CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22404Orig1s000

SUMMARY REVIEW

Division Director Review

Applicant:	BioAlliance Pharma Beckloff Associates, Inc. (applicant's representative)
Drug:	Miconazole
Trade Name:	Oravig [1]
Date of Submission:	June 15, 2009 (received June 16, 2009)
PDUFA Goal Date:	April 16, 2010 (standard 10 month review)
Formulation:	Buccal Tablet
Strength:	50 mg
Indication:	Treatment of Oropharyngeal Candidiasis
IND:	IND 69,578

Material Reviewed:

Project Management: Christina Chi, Judit Milstein
Clinical Review: Hala Shamsuddin, Yuliya Yasinskaya
Cross Discipline Team Leader: Karen Higgins (no separate review)
Microbiology Review: Lynette Berkeley, Shukal Bala
Clinical Pharmacology Review: Yoriko Harigaya, Dakshina Chilukuri, Phil Colangelo
Statistics Review: Xianbin Li, Karen Higgins, Mohammad Huque
Pharmacology/Toxicology Review: Owen McMaster, William Taylor
Chemistry Manufacturing Controls Review: Andrew Yu, Rapti Madurawe, Stephen Miller, Norman Schmuff
Microbiology Product Quality: Bryan Riley, James McVey
Division of Scientific Investigations (DSI): Susan Thompson, Tejashri Purohit-Sheth
Office of Surveillance and Epidemiology (OSE) -
OSE/Division of Medication Error and Prevention Analysis (DMEPA): Tselaine Jones Smith, Denise Toyer, Kristina Arnwine (carton, container, PI, proprietary name) Carol Holquist letter November 10, 2009
OSE/Division of Pharmacovigilence II (DPVII): Chris Jones (preapproval safety conference, no review)
OSE/Division of Drug Risk Evaluation (DRISK): Barbara Fuller, LaShawn Griffiths, Mary Willy (PI, PPI)
Division of Drug Marketing, Advertising and Communication (DDMAC): Kathleen Klemm, Sharon Watson (Patient package insert)
Safety Evaluation and Labeling Development (SEALD): Iris Masucci
Pediatric and Maternal Health Staff: Elizabeth Durmowitz
Regulatory 505(b)(2) issues: Kim Quaintance, David Roeder, Nancy Boocker, Beth Duvall-Miller

[1] previously applicant proposed the names Lauriad® for patented delivery system, (b) (4) for the product

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1 RECOMMENDATIONS

BioAlliance Pharma will be issued an approval letter for the use of Oravig (miconazole) buccal tablets for the treatment of oropharyngeal candidiasis.

The proposed indication and dosage regimen are summarized below. The complete package insert and patient package insert will be attached to the action letter.

1.1 Proposed Indication

Oravig is indicated for the local treatment of oropharyngeal candidiasis (OPC) in adults.

1.2 Proposed Dosage Regimen

The recommended dosing schedule for Oravig is the application of one 50 mg buccal tablet to the upper gum region (canine fossa) once daily for 14 consecutive days.

The following administration instructions will be included in labeling:
Oravig should be applied in the morning, after brushing the teeth. The tablet should be applied with dry hands. The rounded side surface of the tablet should be placed against the upper gum just above the incisor tooth (canine fossa) and held in place with slight pressure over the upper lip for 30 seconds to ensure adhesion. The tablet is round on one side for comfort, but either side of the tablet can be applied to the gum.
Once applied Oravig stays in position and gradually dissolves. [*See Clinical Pharmacology (12.3)*] Subsequent applications of Oravig should be made to alternate sides of the mouth. Before applying the next tablet, the patient should clear away any remaining tablet material. In addition,

- Oravig should not be crushed, chewed or swallowed.
- Food and drink can be taken normally when Oravig is in place but chewing gum should be avoided.
- If Oravig does not adhere or falls off within the first 6 hours, the same tablet should be repositioned immediately. If the tablet still does not adhere, a new tablet should be placed.
- If Oravig is swallowed within the first 6 hours, the patient should drink a glass of water and a new tablet should be applied only once.
- If Oravig falls off or is swallowed after it was in place for 6 hours or more, a new tablet should not be applied until the next regularly scheduled dose. *[see Patient Counseling Information (17)]*.

1.3 Outstanding Issues or Other Requests

None

2 BACKGROUND

Miconazole is an antifungal product initially approved in 1974 for the treatment of vaginal candidiasis, and now available in multiple over-the-counter formulations and presentations (creams, inserts, combinations) for the treatment of candidiasis. The Orange Book currently lists 3 prescription products, approximately 20 OTC products, and 6 discontinued products that contain miconazole for topical use.

BioAlliance Pharma has submitted a 50 mg (b) (4) buccal tablet for the treatment of oropharyngeal candidiasis (OPC).

Currently available therapy for OPC includes clotrimazole, nystatin, fluoconazole, and posaconazole. This formulation is unique in that it represents a buccal tablet to be placed in the canine fossa once daily for 14 days and provide sustained miconazole release for up to 24 hours.

2.1 Regulatory Considerations

The original submission of NDA 22-404 was February 5, 2009 (received February 6). Because the tablet had not been debossed as requested by Chemistry per 21 CFR 206.10, a Refuse-to-File letter was issued April 3, 2009. The matter was discussed with the CMC reviewers April 29, 2009 and proposal acceptable. Once the chemistry issues were corrected, the application was submitted June 15, 2009 (received June 16) and given a 10 month standard review clock, with the PDUFA goal date being April 16, 2010.

The applicant developed the product under IND 69,578 and a pre-NDA meeting was held August 12, 2008. The application was granted a Small Business Waiver of the User Fee. Financial disclosure information was included. Three year exclusivity is being requested. Patent certification was provided. No advisory committee meeting was scheduled since this is not a new molecular entity and no issues warranting public discussion at an AC were identified.

The application is a 505(b)(2) and relies for some of the preclinical information on previous applications. Miconazole has been used in various intravaginal and dermatologic formulations such as ointment, gel, troche, even mouthwash, and has been used in the US and abroad for over 30 years. Generic versions of miconazole have also been available, and various presentations of miconazole have been converted from Rx to OTC use. Conversion to the OTC setting was based in part on the assessment that the product could be used safety in the OTC setting. BioAlliance has listed and relied on several NDAs: NDA 18-888 (Monistat 3-miconazole nitrate-Suppository) and NDA 18-040 (Monistat Injectable), as well as NDA 21-261 (Monistat 3 Combination Pack) and NDA 20-968 (Monistat Dual-Pak). General Counsel considered reliance on the findings of safety and efficacy from NDAs 18-040 and 18-888 acceptable. The other NDAs were not relied on because they were not listed in the orange book (NDA 20-968) or the product is OTC (NDA 21-261) and does not provide pharmacology/toxicology information. However, based on internal discussion of the information needed for

labeling of the pharmacology/toxicology and microbiology resistance parts of the package insert, this information is available from the hamster and mouse study conducted by the applicant, the first two NDAs cited above and from published literature. The manufacturing and clinical studies needed for approval were provided by the applicant.

3 REVIEW

3.1 Chemistry Manufacturing and Controls:

Dr Yu notes in his review of February 23, 2010 that this "NDA has provided adequate information to assure identity, strength, purity, and quality of the drug product."

Dr Riley noted in his review of January 25, 2010 that the product meets approval on the basis of product quality microbiology, once the applicant submitted the information on microbial limits test results that were found to be within the acceptance criteria.

The product is a non-sterile 50 mg tablet formulated with milk protein concentration (b) (4) (b) (4) and is unique in this method of delivery. Stability testing supports a 36 month shelf life.

Oravig contains milk protein concentrate (MPC) and therefore the labeling will carry a caution about use of the product in milk allergic patients.

3.2 Microbiology

Dr. Berkeley reviewed the microbiology information. Miconazole is an imidazole antifungal that inhibits the enzyme cytochrome P450 14α-demethylase which leads to inhibition of ergosterol synthesis, an essential component of the fungal cell membrane. Miconazole also affects the synthesis of triglycerides and fatty acids and inhibits oxidative and peroxidative enzymes, increasing the amount of reactive oxygen species within the cell. She concluded that the application included data showing miconazole is active against *Candida albicans, C. parapsilosis* and *C. tropicalis,* however correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established. *In vitro* studies have shown that some *Candida* strains that demonstrate reduced susceptibility to one antifungal azole may also exhibit reduced susceptibility to other azoles suggesting cross-resistance.

3.3 Toxicology

Miconazole has been marketed since 1974, and available for over-the-counter (OTC) use for vaginal and dermatologic indications. Toxicity information was obtained from 2 hamster studies, one mouse study, previously approved package inserts for NDAs 18-888 and 18-040, and published literature. In hamster studies, a paste containing 1000 mg/kg in the buccal pouch resulted in animals deaths presumed to be due to swallowing and systemic toxicity (by comparison the human dose is 50 mg tablet) while local effects on

the mucosa consisted of epithelial thickening, inflammation and vasodilation. In mice a standard local lymph node assay with lower miconazole doses (5% solution) local irritation was not seen. As noted above, miconazole is currently available in OTC creams and suppositories for treatment of vaginal candidiasis, and there is extensive clinical experience with the product.

The labeling will summarize toxicology information available for the cited package inserts and literature: Miconazole nitrate administered orally at doses of 80 mg/kg/day or higher to pregnant rats or rabbits crossed the placenta and resulted in embryo- and fetotoxicity, including prolonged gestation and increased numbers of stillborn pups in rats and increased fetal resorptions in rabbits. There was no evidence of embryo toxicity or teratogenicity in rats or rabbits dosed intravenously with miconazole at 40 or 20 mg/kg/day respectively, doses that represent at least 7 times the dose a patient would receive if she swallowed an Oravig buccal tablet, based on body surface area comparisons." The product has a Pregnancy Category C - there are no adequate and well-controlled clinical trials of Oravig in pregnant women therefore Oravig should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Because it is not known whether this drug is excreted in human milk, caution should be used, however, the amount of absorption from the 50 mg buccal tablet is very low. No impairment of fertility occurred when female rats were administered miconazole nitrate orally at doses equivalent to a human dose of 53 mg/kg/day based on body surface area conversions.

Because use of miconazole is short term (days to weeks), carcinogenicity studies with miconazole have not been conducted. Miconazole nitrate was not genotoxic when tested *in vitro* for induction of microbial point mutations (Ames test) or *in vivo* for dominant lethal mutation in mouse germ cells or structural chromosome aberrations in mouse or rat bone marrow cells following high oral or intraperitoneal doses (equivalent to a human dose of 52 mg/kg based on body surface area conversions).

As noted earlier, miconazole topical formulations have been used extensively, and the product in various formulations has been found to be safe for OTC use. NDAs for OTC products are not cited given that there is no toxicology summary included in the Drug Facts labeling – furthermore, the OTC status of labeling indicates the product has been considered safe for OTC use.

3.4 Clinical Pharmacology

In healthy volunteers, the duration of buccal adhesion was on average 15 hours following an Oravig 50 mg tablet administration. A 50 mg Oravig tablet provided mean maximum salivary concentrations of 15 mcg/mL and AUC (0-24h) of 55.23 mcg·h/mL 7 hours after application (see table below).

Pharmacokinetic (PK) Parameters of Miconazole in Saliva Following Application of a Single Oravig 50 mg Tablet in Healthy Volunteers (N = 18)

Salivary PK Parameters (N = 18)	Mean ±SD (Min - Max)
$AUC_{0\text{-}24h}$ (mcg.h/mL)	55.2 ±35.1 (0.5 – 128.3)
C_{max} (mcg/mL)	15.1 ±16.2 (0.5 – 64.8)
T_{max} (hour)	7* (2.0 – 24.1)

The plasma concentrations of miconazole were below the lower limit of quantification (0.4 mcg/mL) in 157/162 (97%) samples from healthy volunteers; measurable plasma concentrations ranged from 0.5 to 0.83 mcg/mL. Plasma concentrations of miconazole evaluated after 7 days of treatment in 40 HIV-positive patients were all below the limit of quantification (0.1 mcg/mL).

Miconazole is metabolized by the liver, and less than 1% of miconazole is excreted as unchanged drug in the urine.

3.5 Efficacy Evaluation

The efficacy of Oravig for the treatment of OPC was evaluated in two controlled clinical trials; one in HIV patients, and another in patients with head and neck cancers following radiation therapy. The efficacy of the product in each population is summarized below, and this information will be included in the CLINICAL STUDIES section of labeling. Both studies met the prespecified margin for the analysis population:

Study in HIV Infected Patients (Study BA/2004/01/04)
The efficacy and safety of Oravig in the treatment of OPC was evaluated in a randomized, double-blind, double-dummy, multicenter trial comparing Oravig 50 mg once daily for 14 consecutive days (n = 290) with clotrimazole troches 10 mg 5 times per day for 14 days (n = 287) in HIV-positive patients with OPC. Seventy-five percent of patients were not receiving highly active antiretroviral treatment, 5% had CD4+ cell count < 50 cells/mm^3, and 17% had a history of previous OPC. The mean viral load was 117,000 copies/mL. Patients were required to have symptoms and microbiological documentation of OPC for study entry. Most of the infections were caused by *C. albicans* (85%), followed by *C. tropicalis* (9%), and *C. parapsilosis* (3%). About 2% of the subjects were infected with more than one *Candida* species.

Clinical cure [defined as a complete resolution of both signs and symptoms of OPC at the test of cure (TOC) visit (days 17-22)], and clinical relapse by days 35-38 (21-24 days after end of therapy) are presented in the table below. Mycological cure [defined as eradication (i.e., no yeast isolates) of *Candida* species] at the TOC visit (days 17-22) is also reported in the table.

Clinical Cure and Mycological Cure at the TOC Visit and Relapse at Days 35-38 in HIV Infected Patients

	ORAVIG 50 mg N=290[a] (%)	Clotrimazole troches N=287[a] (%)
Clinical cure†	176 (60.7%)	187 (65.2%)
Clinical relapse‡		
Yes[b]	48 (27.3%)	52 (27.8%)
No	124 (70.5%)	133 (71.1%)
Missing	4 (2.3%)	2 (1.1%)
Mycological cure	79 (27.2%)	71 (24.7%)

[a] Analysis population includes all randomized patients who took at least 1 dose of study medication. One randomized subject excluded from the ORAVIG arm.

[b] In those subjects who relapsed, the mean time to relapse was 15.3 days (SD 4.6) and 15.7 days (SD 6.6), in the ORAVIG and Clotrimazole treatment arms, respectively.

† Difference in clinical cure rates (ORAVIG-miconazole) was -4.5%, with a 95% CI: (-12.4%, 3.4%).

‡ Percentage based on those who had clinical cure.

Study in Head and Neck Cancer Patients (Study BA/2002/01/02)

The efficacy and safety of Oravig 50 mg was evaluated in an open-label, randomized, multicenter trial comparing Oravig 50 mg once daily for 14 days to miconazole oral gel 125 mg four times daily for 14 days in head and neck cancer patients who had received radiation therapy. Most of the infections were caused by *C. albicans* (71%), and *C. tropicalis* (8%). About 7% of the subjects were infected with more than one *Candida* species. Success rates of treatment at day 14 [defined as a complete (complete disappearance of candidiasis lesions) or partial response (improvement by at least 2 points of the score for extent of oral lesion compared with the score at day 1) based on a blind assessment] are shown in the table below. Also reported in Table 6 are relapse rate at day 30, and mycologic cure assessed at day 14.

Clinical Success and Mycological Cure at Day 14, in Patients with Head and Neck Cancer Who Had Received Radiation Therapy

	ORAVIG 50 mg N=148[a (%)]	Miconazole oral gel N=146[a (%)]
Success rate (CR+PR)[b]	79 (53.4%)	69 (46.6%)
CR †	74 (50.0%)	64 (43.8%)
Clinical relapse‡		
Yes[c]	14 (18.9%)	8 (12.5%)
No	59 (79.7%)	56 (87.5%)
Missing	1 (1.4%)	0
Mycological cure	66 (44.6%)	78 (53.4%)

[a] Analysis population includes all subjects who received at least one dose of study medication. Reasons for not receiving treatment included negative mycological culture, informed consent withdrawn, or lost during screening. Six patients excluded per arm.

[b] CR: complete response; PR: partial response

[c] In those subjects who relapsed, the mean time to relapse was 18.8 days (SD 16.3) and 20.6 days (SD 13.5), in the ORAVIG and Miconazole oral gel group, respectively.
† Difference in clinical complete response rates (Oravig-Miconazole oral gel) was 6.2%, with a 95% CI: (-5.2%, 17.6%).
‡ Percentage based on those who had complete response.

3.5.1 Noninferiority Margin

Because both of the clinical studies used the non-inferiority design and did not compare the activity of Oravig to a placebo, previously conducted studies of OPC were reviewed by the applicant and by the reviewers (Dr Li and Dr Shamsuddin) to determine an applicable non-inferiority margin for these studies.

Briefly, the placebo effect was assessed from six studies, and based on a meta-analysis using a random effect model; the placebo rate was 11.5% with a 95% confidence interval [4.3%, 18.7%]. However, by excluding 3 studies which differed in mortality, timing of endpoint or definition of outcome from the current Study 04, the most conservative placebo effect was estimated to be 11.6 with a 95% confidence interval of [-0.1%, 24.1%]. Thus the placebo effect was considered to be **24%** for Study 04.

For the HIV positive patient Study 04, clotrimazole was used as the control. The effect of clotrimazole was assessed from 9 clinical trials, 6 in HIV positive patients.
The estimated cure rate from a random effects model was 76.2% from these 6 studies, with a two-sided 95% confidence interval of [69.1%, 83.3%]. Therefore, using the lower bound from this confidence interval, a conservative cure rate for clotrimazole in HIV positive subjects is **69%**. The difference in treatment effect is 69% (clotrimazole) – 24% (placebo) = 45%. Therefore, a margin of 15% for Study 14 preserves a significant proportion of the effect.

For the head and neck cancer patient Study 02, the efficacy of miconazole oral gel was assessed from 8 clinical trials and a meta-analysis using a random effect model was conducted to combine the results from the studies. The estimated cure rate was 83.5% with a 95% confidence interval of [74.6%, 92.3%]. Various other analyses were done excluding studies with cure rates of 100%, and where the definition of outcome was not clear. In the end, a conservative estimate of **50%** cure was used, and the treatment effect was estimated as 50% (miconazole) – 25% (placebo) = 25%. Although the company proposed a 20% margin, the reviewer chose a more conservative 12.5% margin to preserve 50% of the treatment benefit.

Thus, a noninferiority (NI) margin was justified for each of the two controlled studies and preserved at least 50% of the conservative estimate of treatment effect of active over placebo. Each study met the justified NI margin.

3.5.2 Subset analyses

Race, Age, Gender
Although some differences were seen in outcomes based on gender, race and age, none of these differences reached statistical significance. There were also treatment by country interactions with better outcomes in France, Tunisia, Algeria, and lower rates in the US and Morocco, and similar in Canada.

Pediatric Patients
Safety and effectiveness of Oravig in pediatric patients below the age of 16 years have not been established. The ability of pediatric patients to comply with the application instructions has not been evaluated. Use in younger children is not recommended due to potential risk of choking.

Geriatric Patients
Clinical studies of Oravig did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

3.6 Safety

The overall adverse event profile was not significantly different from the control regimens and is summarized below. Adverse reactions reported in the overall safety database of 480 subjects who received miconazole buccal tablet is listed below.

Adverse Reactions reported in ≥ 2% of patients and healthy subjects who received Oravig in Clinical Trials

Adverse reaction - (MedDRA v 9.1 System Organ Class and Preferred Term)	ORAVIG N = 480 (%)
Patients with at least one AE	209 (43.5)
Gastrointestinal disorders	**20.6**
Diarrhea	6.0
Nausea	4.6
Abdominal pain upper	2.5
Vomiting	2.5
Infections and infestations	**11.9**
Nervous system disorders	**10.6**
Headache	5.0
Dysgeusia	2.9

Oravig is contraindicated in patients with allergies to miconazole and milk protein concentrate. Hypersensitivity reactions characterized by rash or pruritis have been reported.

Discontinuation of ORAVIG due to adverse drug reactions occurred in 0.6% overall.

Concomitant administration of miconazole and warfarin has resulted in enhancement of anticoagulant effect, and cases of bleeding and bruising have been reported. When the two are administered together, anticoagulation tests is warranted as well as monitoring for evidence of bleeding.

Miconazole is a known inhibitor of CYP2C9 and CYP3A4, and although systemic absorption is low, drug interactions cannot be ruled out.

4 CONSULTATIVE REVIEWS

4.1 Compliance

Inspections of manufacturing sites were found acceptable as noted in the CMC review dated March 23, 2010.

4.2 Division of Scientific Investigations (DSI)

Study sites in South Africa, Tunisia, and Morocco were inspected and Dr. Thompson of DSI concluded that the study data can be used to support the indication in this application.

4.3 OSE/Division of Medication Error and Prevention Analysis (DMEPA)

DMEPA found the proposed trade name of Oravig acceptable in the letter issued November 10, 2009 by Dr Carol Holquist. The labeling recommendations were incorporated into final labeling.

4.4 OSE/Division of Pharmacovigilence II (DPVII)

During the preapproval safety conference, it was noted that no particular safety issues had been identified with this product.

4.5 OSE/Division of Drug Risk Evaluation (DRISK)

The patient package insert recommendations were incorporated in labeling.

4.6 Division of Drug Marketing, Advertising and Communication (DDMAC)

Labeling recommendations were addressed and incorporated.

4.7 Pediatric and Maternal Health Staff

The applicant requested waiver in younger patients and deferral of studies in older children. The proposal was discussed before the Pediatric Review Committee (PeRC) on March 17, 2010. The recommendation was that studies should be waived in patients under 5 years of age due to choking hazard, and studies should be deferred in older children given the application is ready for approval. The plan is to extrapolate efficacy

and safety from adult patients, and start by evaluating adolescents for ability to comply with dosing instructions. Subsequently, younger age groups (8-11 years, 6-7 years) can be evaluated. The company may submit a study plan as well as a Proposed Pediatric Study Request (PPSR) for a Pediatric Written Request.

In the meantime, the Pediatric Use section of labeling will state that safety and effectiveness of ORAVIG in pediatric patients below the age of 16 years have not been established. The ability of pediatric patients to comply with the application instructions has not been evaluated. Use in younger children is not recommended due to potential risk of choking. The approval letter will summarize the waiver of studies in children under 5 years and deferral of the studies in older children until December 2013, and final study report until March 31, 2014.

4.8 Study Endpoints and Labeling Development team (SEALD)

Labeling recommendations were incorporated.

5. CONCLUSIONS

The applicant has submitted two adequate and well controlled clinical trials showing that miconazole buccal tablet used daily for 14 days is safe and effective in the treatment of oropharyngeal candidiasis. Labeling has been reviewed and is acceptable. All inspections have been completed and are acceptable. This is a 505(b)(2) application that relies in part on pharmacology and toxicology information from previous applications and the published literature. After discussion with OND and the Office of Chief Counsel, it was determined that the appropriate NDAs had been cited. There are no outstanding issues. An approval letter will be issued.

End of document

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/

RENATA ALBRECHT
04/16/2010