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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Clinical Team Leader Review

Date	March 10, 2010
From	Yuliya Yasinskaya, M.D.
Subject	Clinical Team Leader Review
NDA/BLA #	22-404/S-000
Supplement#	
Applicant	Bioalliance Pharma
Date of Submission	June 15, 2009
PDUFA Goal Date	April 16, 2010
Proprietary Name / Established (USAN) names	Oravig [®] (miconazole)
Dosage forms / Strength	50 mg buccal tablet
Proposed Indication(s)	Oropharyngeal Candidiasis
Recommended:	<i>Approval</i>

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1. Introduction

Miconazole, an imidazole antifungal, has been marketed in the US since 1970s in various systemic and topical preparations for the treatment of the spectrum of *Candida* infections from vulvovaginal and oropharyngeal candidiasis to systemic *Candida* infections. The submission under review is a 505(b)(2) submission for Oravig (miconazole) in a new formulation of buccal tablet for the treatment of oropharyngeal candidiasis (OPC). This formulation provides for a sustained release of miconazole into saliva at the site of the infection (oropharyngeal mucosa) allowing for once daily administration. Miconazole administered in this manner is not absorbed and does not exhibit systemic toxicity. The body of evidence provided by the Sponsor and evaluated by the review team is sufficient to conclude that Oravig (miconazole buccal 50 mg tablet) once daily for 14 days is safe and efficacious and could be approved for the treatment of oropharyngeal candidiasis in adult patients.

2. Background

Oropharyngeal candidiasis (OPC) is an opportunistic *Candida* infection of the oral mucosa. It occurs primarily in patients with acquired or congenital T cell immune deficiency and patients with other predisposing conditions such as increased salivary glucose or salivary pH or decreased salivary flow, denture wearers, elderly, and neonates. HIV infected patients and patients who have received radiation to the head and neck area are especially at risk. Topical therapies marketed in the US for this indication include clotrimazole troches and nystatin requiring multiple daily dosing. Systemic antifungal treatment with fluconazole or posaconazole is usually reserved for the treatment of patients with severe, recurrent, or recalcitrant OPC.

The Sponsor submitted this 505(b)(2) NDA relying on nonclinical data from published scientific literature and the following NDAs: 18-888 for Monistat-3, Monistat Injectable 18-040, and 20-968 for Monistat DUAL-PAK (miconazole nitrate vaginal insert Soft Gel Vaginal Insert 1200 mg and miconazole nitrate cream External Vulvar Cream 2%). The clinical development program consisted of 4 studies:

- BA2000/01/01 - PK/PD study of Oravig 50 mg single dose in healthy subjects
- BA2002/01/03 - An open label non-comparative trial of Oravig 50 mg for 14 days in HIV+ patients with OPC
- BA2002/01/02 - Randomized controlled trial of Oravig 50 mg for 14 days in patients with OPC with head and neck cancers status post radiation therapy
- BA2004/01/04 - Randomized double blind active control trial of Oravig 50 mg once daily for 14 days versus clotrimazole troches 10 mg four times daily for 14 days in HIV+ patients with OPC.

Regulatory activity pre-submission consisted of pre-IND and pre-NDA meetings that focused on the primary efficacy endpoints for the OPC studies to be submitted in the marketing application and the non-inferiority margin for the clinical trials that used active control. The NDA 22-404 was first submitted on February 5, 2005; however, it was not

filed due to the CMC issue – the lack of imprint on the tablets. After successfully addressing the imprint issue, the Sponsor resubmitted the NDA on June 15, 2009. The NDA was determined to be filable by the review team during the July 27, 2010 filing meeting.

3. CMC/Device

Miconazole USP (C₁₈H₁₄Cl₄N₂O) is the active ingredient in miconazole buccal tablets (MBT). MBT contains Milk Protein Concentrate (MPC) produced in New Zealand from bovine spongiform encephalopathy (BSE)-free material. MPC contains approximately 82% casein and 18% whey proteins (β -lactoglobulin). Upon ingestion, casein and β -lactoglobulin can induce hypersensitivity/allergic reaction in 0.1-0.5% of adults (Crittenden 2005).

The CMC Reviewer, Dr. Andrew Yu, concludes that the NDA submission contained 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. He also finds that the shelf life of 36 months at controlled room temperature is supported by both the initial stability data on non-debossed tablets packaged in the same container and the results of the bridging study agreed upon during initial NDA submission to ensure that debossing has no undesirable effect on stability of the product. In addition, the office of Compliance has issued an overall “Acceptable” recommendation upon inspection of manufacturing facilities for Oravig.

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster, pharmacology toxicology reviewer, evaluated the results of 2 local tolerance/hypersensitivity potential studies for Oravig buccal tablets contained in this 505(b) (2) submission. He concludes that a good local tolerance animal model for the administration of Oravig does not exist, but the limited data from the hamster pouch study submitted suggests that the irritation potential of Oravig is not great. Dr. McMaster also notes that Oravig did not induce contact hypersensitivity in mice in the local lymph node assay and did not cause significant lymphoproliferation or local irritation at concentrations up to 5%.

Dr. McMaster points out in his review that given the extensive clinical experience with higher oral doses of miconazole in a gel formulation and with Oravig in countries outside the United States for the last 3 decades, the proposed dose of miconazole in Oravig, 50 mg/day, appears to be safe.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Yoriko Harygaya concludes that clinical pharmacology data provided in Oravig NDA is sufficient to support approval and documents the following findings in her review of the pharmacokinetic (PK) data submitted (trials BA2000/01/01, BA2004/01/04, and BA2002/01/03):

- Oravig Salivary Exposure: The single Clinical Pharmacology study in healthy subjects describes the PK profile of Oravig 50 mg and 100 mg in plasma and saliva. Oravig 50 mg (once daily) salivary exposures (AUC₀₋₁₂ & AUC₀₋₂₄) to miconazole were 10x

greater than those achieved with the miconazole oral gel (Daktarin®) 125mg three times daily with median Tmax of 6 to 7 hours after Oravig application. The mean duration of miconazole saliva concentrations >1.0 µg/mL (The MIC90 value for *C. albicans* and most non-albicans species involved in OPC) was 13.3 ± 5.2 and 14.4 ± 7.9 hours after Oravig application. However, no studies establishing the dose-response relationship (PK/PD) for efficacy were conducted by the Applicant.

- Oravig systemic bioavailability: The plasma concentrations obtained after administration of Oravig 50 mg and 100 mg in Study BA2000/01/01 were below the limit of quantification (LOQ = 0.4 µg/mL) for over 97% of the samples collected. In 2 Phase 3 studies (BA2004/01/04, BA2002/01/03) with Oravig 50 mg, plasma concentrations of miconazole from 40 HIV positive patients were essentially undetectable (LLOQ = 0.1 µg/mL). Since the pharmacokinetic study (BA 2000/01/01) confirmed the absence or the low systemic absorption of miconazole from Oravig, a dosage adjustment in patients with renal or hepatic impairments is not necessary.
- Potential for Drug-Drug interactions with Oravig: No formal drug interaction studies have been performed with Oravig. Although miconazole is a known inhibitor of CYP2C9 and CYP3A4, the potential for drug-drug interactions is minimal with the low miconazole systemic exposure. Specifically, miconazole inhibitory potency (Ki) for warfarin is 0.01 mcM. The highest miconazole plasma concentration with Oravig observed in healthy volunteer study (BA2000/01/01) was 0.83 mcg/mL, which gives (plasma concentration of miconazole) / Ki of 0.00021. (Plasma concentration of miconazole) / Ki = 0.1 is the cut off point for deciding whether the clinical study is necessary.

6. Clinical Microbiology

Dr. Lynnette Berkeley reviewed the microbiological outcomes of all clinical efficacy trials of Oravig in oropharyngeal candidiasis. Although Dr. Berkeley notes numerically lower mycological eradication rates for Oravig as compared to clotrimazole or miconazole gel, she emphasizes the absence of correlation between the rates of mycological eradication and clinical cures. She concludes that all three clinical trials support efficacy of Oravig for the treatment of OPC in patients infected with *C. albicans*, *C. tropicalis* and *C. parapsilosis*.

7. Clinical/Statistical- Efficacy

In the clinical development program, the results of two randomized controlled clinical trials BA2002/01/02 and BA2004/01/04 formed the basis for the determination of Oravig efficacy in oropharyngeal candidiasis. The efficacy results for the single non-comparative trial of Oravig in HIV+ patients are supportive of Oravig efficacy in randomized controlled clinical trials and are presented separately. The primary efficacy endpoint differed somewhat between the trials. Trials BA2000/01/03 (non-comparative study of miconazole buccal tablet for the treatment of OPC in HIV+ adults) and BA2002/01/02 (miconazole buccal tablet vs. miconazole gel for the treatment of OPC in patients with head and neck cancer who had received radiation therapy) defined efficacy as a clinical success: complete or partial resolution of oral lesions at EOT. Study BA2004/01/04 (miconazole tablet vs. clotrimazole troches for the treatment of OPC in

HIV+ adults) defined efficacy as a clinical cure: complete resolution of oral lesions and symptoms on day 21. As both controlled trials utilized active control they were of a non-inferiority design. The Sponsor attempted to justify a non-inferiority margin of -20% for both trials; however, upon review of the submitted information and the results of the additional publication search and review, FDA statistical and clinical reviewers determined that a -15% and -12.5% margins would be more appropriate for trials BA2004/01/04 and BA2002/01/02, respectively. For the details of the non-inferiority margin justification please refer to the respective reviews by Dr. Hala Shamsuddin, the medical reviewer, and Dr. Xianbin Li, the statistical reviewer.

While relapse assessments were performed in HIV+ patients with complete or partial response, in head and neck cancer patients relapse assessments were limited to patients with complete response only.

Table 1 Integrated efficacy – all efficacy studies combined – FDA mITT* population

Efficacy	MBT 50 mg			Comparator	
	Noncomparative	Controlled		Clotrimazole	Miconazole gel
	HIV infected N = 25	HIV infected N = 290	H&N cancer N = 148	HIV infected N = 287	H&N cancer N = 146
Resolution of lesions and symptoms (Clinical Cure)	13 (52%)	176 (60.7%)	55 (37.2%)	187 (65.2%)	55 (37.7%)
Difference in cure rates for Oravig-comparator (95%CI)		-4.5% (-12.3, 3.4)			
Resolution of lesions (complete clinical success)	13 (52%)	188 (64.8%)	74 (50%)	198 (69%)	64 (43.8%)
Difference in cure rates (95%CI)			6.2% (-5.2, 17.6)		
Mycologic cure	7 (28%)	79 (27.2%)	64 (45.4%)	71 (24.7%)	77 (54.6%)
Relapse	8 (35%)	51 (27.9%)	14 (18.9%)	53 (26.9%)	8 (12.5%)

* All patients with OPC that received at least one dose of study drug
 Modified from the clinical review by Dr. Hala Shamsuddin

In both randomized controlled trials in patients with oropharyngeal candidiasis Oravig was non-inferior to the active comparator in mITT and PP study populations with the lower bound of the 95% confidence interval for efficacy falling within conservatively justified NI margin (-15% for the study in HIV+ patients and -12.5% for the patients with head and neck cancer).

Dr. Shamsuddin and Dr. Li performed multiple exploratory analyses of efficacy in different patient populations and assessed the effects of gender, race, geographic location as well as OPC severity, general debility, salivary function, and underlying immunosuppression on the efficacy of Oravig in OPC. From their reviews it becomes apparent that the country, gender, and race effects were related in the study of OPC in HIV+ patients. The numerically higher cure rate among US patients on clotrimazole arm mirrored the higher cure rate among white patients on clotrimazole arm and reflects the fact that almost all the white patients were enrolled in the US. In addition, males were more likely to have been enrolled in the US. Patients from the US were five times more likely to be on antiretroviral therapy, more likely to have less severe OPC and to be more functional (lower ECOG grade) compared to patients from South Africa. In addition, US patients who received clotrimazole were more likely to be

on antiretroviral therapy, to have less severe OPC and lower ECOG score compared to US patients who received MBT or South African patients who received either treatment. For greater detail and sensitivity analyses please refer to the statistical and clinical reviews by Dr. Xianbin Li and Dr. Hala Shamsuddin, respectively.

In her review Dr. Shamsuddin notes that the resolution of lesions occurred more frequently in HIV+ patients compared to patients with head and neck cancer regardless of the treatment administered, and that the lower response rate in patients with head and neck cancer is consistent with that of the response rates for this population reported in the literature. She summarizes the publications reviewed pointing out that patients with head and neck cancer treated with fluconazole experienced lower cure rate compared to HIV+ patients, most likely attributed to lower penetration of the drug into saliva in head and neck cancer patients due to radiation-induced xerostomia (cure rate 21-73% vs. 87-100%).

The relationship between the salivary function and the rate of the OPC lesions resolution might also reflect itself in different efficacy rates between head and neck cancer patients and HIV+ patients treated with Oravig. Salivary secretion was either absent or decreased in 97.5% of OPC patients with head and neck cancer compared to 53% of HIV+ OPC patients. Patients with decreased salivary gland function responded to treatment less frequently regardless of the treatment administered. In addition, patients with head and neck cancer had a lower percentage of tablets adhering to the oral mucosa at least 6 hours (91% vs. 75%), potentially resulting in lower salivary concentrations/ local drug exposure.

Dr. Shamsuddin also points out the differences between the two study populations in regards to the respective primary endpoints. In HIV+ patients rates of resolution of lesions and resolution of lesions and symptoms were similar, indicating that resolution of symptoms accompanied lesion resolution. In contrast, in patients with head and neck cancer, resolution of lesions occurred more frequently than resolution of lesions and symptoms suggesting that resolution of symptoms does not necessarily accompany lesion resolution, as symptoms of OPC could mimic symptoms post radiation therapy.

Relapse rates in HIV+ patients were in the range reported in the literature for other antifungal agents: 44% for HIV+ patients treated with nystatin, around 50% for patients treated with clotrimazole, and around 20% for patients treated with fluconazole.

Mycological cure was lower in HIV+ patients compared to patients with head and neck cancer, despite higher frequency of tablet adhesion and better salivary function. In addition, HIV infected patients were more likely to relapse and to have a shorter time-to-relapse regardless of treatment. The lower mycological cure and rate of relapse probably reflect the higher degree of underlying systemic immunosuppression of HIV infected patients compared to patients with head and neck cancer.

In agreement with findings in the review by Dr. Lynnette Berkeley, microbiology reviewer, Dr. Shamsuddin finds that mycological cure did not correlate with clinical cure, which is consistent with literature reports for other antifungal agents in the treatment of OPC. Clinical progression of OPC was infrequent, occurring in less than 1% of patients in either treatment arm.

The correlation between tablet adhesion and clinical response was poor. Around 91% of the tablets adhered for at least 6 hours (please refer to safety/drug exposure section). The poor correlation between adhesion time and response indicates that adherence for longer than 6 hours may not provide additional clinical benefit.

8. Safety

The Oravig safety database of 480 subjects who received at least one dose of study drug (50 mg miconazole buccal tablet) included 18 healthy subjects, 315 HIV+ patients (290 in BA2004/01/04 and 25 in BA2000/01/03), and 147 patients with head and neck cancer. Two hundred and eight seven (287) HIV infected patients received at least one dose of clotrimazole. One hundred and sixty-five (165) individuals received miconazole gel: 18 healthy subjects and 147 patients with head and neck cancer.

Table 2 Subjects with Treatment Emergent Adverse Reactions – Overall Oravig Clinical Trials Experience

	MBT 50 mg N = 480	Clotrimazole N = 287	Miconazole Gel N = 165
Patients with At least one AE	206 (42.9%)	146 (50.9%)	43 (26%)
Patients with Serious AE (including deaths)	11 (2.3%)	9 (3.1%)	7 (4.2%)
Patients with Drug related AE	98 (20.4%)	65 (22.6%)	23 (13.9%)
Patients with Serious drug related AE	0	0	0
Study discontinuation due to AE	5 (1.0%)	3 (1.0%)	6 (3.6%)
Drug discontinuation due to AE	3 (0.6%)	0	2 (1.2%)
Deaths	5 (1.0%)	6 (2.1%)	3 (1.8%)

Adapted from clinical review by Dr. Hala Shamsuddin

Deaths and Serious Adverse Reactions

There were five deaths (1.0%) in patients who received Oravig. The narratives of deaths were reviewed by Dr. Shamsuddin, who agreed with the applicant that it is unlikely that the deaths were related to the study drug. It was also determined in clinical review that of 11 Oravig patients (2.3%) experienced a serious adverse reaction none had a reaction attributed to the study drug.

Adverse Reactions that resulted in study drug discontinuation

Three patients (0.6%) discontinued the drug due to an adverse event: one HIV+ patient with dysphagia on Day 8, 1 HIV+ patient with nausea on Day 12, and one patient with head and neck cancer with local edema at the site of the tablet application on Day 7 of therapy. The adverse reactions of nausea and local edema at the Oravig application site were considered probably related to Oravig. Adverse event of dysphagia was considered unlikely to be related to Oravig administration.

All causality adverse events, events of special interest and laboratory abnormalities

Overall treatment emergent adverse reactions were more frequent in HIV+ patients compared to patients with head and neck cancer regardless of treatment received. Dr. Shamsuddin notes in her review that among HIV+ patients, adverse reactions were numerically more frequent in females compared to males, possibly as a result of the greater use of concomitant medications and higher ECOG scores in females enrolled in the study. However, such gender difference in the rates of the adverse reactions between the study arms was not observed in patients with head and neck cancer.

Table 3 Treatment Emergent Adverse Reactions occurring in $\geq 2\%$ of Patients and Healthy Subjects, Overall Oravig Clinical Trials Experience

System Organ Class/Preferred term MedDRA version 9.1	Oravig HIV+ controlled N=290	Oravig Head and Neck controlled N=147	All MBT N = 480	Clotrimazole N = 287	Miconazole gel N = 165
Gastrointestinal disorders	75 (25.9%)	13 (8.8%)	99 (20.6%)	68 (23.7%)	25 (15.1%)
Diarrhea	26 (9.0%)	0	29 (6.0%)	23 (8.0%)	1
Nausea	19 (6.6%)	1 (0.7%)	22 (4.6%)	22 (7.7%)	4 (1.2%)
Abdominal pain upper	5 (1.7%)	2 (1.4%)	12 (2.5%)	8 (2.8%)	3 (1.8%)
Vomiting	11 (3.8%)	1 (0.7)	12 (2.5%)	9 (3.1%)	3 (1.8%)
Infections and infestations	46 (15.9%)	7 (4.8%)	57 (11.9%)	49 (17.1%)	8 (4.8%)
URI	6 (2.1%)	0	6 (1.2%)	7 (2.4%)	0
Nervous system disorders	38 (13.1%)	8 (5.4%)	52 (10.8%)	24 (8.4%)	5 (3.0%)
Headache	22 (7.6%)	1 (0.7%)	23 (4.8%)	19 (6.6%)	1 (0.6%)
Dysgeusia	4 (1.4%)	6 (4.1%)	14 (2.9%)	3 (1.0%)	1 (0.6%)
General and admin site	20 (6.9%)	6 (4.1%)	26 (5.4%)	23 (8.0%)	6 (3.6%)
Skin	17 (5.9%)	5 (3.4%)	23 (4.8%)	12 (4.2%)	1 (0.6%)
Musculoskeletal	15 (5.2%)	5 (3.4%)	20 (4.2%)	18 (6.3%)	2 (1.2%)
Respiratory	15 (5.2%)	2 (1.4%)	17 (3.5%)	22 (7.7%)	6 (3.6%)
Blood	20 (6.9%)	1 (0.7%)	21 (4.4%)	24 (8.4%)	0
Investigations	16 (5.5%)	1 (0.7%)	16 (3.3%)	18 (6.3%)	0

Modified from clinical review of Dr. Hala Shamsuddin

There were no differences in the overall incidence and the profile of the adverse reactions between the study arms and between the studies.

Table 4 Treatment Emergent Local Adverse Reactions occurring in $\geq 2\%$ of Patients and Healthy Subjects, Overall Oravig Clinical Trials Experience

	Oravig HIV+ controlled N=290	Oravig Head and Neck controlled N=147	All MBT N = 480	Clotrimazole N = 287	Miconazole gel N = 165
Local Adverse Reactions*	35 (12.1%)	14 (9.5%)	50 (10.4%)	27 (9.4%)	16 (10.9%)

* Local adverse reactions included MedDRA PT: oral discomfort, oral burning, oral pain, gingival pain, gingival swelling, gingival pruritis, tongue ulceration, mouth ulceration, glossodynia, dry mouth, application site pain or discomfort, toothache, loss of taste, and altered taste

The combined rates of local oral adverse reactions that included: oral discomfort, oral burning, oral pain, gingival pain, gingival swelling, gingival pruritis, tongue ulceration, mouth ulceration, glossodynia, dry mouth, application site pain or discomfort, toothache, loss of taste, and altered taste, were comparable between Oravig and its comparators: clotrimazole and miconazole gel.

Table 5 Treatment Emergent Hepatic Laboratory Abnormalities, All Clinical Studies Combined

Liver function test elevations (all studies combined)	MBT N = 480	Clotrimazole N = 287	Miconazole gel N = 165
ALT > 3x baseline	5 (1.0%)	7 (2.4%)	6 (3.6%)
ALT > 5x baseline	0	1 (0.3%)	0
AST > 3x baseline	2 (0.4%)	3 (1.0%)	3 (1.8%)
AST > 5x baseline	0	1 (0.3%)	2 (1.2%)
Alkph > 3x baseline	0	0	1 (0.6%)
Alkph > 5x baseline	0	0	0
GGT > 3x baseline	8 (1.7%)	6 (2.1%)	4 (2.4%)
GGT > 5x baseline	3 (0.6%)	1 (0.3%)	1 (0.6%)

Adapted from clinical review by Dr. Hala Shamsuddin

Elevations of liver function tests were infrequent. Dr. Shamsuddin confirms that the abnormalities in laboratory parameters are unlikely to be attributed to the study drug.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

Oravig is not approved for use in pediatric patients. Pediatric assessment as proposed by the Applicant and modified by the Review Division was discussed with the Pediatric Review Committee (PeRC) on March 17, 2010. It was concluded that the waiver for children ≤ 5 years of age could be granted due to the potential risk of choking, and inability to comply with administration instructions.

The PeRC has agreed that a deferral of studies in children > 5 years of age. The recommendation was made assess Oravig safety, PK, efficacy, and compliance in pediatric OPC patients 6-16 years of age in a step-wise fashion (12 to 16 years, 8 to 11 years, and 6 to 7 years)

A study of Oravig for the treatment of oropharyngeal candidiasis in pediatric patients ages 6 to 16 years is deferred until March 31, 2014.

11. Other Relevant Regulatory Issues

The Sponsor submitted this 505(b)(2) NDA relying on nonclinical data from published literature and the following NDAs: 18-888 for Monistat-3, 18-040 for Monistat Injectable, and 20-968 for Monistat DUAL-PAK (miconazole nitrate vaginal insert Soft Gel Vaginal Insert 1200 mg and miconazole nitrate cream External Vulvar Cream 2%). However, upon regulatory review it was found that although the labeling for Monistat DUAL-PAK (NDA 20-968) could be found at Drugs@FDA website, this NDA listing is absent from the Orange book when a search was performed in the prescription, over-the-counter, and discontinued products under the following keywords: miconazole or Monistat DUAL-PAK. Therefore, based on the recommendations from ORP and OCC the reviewer has concluded that for the purposes of relying on nonclinical information from the reference listed drugs Oravig NDA can only rely on the NDA 18-888 for Monistat-3, and NDA 18-040 for Monistat Injectable.

12. Labeling

Applicant proposed Oravig labeling, including PI and PPI in PLR format were significantly modified by all review disciplines in consultation DMEPA, DRISK, SEALD, and DDMAC. The final labeling was agreed upon during labeling negotiations between the Review Division and the Applicant.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:**
Approval of Oravig (miconazole) buccal tablet for the indication of oropharyngeal candidiasis in adult patients
- **Risk Benefit Assessment**
The clinical development program demonstrated that Oravig is efficacious in treatment of oropharyngeal candidiasis on the basis of two adequate and well controlled studies in HIV+ patients and patients with head and neck cancer status post radiation therapy. In both trials Oravig was found to be non-inferior to the concurrent active control by meeting conservatively estimated NI margin. Due to minimal systemic absorption Oravig safety profile (systemic and local) is favorable and comparable to that of clotrimazole and miconazole gel.
- **Recommendation for Postmarketing Risk Management Activities**
None
- **Recommendation for other Postmarketing Study Commitments**

A study of Oravig safety, pharmacokinetics, efficacy, and compliance with use instructions in pediatric patients with oropharyngeal candidiasis ages > 5 to <17 years is deferred until December 31, 2013.

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/

YULIYA I YASINSKAYA
04/12/2010