

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22404Orig1s000

CHEMISTRY REVIEW(S)

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:22-404

Supplement Number and Type:

Established/Proper Name:

Lauriad (miconazole)

(b) (4)

Applicant: BioAlliance
Pharma

Letter Date: 6/29/09

Stamp Date: 7/1/09

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		<p align="center">Site information was obtained by correspondence with applicant and now complete.</p>

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	x		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Optional information only
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Consult made on milk protein concentrate for microbiological review.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Miconazole				Pending
	II	(b) (4)	(b) (4)				Pending
	III	(b) (4)					Pending

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	x		Imprinting of the tablets per 21 CFR 206 previously a RTF issue has been adequately addressed by applicant in the resubmission.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			None identified at this point.

{See appended electronic signature page}

Name of Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer

Rapti Madurawe / Andy Yu Date: 7/27/09

Division of Pre-Marketing Assessment #DPM2/Branch 4

Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of

Branch Chief Date: **Norman Schmuff**

Division of Pre-Marketing Assessment #DPM2/Branch4

Office of New Drug Quality Assessment

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

/s/

ANDREW B YU
07/27/2009

NORMAN R SCHMUFF
07/27/2009

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Special Pathogens and Transplant Products
NDA: 22-404
Applicant: BioAlliance Pharma
Stamp Date: 06-Feb-2009
PDUFA Date: 06-Dec-2009
Trademark: (b) (4)
Established Name: Miconazole
Dosage Form: (b) (4) extended-release buccal tablet
Route of Administration: Buccal
Indication: Oropharyngeal candidiasis
PAL: Rapti D. Madurawe

	YES	NO
ONDQA Fileability:	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues

A: Application Summary and Review

General

BioAlliance Pharma has submitted NDA 22-404 as a 505(b)(2) application for (b) (4) (miconazole) 50 mg (b) (4) buccal tablets for the treatment of oropharyngeal candidiasis. The applicant references Monistat 3 Suppository (NDA 18-888) and Monistat Dual-Pak (NDA 20-968) in support their NDA. Miconazole is a synthetic imidazole broad-spectrum antifungal agent approved in the U.S. since 1974. Intravaginal and external dermal formulations (ointment, oral gel, troche, mouthwash, etc.) of miconazole are currently available in the U.S. NDA 22-404 provides for a new dosage form of miconazole. Appropriate terminology for the dosage form is discussed in the review.

NDA 22-404 was developed under IND 69,578. Several CMC questions were submitted to the Agency during IND development. Some of the CMC responses are in DARRTS and the IND reviewer was asked to provide copies, if available, of all responses sent to the company. Major issues discussed at the pre-NDA meeting are: (1) No DMF will be submitted for milk protein concentrate. Available manufacturing process, controls and stability information will be presented in the NDA; (2) Stability data from a (b) (4) batch will be provided to support a (b) (4) modified commercial manufacturing process. Stability data will be provided during review of the NDA. (3) The tablet will not be imprinted as required by 21 CFR 206.10 and a written request for an exemption from this requirement will be submitted which the Agency will refer to the Division of Medication Error Prevention and Analysis (DMEPA). Agreement was reached on the first two issues, but with regards to the imprinting exemption request, the Agency requested that the applicant demonstrate that imprinting is not feasible by providing failed samples to the Agency. This is consistent with 21 CFR § 206.10 and 21 CFR § 206.7 which respectively state, “*Unless exempted under § 206.7, no drug product in solid oral dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint that, in conjunction with the product’s size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product...*” and “*....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...*”

During the IQA review, the applicant was informed that a formal request for exemption from imprinting was not located in the NDA and failed imprinting samples were not submitted to the Agency. The applicant's 13-Mar-2009 email to the Project Manager stated that, "In response to the e-mail below regarding imprinting of the tablets, and as a follow up to our telephone call this morning, BioAlliance is currently conducting the CMC testing necessary to address the response received from FDA in correspondence dated November 3, 2008 to demonstrate if the imprinting is feasible. Once that testing is complete, BioAlliance will re-evaluate whether an exemption of the imprinting requirement will be requested." (b) (4) technology does not necessarily preclude tablet imprinting as there are appropriately imprinted (b) (4) buccal tablets currently marketed in the US, such as the debossed STRIANT (testosterone buccal system) tablet. If the applicant's tests show tablet imprinting is possible, additional CMC information, such as stability data for the imprinted tablet, maybe required. As the application currently does not comply with 21 CFR 206 imprinting requirements, and for the reasons stated above, it is recommended that NDA 22-404 is not filed.

Drug Substance

All drug substance and drug product manufacturing/testing facility addresses and functions were verified during IQA review. Facilities were submitted to the Establishment Evaluation System on 24-Feb-09 by the primary reviewer, Dr. Andrew Yu.

Manufacture of the miconazole drug substance is referenced to two Type II DMFs, (b) (4) held by (b) (4) DMF (b) (4) provides for "Miconazole as manufactured in (b) (4)," and DMF (b) (4) provides for (b) (4) as manufactured at (b) (4). The NDA contains Letters of Authorization to access both DMFs. During this review, we confirmed that the (b) (4) address given in DMF (b) (4) is the site of the corporate office and that both miconazole and (b) (4) are manufactured at the same facility in (b) (4). The (b) (4) facility was last inspected in Jun-2004 and found acceptable.

DMF (b) (4) has never been reviewed. DMF (b) (4) was last reviewed and found adequate in Feb-2005. Amendments submitted after Feb-2005 remains to be reviewed.

Drug substance information provided in the NDA is described and reviewed below.

(b) (4) is identified as the starting material for miconazole drug substance manufacture. Manufacturing steps are (b) (4)

[REDACTED]

The NDA gives the structures of (b) (4) drug substance related impurities; all of which are derived from the synthesis of (b) (4) and are present as mixtures of enantiomers. (b) (4)

(b) (4)

is a potential mutagen and should be referred to the toxicology reviewer for evaluation. Its level is controlled to (b) (4) in the drug substance specification. No inorganic impurities are said to be present as no catalysts are used in the synthesis. (b) (4) are the Class 3 solvents (u) (4). Both are controlled to (u) (4) in the drug substance specification, a level below the ICH recommended limit of 5000 ppm. Typical values in miconazole batches are said to be around (b) (4)

The proposed drug substance specifications and test methods are given in Table 1. These are significantly better than the USP monograph and appear to be reasonable. Qualified levels of impurities would need to be verified. The drug substance is tested upon receipt and used without further modification.

(b) (4)

Batch data are presented for the 3 primary stability lots, one of which was the US clinical lot. All 3 lots were manufactured in Feb/May 2004 at a batch size range of (b) (4). Impurity levels are reported as below the specification limit. Actual test results should be reported.

The drug substance is stored in an (b) (4)

(b) (4) It is advisable to specify the storage temperature and any light protection condition. The NDA refers to DMF (b) (4) for all stability data and states that a (b) (4) retest period is assigned to the drug substance.

Drug Product

The drug product is manufactured and packaged at (b) (4). The proposed proprietary name is (b) (4). Although the NDA refers to Lauriad as the proprietary name, the applicant has confirmed that Lauriad is the patented trademark for the mucoadhesive buccal delivery system, and not the proprietary name. The drug product is a tablet containing 50 mg miconazole per tablet. The tablet is white to (b) (4) in color, unscored, rounded on one side and flat on the other side. Tablets are not imprinted. This refuse-to-file issue is discussed earlier in the review and is not re-iterated here. Tablets are packaged in 14-count in round 15-ml HDPE bottles and closed with a child-resistant closure mounted with a desiccant. Physician samples will contain 2 tablets in the same bottle/closure system.

The tablet adheres to the upper gum just above the incisor tooth with the flat surface facing the cheek mucosa. The NDA describes the drug product as “a (b) (4) buccal tablet providing extended-release of miconazole in the oral cavity.” The proposed dosing regimen is one tablet daily for 14 consecutive days. The tablet is intended for local delivery of the drug. Although significant miconazole concentrations are achieved in saliva following tablet usage, systemic absorption through the buccal mucosa or the gastrointestinal tract after swallowing saliva is low. Mucoadhesive is not listed in the CDER Data Standards Manual (CDST) while buccal route of administration is listed as “administration directed toward the cheek, generally from within the mouth.” CDST defines extended release tablet as “a solid dosage form containing a drug which allows at least a reduction in dosing frequency as compared to that drug presented in conventional dosage form.” Although release profiles show drug release over a long period of time (from <1 to >13 hours), there is no conventional immediate-release tablet for comparison. It is important the dosage form terminology be descriptive of the administration method to prevent swallowing of the tablet. The terminology, (b) (4) (miconazole) buccal tablet, extended-release” appears to be appropriate. However, if the buccal route also infers a mucosal route of absorption, this terminology may be inappropriate. The dosage form terminology should be referred to the nomenclature group/ONDQA management for approval.

The drug product formulation is given in Table 2. All excipients except milk protein concentrate (MPC) used for (b) (4) (b) (4) are compendial and meet USP/NF standards. MPC is characteristics and patent numbers US 5,362,498 / Patent No. EP 0 542 824 B1 are provided (*why?*). Primary components of MPC are casein and lactose while minor components are milk-derived proteins such as albumin and globulins, fat, water and minerals. Although MPC is widely used in the food industry and stated to be a non-novel excipient in the NDA, it however appears to be a novel excipient for the US as it is not listed in the inactive ingredient database and I was not able to locate any approved NDAs with MPC excipient using FDAsearch. MPC is manufactured by (b) (4) in (b) (4) and is obtained by ultrafiltration (UF) of creamed and pasteurized cow milk. The

processing plant and raw milk comply with (b) (4) regulatory authority requirements and a BSE-/TSE-free certificates are provided. The NDA contains the specifications, test methods, the typical qualitative/quantitative composition and the manufacturing flow chart of MPC, but offers little process and characterization detail. The product quality microbiology group should be consulted for evaluation of the microbial/fungal/viral control procedures and tests. All excipients except milk protein concentrate (MPC) used for (b) (4) are compendial and meet USP/NF standards.

The regulatory requirements for accepting this apparently novel excipient which is a well-established dietary product need to be decided early during the review cycle to enable the applicant to provide additional documentation as needed. For example, is a description of the manufacturing process or further characterization of MPC necessary? The current amount of documentation for MPC made by this (b) (4) a large and well-known milk product supplier in (b) (4), appears to be sufficient if the specifications/tests are reviewed and found to be adequate. What is of concern here is the adequacy of the safeguards and tests for product identification and detection of potential extraneous contaminants (b) (4) if the supplier were to change. It is recommended that agreement is reached to report to the Agency any changes to the MPC supplier (*as a PA supplement?*) and new documentation provided as needed to assure the quality, reliability and acceptability of MPC from the new supplier.

The review team should be notified that the drug product contains milk proteins as the product label may need to indicate the potential for milk allergies.

Table 2: Composition of (b) (4) (b) (4) Buccal Tablet, 50 mg

Compound	Reference to Quality Standard	Function	Quantity per Tablet	
			mg	% w/w
Active Ingredient:				
Miconazole Base	Current USP	Drug Substance	50.00	43.48
Excipients:				
Hypromellose (b) (4)	Current USP	(b) (4)		
Milk Protein Concentrate	In-house standard			
Maize Starch ^b	Current USP/NF			
Lactose Monohydrate	Current USP/NF			
Sodium Laurilsulfate ^c	Current USP/NF			
Magnesium Stearate	Current USP/NF			
Talc	Current USP			
(b) (4)				
Total			115.00 ^e	100.00

(b) (4)

(b) (4)

The major drug product manufacturing processes are (b) (4)
Although the commercial batch size was stated to be (b) (4) at the
pre-NDA meeting, the batch size and equipment given in the NDA is for a (b) (4)
(b) (4) process. The applicant should provide the master batch record, equipment and process
parameters for the (b) (4) commercial process. (b) (4)

Type III DMF (b) (4) is referenced for (b) (4) (b) (4)
(b) (4) The DMF was last reviewed for (b) (4)
(b) (4) and found adequate on 9/12/2005.

The pharmaceutical development section states that the main characteristics of the formulation
are (b) (4)

The same formulation is used in the clinical, stability and
proposed commercial drug product lots. The three clinical trial lots were manufactured at an
approximate batch size of (b) (4)

(b) (4) while the stability batches were manufactured at the
(b) (4) Manufacturing process and equipment
differences/comparability at the two sites, if any, are not given. Comparability of the clinical
batches to the proposed commercial batches needs to be established during review and may be
challenging as clinical lots were tested according to a different set of specifications used during
IND development. A preliminary evaluation of the dissolution data indicate a slower drug
release profile over the first 8 hours for the (b) (4) commercial site/stability lots compared
to the (b) (4) clinical lots. Although (b) (4) dissolution is achieved at 24 hours for both
clinical and stability batches, drug release over the first 8 to 12 hours is important for product
performance (and is claimed as such in the application). Whether the differences seen are
significant or not need to be determined during review. It is not clear if the drug substance and
drug product impurities have been qualified. No batches are identified as toxicology batches.
Qualified impurity/degradant levels should be discussed with the toxicology reviewer.

The proposed drug product specifications are given in Table 3.

(b) (4)



Proposed specifications appear to be reasonable. Tablet adhesivity and dissolution would be important for establishing product performance and need to be carefully evaluated (b) (4)

It is not clear to me if this adhesion test is adequate and how the proposed specification relates to

tablet adhesion in the mouth. The clinical submission contains information on adherence of the tablet to the gum. Mouthwash, normal meals and drinks are said to have no effect on tablet dislodgment. As a dislodged tablet would be ineffective, adhesivity information should also be evaluated by the CMC reviewer. The dissolution test is performed in a USP Type I apparatus using (b) (4). (b) (4) Has the applicant provided an appropriate justification for use of this medium? The extended-release dissolution specification lists 3 test points at 1, 4 and 8 hours. It seems to me that (b) (4) dissolved at 8 hours is not sufficient as the final test point for an extended-release tablet that is dosed once daily. Perhaps a 12 or 16 hr dissolution criterion should be added to verify that most of the drug is released from the tablet. *What happens to the tablet after 12 hours? Does it disintegrate or dissolve completely?*

Stability test conditions are 40°C/75% RH, 30°C/65% RH and 25°C/60% RH. Up to 6 months accelerated, 36-months intermediate and 36 months long-term stability data are presented for the (b) (4) scale primary stability batches manufactured at (b) (4). (b) (4). Although bulk stability data is given, the manufacturing section did not discuss bulk packaging/storage. Not all of the ICH-recommended test time points are submitted for the primary stability batches. For example, only 0, 9 and 36 months long-term data is submitted for lot E213X013, E213X012 and E213X011 while no long-term data is submitted for batch E213X021. The applicant should re-submit all stability data as per ICH Q1A test points. No stability data is given for the 2-count physician samples. Since the same bottle is used with just 2 tablets, the increased head-space could affect the stability outcome. Stress test studies show drug product degradation under oxidative conditions. If stability data is not available, the 2-count physician sample should be withdrawn from the application.

The applicant has proposed a shelf-life of 36-months for the drug product when stored at room temperature in tightly closed containers. Accelerated stability data indicate that tablet dissolution decreases over storage; some failed values are obtained at 3 months for level L1 testing, and some minimal acceptable values are obtained for level L2 testing. The adhesivity force shows no discernible trends over stability; both increases and decreases are observed over storage for different lots. Total impurity level is low and no trends are discernible as individual impurities are either not detected or (b) (4) (b) (4) while total impurities are listed as (b) (4). Miconazole reference standard, placebo solution and the drug product were subjected to forced degradation studies. The stress test chromatographs need to be re-scaled to enable adequate evaluation of the data. It appears that both the drug substance and drug product degrade under (b) (4) while remaining relatively stable under base, heat and light stress.

B. Issues to address during review, Comments and Recommendation

Issues are discussed in the review and are only briefly listed here.

1. Tablet dissolution test/medium, data and specification.
2. Adequacy of adhesivity test and relevance of proposed specification for adequate tablet adhesion to mouth/buccal.
3. Comparability of the manufacturing process and equipment at the German and French sites.
4. The bulk drug product packaging and storage information should be requested, if not in the NDA.
5. (b) (4) (b) (4) is a potential mutagen and should be referred to the toxicology reviewer for evaluation.
6. Check qualified levels of drug substance and drug product impurities/degradants with the toxicology reviewer. It is not clear what batches, if any, were used for toxicology studies.

7. Notify the review team that the drug product contains milk proteins as the product label may need to indicate the potential for milk allergies.

C. Critical Issues for Review Issues

1. Adhesivity of tablet to mouth.
2. Drug product dissolution (i.e. extended-release profile) from product release to end of shelf-life.
3. Comparability of clinical/pre-clinical batches manufactured in France to the proposed commercial batches manufactured in Germany.
4. Is the documentation/specification provided for MPC sufficient. If not, additional information needed should be requested in the 74-day letter.
5. Criteria for (b) (4) and the methods used.
6. Adequacy of the Type II DMFs, (b) (4) referenced for drug substance.
7. (b) (4) form and particle size of the drug substance (to be reviewed in the DMF)

D. Fileability Issue

Tablets are not imprinted and a request for an exemption from the imprinting requirement with 'demonstration' that imprinting is not possible has not been submitted. The applicant has indicated that tablet imprinting studies are still in progress. It is recommended that the application is "refused-to-file."

E. Review Comments for 74-Day Letter

1. Although the stability protocol provides for testing at 0, 1, 3, 6, 9, 12, 18, 24 and 36 months and is in accordance with the ICH Q1A guidance, not all of the test data is presented in the NDA. Resubmit stability data for all time points.
2. Provide stability data for the physician sample (2 tablets/bottle) configuration.
3. (b) (4) is not acceptable as the starting material for miconazole drug substance manufacture. Please re-designate a suitable starting material. Starting materials from the (b) (4) maybe more appropriate as the starting materials for miconazole drug substance.
4. (b) (4) is not acceptable as the starting material for miconazole drug substance manufacture. Expect this issue to be relatively easily resolved as discussed in the review.
5. Provide a comparison of the manufacturing process, process parameters and equipment used to make the clinical batches in France and the proposed commercial batches in Germany.

Rapti D. Madurawe
Pharmaceutical Assessment Lead

02-April-2009
Date

Norman R. Schmuff
Branch Chief

02-April-2009
Date

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

/s/

Rapti Madurawe
5/1/2009 01:09:02 PM
CHEMIST

Norman Schmuff
5/1/2009 02:17:56 PM
CHEMIST

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22-404

Applicant: BioAlliance Pharma

Stamp Date: 2/06/09

Drug Name: Lauriad
(miconazole) (b) (4)
Buccal Tablet

NDA/BLA Type: 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	x		Two Facility addresses were incomplete but resolved after contacting applicant. A French testing facility was new and not in EES. Compliance was notified and documented in EESquestions.
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	x		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	x		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	x		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	x		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?		x	Imprinting of the tablets per 21 CFR 206 not adequately responded by applicant.
8	Have draft container labels and package insert been provided?	x		
9	Have all DMF References been identified?	x		
10	Is information on the investigational formulations included?	x		
11	Is information on the methods validation included?	x		
12	If applicable, is documentation on the sterilization process validation included?	x		Microbiology consult prepared on milk protein concentrate (MPC) test validation.

IS THE CMC SECTION OF THE APPLICATION FILEABLE? ___No___

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Chemical Manufacturing Controls (CMC) Filing Checklist for NDA_BLA or Supplement 010908

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Imprinting of the tablets per 21 CFR 206 was not adequately responded by applicant. (Memo to team by N. Schmuff dated 3/17/09):

*We also refer to your amendment dated August 18, 2008, requesting exemption of the imprinting requirement of the product's proposed name on the tablet based on 21 CFR 206.7(b)(1).
We have reviewed your submission and have the following request:
Please 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.
Based on an email response of 3/13, it appears no attempt was made to imprint or otherwise mark the tablets.*

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. *None identified at this point other than the imprinting issue above.*

Andy Yu	3/17/09
Reviewing Chemist	Date
Rapti Madurawe	
<hr/>	
Team Leader/Supervisor	Date

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

DMFs : LOAs were provided for all DMFs cited below.

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Miconazole				Pending
	II	(b) (4)	(b) (4)				Pending
	III	(b) (4)					Pending

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

/s/

Andy Yu
3/23/2009 02:33:13 PM
CHEMIST

NDA 22-404
Review #2

Oravig® Buccal Tablet

BioAlliance Pharma

Andrew Yu PhD
ONDQA, Branch IV

HFD-590

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	10
S DRUG SUBSTANCE [Oravig buccal tablets, BioAlliance Inc]	10
P DRUG PRODUCT [Oravig buccal tablets, Tablets].....	15
A APPENDICES	62
R REGIONAL INFORMATION	62
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	63
A. Labeling & Package Insert	63
B. Environmental Assessment Or Claim Of Categorical Exclusion	68
III. List Of Deficiencies To Be Communicated.....	69

Chemistry Review Data Sheet

1. NDA: 22-404

2. REVIEW #2

3. REVIEW DATE: 3/15/09

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 69,578	8/18/08

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA (RTF)	2/6/09
Amendment (Facility update)	1/30/09
Amendment (IR response/stability update)	2//15/09
Amendment (IR response)	4/16/09
Resubmission (After RTF)	6/15/09
Amendment (IR response & stability update)	9/29/09
Amendment (IR response)	12/29/09
Amendment (IR response -Quality Microbiology)	1/14/09
Amendment (Revised carton label)	3/12/10

7. NAME & ADDRESS OF APPLICANT:

Name: BioAlliance Pharma

Address: 49 Boulevard du General Martial Valin
75015 Paris France

Chemistry Review Data Sheet

Representative Beckloff Associates, Inc.
Commerce Plaza II, Ste 300
7400 West 110 Street Overland Park, KS 66210

Contact person: Lavonne M. Patton, Ph.D.

Telephone: 913-451-3955

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Oravig buccal tablets
b) Non-Proprietary Name (USAN): Miconazole buccal tablets
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)**10. PHARMACOL. CATEGORY: Antifungal****11. DOSAGE FORM: Buccal Tablet****12. STRENGTH/POTENCY: 50 mg****13. ROUTE OF ADMINISTRATION: Buccal****14. Rx/OTC DISPENSED: Rx OTC****15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)**

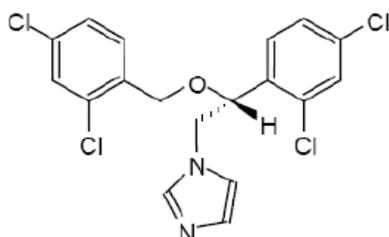
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[(2RS)-2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole

USAN	Miconazole
Molecular weight	416.13
Molecular Formula	C ₁₈ H ₁₄ Cl ₄ N ₂ O
Other Name	MICO-10 (2910)

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Miconazole	1		Andy Yu 2/16/10	Adequate
	II	(b) (4)	(b) (4)	3		S. Pittinger 2/28/05	Adequate
	III	(b) (4)	(b) (4)	4		2/20/10	Adequate

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox	Acceptable		Owen McMaster
Biopharm			
LNC			
Methods Validation			
OPDRA (DMETS)	Oravig name accepted	1/5/2010	Kristina C. Arnwine (Safety review)
EA	EA exclusion waiver found acceptable	2/20/10	Andrew Yu
Microbiology	Acceptable	1/20/2010	Bryan Riley

19. ORDER OF REVIEW (OGD Only) N/A

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes
 ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-404

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The office of Compliance has issued an overall “Acceptable” recommendation, and the previously pending issues on the label in review #1 are resolved.

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance miconazole, is manufactured by (b) (4) under DMF (b) (4) Information requests to the DMF holder concerning impurity and analytical method validation have been adequately resolved and the DMF is acceptable. The DMF for (b) (4) and the type III DMF covering (b) (4) are current and adequate to support the NDA.

The drug product is a buccal tablet designed to be administered one tablet every 24 hours. The tablet contains 50 mg drug and is formulated with milk protein concentrate to (b) (4). The manufacturing of the tablet (b) (4)

(b) (4). Issues with debossing difficulty due to stickiness to tablet punches during a prior submission has been resolved and the tablet has markings as required. The manufacturing processes are validated with a production size batch and controlled with in-process parameters. The shelf life of 36 months at controlled room temperature is based on three stability batches of long term stability data at 36 months and six months of stability data at accelerated condition. The stability data were performed initially based on non-debossed tablets packaged in the same container. A bridging study was agreed upon during pre-NDA to ensure that debossing has no undesirable effect on stability of the product. The stability data on the debossed tablets were received during the review cycle and support the shelf life proposed.

The dissolution rates of the tablets at 4 and 8 hours in the stability batches generally slow down (b) (4) during storage when compared to initial dissolution rate. This slowing is somewhat moderated when the tablet is debossed. During information

requests on this issue, the applicant presented more batches and additional data at 12 hours showing higher dissolution beyond 8 hours (b) (4). The response is acceptable. The primary stability batches and the clinical batch and are comparable during storage. The applicant provided data showing that dissolution continues after 8 hours and the in vitro dissolution is not related in vivo dissolution in the saliva. The extent of slowing observed is acceptable for this product as the dissolution and the exposure issues were discussed with Clinical pharmacology for this product. A impurity issue concerning the acceptance criteria of (b) (4) in miconazole drug substance was resolved. The applicant has revised the acceptance criteria to a level acceptable by both Chemistry and Pharm/Tox. The impurity, (b) (4) is a (b) (4) impurity present in the drug substance during synthesis.

B. Description of How the Drug Product is Intended to be Used

Oravig® buccal tablets are off-white tablets containing 50 mg of miconazole. *Oravig*® tablets have a rounded side and a flat side with an “L”. *Oravig*® tablets are packaged in bottles of 14 tablets (NDC 49884-082-26). The storage condition is: Store at 20-25 °C (68-77°F) See USP controlled room temperature, excursions between 15 to 30 °C permitted.

Oravig® buccal tablet is intended for buccal administration for the treatment of fungal infection as described in the package insert. The usual dose is one tablet of ORAVIG applied to the upper gum once a day. The patient may find it convenient to apply ORAVIG in the morning after brushing the teeth following breakfast. DO NOT CHEW, CRUSH OR SWALLOW ORAVIG. ORAVIG may be used with food and drinks.

Oravig® buccal tablets are supplied in HDPE bottles of 14 tablets with desiccant and Child-Resistant Closure.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the shelf life of the product. The office of Compliance has issued an overall “Acceptable” recommendation, and the previously pending CMC issues on the label are resolved. Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative

A. Reviewer’s Signature

See DARRTS

B. Endorsement Block

See DARRTS

C. CC Block

78 pages have 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)

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

/s/

ANDREW B YU
03/23/2010

STEPHEN P MILLER
03/23/2010

NDA 22-404

Oravig® Buccal Tablet

BioAlliance Pharma

**Andrew Yu PhD
ONDQA, Branch IV**

HFD-590

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	10
S DRUG SUBSTANCE [Oravig buccal tablets, BioAlliance Inc].....	10
P DRUG PRODUCT [Oravig buccal tablets, Tablets].....	16
A APPENDICES	65
R REGIONAL INFORMATION	65
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	66
A. Labeling & Package Insert	66
B. Environmental Assessment Or Claim Of Categorical Exclusion	70
III. List Of Deficiencies To Be Communicated.....	71

Chemistry Review Data Sheet

1. NDA: 22-404
2. REVIEW #1
3. REVIEW DATE: 2/6/09
4. REVIEWER: Andrew Yu
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 69,578	8/18/08

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA (RTF)	2/6/09
Amendment (Facility update)	1/30/09
Amendment (IR response/stability update)	2//15/09
Amendment (IR response)	4/16/09
Resubmission (After RTF)	6/15/09
Amendment (IR response & stability update)	9/29/09
Amendment (IR response)	12/29/09
Amendment (IR response -Quality Microbiology)	1/14/09

7. NAME & ADDRESS OF APPLICANT:

Name: BioAlliance Pharma

Address: 49 Boulevard du General Martial Valin
75015 Paris France

Chemistry Review Data Sheet

Representative Beckloff Associates, Inc.
Commerce Plaza II, Ste 300
7400 West 110 Street Overland Park, KS 66210

Contact person: Lavonne M. Patton, Ph.D.

Telephone: 913-451-3955

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Oravig buccal tablets
b) Non-Proprietary Name (USAN): Miconazole buccal tablets
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)**10. PHARMACOL. CATEGORY: Antifungal****11. DOSAGE FORM: Buccal Tablet****12. STRENGTH/POTENCY: 50 mg****13. ROUTE OF ADMINISTRATION: Buccal****14. Rx/OTC DISPENSED: Rx OTC****15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)**

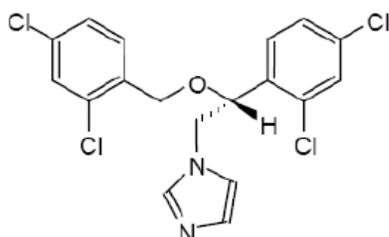
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[(2RS)-2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole

USAN	Miconazole
Molecular weight	416.13
Molecular Formula	C ₁₈ H ₁₄ Cl ₄ N ₂ O
Other Name	MICO-10 (2910)

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Miconazole	1		Andy Yu 2/16/10	Adequate
	II	(b) (4)	(b) (4)	3		S. Pittinger 2/28/05	Adequate
	III	(b) (4)	(b) (4)	4		2/20/10	Adequate

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox	Acceptable		Owen McMaster
Biopharm			
LNC			
Methods Validation			
OPDRA (DMETS)	Oravig name accepted	1/5/2010	Kristina C. Arnwine (Safety review)
EA	EA exclusion waiver found acceptable	2/20/10	Andrew Yu
Microbiology	Acceptable	1/20/2010	Bryan Riley

19. ORDER OF REVIEW (OGD Only) N/A

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes
 ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-404

The Executive Summary

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided adequate information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability is established and the pending labeling is completed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance miconazole, is manufactured by (b) (4) under DMF (b) (4). Information requests to the DMF holder concerning impurity has been adequately resolved and the DMF is acceptable. The DMF for (b) (4), (b) (4), (b) (4) and the type III DMF (b) (4) are current and adequate to support the NDA.

The drug product is a buccal tablet designed to be administered one tablet every 24 hours. The tablet contains 50 mg drug and is formulated with milk protein concentrate to (b) (4), (b) (4), (b) (4). The manufacturing of the tablet (b) (4).

(b) (4). Issues with debossing difficulty due to stickiness to tablet punches during a prior submission has been resolved and the tablet has markings as required. The manufacturing processes are validated with a production size batch and controlled with in-process parameters. The shelf life of 36 months at controlled room temperature is based on three stability batches of long term stability data at 36 months and six months of stability data at accelerated condition. The stability data were performed initially based on non-debossed tablets packaged in the same container. A bridging study was agreed upon during pre-NDA to ensure that debossing has no undesirable effect on stability of the product. The stability data on the debossed tablets were received during the review cycle and support the shelf life proposed.

The dissolution rates of the tablets at 4 and 8 hours in the stability batches generally slow down (b) (4) during storage when compared to the initial dissolution rate. This slowing is somewhat moderated when the tablet is debossed. Responding to information requests on this issue, the applicant presented more batches and additional data at 12 hours showing higher dissolution beyond 8 hours (b) (4). The response is acceptable. The primary stability batches and the clinical batch and are comparable during storage. The extent of slowing observed is acceptable for this product as the dissolution and the exposure issues were discussed with Clinical pharmacology for this product. The responses to all IRs are adequate and summarized at the end of the review (page 72- 89). A impurity issue concerning the acceptance criteria of (b) (4) (b) (4) in miconazole drug substance was resolved. The applicant has revised the acceptance criteria to a level acceptable by both Chemistry and Pharm/Tox. The impurity, (b) (4) is a (b) (4) impurity present in the drug substance during synthesis.

B. Description of How the Drug Product is Intended to be Used

Oravig® buccal tablets are off-white tablets containing 50 mg of miconazole. *Oravig*® tablets have a rounded side and a flat side with an “L”. *Oravig*® tablets are packaged in bottles of 14 tablets (NDC 49884-082-26). The storage condition is: Store at 20-25 °C (68-77°F) See USP controlled room temperature, excursions between 15 to 30 °C permitted.

Oravig® buccal tablet is intended for buccal administration for the treatment of fungal infection as described in the package insert. The usual dose is one tablet of ORAVIG applied to the upper gum once a day. The patient may find it convenient to apply ORAVIG in the morning after brushing the teeth following breakfast. DO NOT CHEW, CRUSH OR SWALLOW ORAVIG. ORAVIG may be used with food and drinks.

Oravig® buccal tablets are supplied in HDPE bottles of 14 tablets with desiccant and Child-Resistant Closure.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the shelf life of the product. The labels have the required CMC information.

One facility remains to be inspected. Therefore, a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review.

III. Administrative**A. Reviewer's Signature**

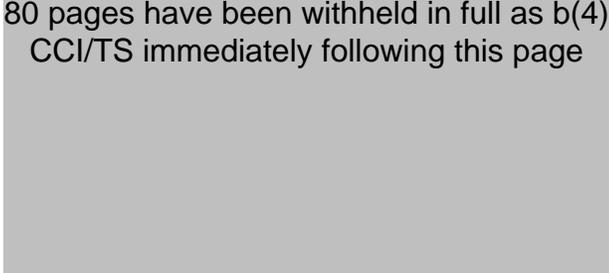
See DARRTS

B. Endorsement Block

See DARRTS

C. CC Block

80 pages have 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)

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

/s/

ANDREW B YU
02/23/2010

STEPHEN P MILLER
02/23/2010