submission of this information does not guarantee our ability to review it prior to the filing deadline.

We would like to discuss the above comments with you as soon as possible.

We are providing the above information by email for your convenience. Contact me at 301-796-4018 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Sherry Spriggs, M.P.H.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

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/s/

Sherry Spriggs
2/25/2009 11:48:29 AM
CSO

David, Jeannie C

From: Patton, Lavonne [LPatton@beckloff.com]
Sent: Thursday, February 19, 2009 4:07 PM
To: David, Jeannie C
Cc: Spriggs, Sherry
Subject: BioAlliance Pharma; NDA 22-404; Response to CMC questions of February 17, 2009

Hi Jeannie,

As just discussed by telephone, I can provide the following information regarding one of your requests during our telephone discussion on February 17, 2009. One of your questions was:

The manufacturer for the Drug Substance address listed on the Establishment Information page is different than the address in Module 3, Section 3.2.S.2.1. Please confirm which address is correct...or why they are different. Please provide the address where the drug substance is actually manufactured.

Response: The address for (b) (4) listed in Module 3, Section 3.2.S.2.1 is the address for the production site and is provided below for your convenience. The address listed on the Establishment Information page is the address of the company headquarters.

(b) (4)

The Central File Number for this facility is 9610254. The FDA Establishment Identifier is 3002808159.

As discussed, this information will be provided as an official amendment to the NDA once all information has been collected, but is being provided now for your convenience.

Please let me know if you have any questions.

Best regards,

Lavonne

Lavonne M. Patton, Ph.D.
Director, Managing Consultant
Beckloff Associates, Inc.
(a wholly owned Cardinal Health Company)
7400 West 110th Street, Suite 300
Overland Park, Kansas 66210
913-451-3955 (phone)
913-451-3846 (fax)
www.beckloff.com

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(b) (4)

David, Jeannie C

From: David, Jeannie C
Sent: Thursday, February 19, 2009 4:48 PM
To: Madurawe, Rapti
Cc: Yu, Andrew B; Schmuff, Norman R; Spriggs, Sherry
Subject: RE: NDA 22-404 Lauriad Buccal Tablet - List of Facility confirmation/EES

Hi Rapti,

Just to follow up by email (even though we spoke about this in person yesterday), so that Andy can get up-to-date on our communications:

There are actually two places in the NDA where it states the drug substance manufacturing facility as responsible for "manufacturing, packaging, labeling, release testing and stability testing of the drug substance": in the Attachment to Form 356h (Module 1.1.2, first entry, leftmost column, of page 1), and in the section for DS Manufacturer (Module 3.2.S.2.1, last sentence of page 1).

FYI, there has been some initial response from the U.S. contact for the applicant on our questions about the facilities, but there are still some out-standing issues. I will forward that email next. I confirmed with the U.S. contact that once all of their updates are assembled, that they will submit this as a formal amendment to the application.

Jeannie

From: Madurawe, Rapti
Sent: Wednesday, February 18, 2009 9:09 AM
To: David, Jeannie C
Subject: RE: NDA 22-404 Lauriad Buccal Tablet - List of Facility confirmation/EES

Jeannie: . Thanks. We need the following info as well. If these operations are done at the DS mfg site, we need a statement to say so.

No facilities are identified for drug substance packaging, release and stability testing.

From: David, Jeannie C
Sent: Tuesday, February 17, 2009 4:35 PM
To: Madurawe, Rapti
Cc: Spriggs, Sherry; Schmuff, Norman R
Subject: RE: NDA 22-404 Lauriad Buccal Tablet - List of Facility confirmation/EES

Hi Rapti,

One other point I didn't mention, which is that I requested that the applicant submit their updated information as a formal amendment to the NDA, as well as provide a courtesy copy to me if possible. I will forward you and Sherry a copy of what I receive.

Thanks,

Jeannie

From: David, Jeannie C
Sent: Tuesday, February 17, 2009 4:26 PM
To: Madurawe, Rapti
Cc: Spriggs, Sherry; Schmuff, Norman R
Subject: RE: NDA 22-404 Lauriad Buccal Tablet - List of Facility confirmation/EES

Hi Rapti,

After looking through **NDA 22-404** (BioAlliance Pharma) for establishment information in the attachment to Form 356h, in the QOS, and in Module 3, it seems that there is a facility identified for the drug substance, but that the address is not consistent in the application. Also the applicant does claim in the application that all facilities are ready for inspection (in the attachment to Form 356h).

To further look into the points you raised in order to complete the EES, I placed a call with the U.S. contact for the applicant to request further clarification. Specifically, I requested:

- Confirmation that the list given in the attachment to Form 356h includes ALL facilities,
- Confirmation that all facilities are ready for inspection,
- Provide the appropriate address for the site of drug substance manufacturing, and provide a CFN and/or FEI number,
- Clarification as to whether or not the Microbiological and Adhesion testing facilities perform drug product release testing and/or stability testing.

The U.S. contact (Lavonne Patton, Beckloff Associates) for this applicant agreed to work on the issues we spoke of above and hopes to get back to me by early next week. Her main contact at BioAlliance Pharma is currently out of town, but she will work to clarify the information through other contacts in the company.

I will keep you updated of what I learn. Please let me know if there are any other issues on this matter that you would like me to communicate.

Thanks,

Jeannie

From: Madurawe, Rapti
Sent: Friday, February 13, 2009 3:19 PM
To: David, Jeannie C
Cc: Spriggs, Sherry
Subject: NDA 22-404 Lauriad Buccal Tablet - List of Facility confirmation/EES
Importance: High

<< File: Doc1.doc >>

Hi Jeannie:

Please ask BioAlliance Pharma to

- Send us a list of ALL facilities associated with NDA 22-404 drug substance and drug product manufacturing, packaging, release testing and stability testing for entry into EES
- Provide a statement that all facilities are ready for inspection.
- No facilities are identified for drug substance packaging, release and stability testing. Provide addresses and contact info for these in the NDA
- Clarify if the two French facilities listed as drug Microbiological testing and Adhesion testing are drug product release and stability testing facilities performing the identified tests.

BioAlliance contact info is in the attached document along with the facility info they have provided in the NDA. The NDA is in EDR if you want to check out the facilities.

As there are several foreign facilities, we want to get the facilities into EES as soon as possible.

Sherry Spriggs is the PM for this NDA. Please cc her in all correspondence.

Thanks,

Rapti

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/s/

Jeannie David
2/20/2009 01:07:07 PM
PROJECT MANAGER FOR QUALITY



NDA 22-404

NDA ACKNOWLEDGMENT

BioAlliance Pharma
c/o Beckloff Associates, Inc.
Attention: Lavonne Patton, Ph.D.
Director, Managing Consultant, Scientific Consulting
Commerce Plaza II, Ste 300
7400 West 110th Street
Overland Park, Kansas 66210

Dear Dr. Patton:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Lauriad[®] (miconazole) (b) (4) Buccal Tablet, 50 mg

Date of Application: February 5, 2009

Date of Receipt: February 6, 2009

Our Reference Number: NDA 22-404

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 8, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call Sherry Spriggs, Regulatory Project Manager, at (301) 796-4018.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Judith Milstein
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NDA 22-404 Acknowledgment Letter