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APPLICATION NUMBER:

205223Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 12, 2014
From	Thomas Smith, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205223
Applicant	Valeant Pharmaceuticals North America LLC
Date of Submission	May 24, 2013
PDUFA Goal Date	March 24, 2014
Proprietary Name / Established (USAN) names	Metronidazole Vaginal Gel, 1.3%
Dosage forms / Strength	Vaginal gel, 1.3%
Proposed Indication	Treatment of bacterial vaginosis in nonpregnant women
Recommended:	Approval

1. Introduction

NDA 205223 was submitted by Valeant Pharmaceuticals North America on May 24, 2013, for the use of metronidazole vaginal gel, 1.3%, as a single-dose treatment for bacterial vaginosis (BV) in nonpregnant women. The clinical program, conducted under IND 107484, included one phase 1 study, one phase 2 study, and one phase 3 study. Metronidazole vaginal gel, 0.75%, is currently approved for the treatment of bacterial vaginosis at a dose of one applicator (approximately 5 g, containing approximately 37.5 mg metronidazole) once or twice daily for 5 days (Metrogel - Vaginal) or once daily for 5 days (Vandazole). The Metrogel - Vaginal product is also owned by Valeant.

This review will summarize the findings of the review team and highlight notable issues.

2. Background

Bacterial vaginosis is a clinical syndrome characterized by alteration of the normal vaginal microbial environment, with replacement of *Lactobacillus* species with high concentrations of anaerobic bacteria (e.g., *Prevotella* spp. and *Mobiluncus* spp.), *Gardnerella vaginalis*, and genital mycoplasmas. Signs and symptoms include abnormal vaginal discharge with a fishy odor, but most women with BV are asymptomatic. In addition to metronidazole vaginal gel, FDA-approved treatments include metronidazole extended release tablets, 750 mg qd for 7 days; clindamycin phosphate vaginal cream, 2%, administered as a single dose of approximately 100 mg clindamycin (or for 3 or 7 days); clindamycin vaginal suppositories, one 100 mg suppository qd for 3 days; and tinidazole tablets, 2 g qd for 2 d or 1 g qd for 5 d.

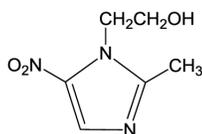
IND 107,484 was submitted by Graceway Pharmaceuticals in December, 2009. At the end-of-phase 2 meeting in August, 2010, the Division of Special Pathogens and Transplant Products (DSPTP) recommended that a placebo-controlled phase 3 trial be performed and stated that in view of the known safety and efficacy of the approved metronidazole 0.75% formulation, a single phase 3 study could potentially support approval of the 1.3% formulation. The phase 3

protocol was submitted for special protocol assessment. The Division of Anti-Infective Products (DAIP), which assumed responsibility for this IND following reorganization of the Office of Antimicrobial Products, issued a non-agreement letter because of a change in the recommendation for primary endpoint assessment. The applicant submitted a revised protocol which incorporated the division's recommendations; special protocol assessment was not requested. In December, 2011, the IND was transferred to Medicis Pharmaceutical, which was acquired by Valeant Pharmaceuticals in December, 2012.

3. CMC/Device

The CMC reviewer was Lin Qi, Ph.D., and the product quality microbiology reviewer was Bryan Riley, Ph.D. Their findings are summarized below.

Metronidazole (chemical name: 2-methyl-5-nitroimidazole-1-ethanol; 2-(5-nitro-2-methylimidazol-yl) ethanol) is a white to pale yellow crystalline powder that is sparingly soluble in water and in alcohol. It has the molecular formula $C_6H_9N_3O_3$ with a molecular weight of 171.2 and the following structural formula:



The drug master file for the drug substance, DMF (b) (4) held by (b) (4) was referenced for CMC information and was found to be adequate to support this NDA. Metronidazole is tested for acceptance at DPT Laboratories, Ltd., San Antonio, TX. All tests, except description, are according to the current USP monograph. Acceptance specifications include tests for description, identification, loss on drying, residue on ignition, heavy metals, impurities, assay, and residual solvents, and are considered acceptable.

The drug product, metronidazole vaginal gel, 1.3%, is an aqueous gel containing metronidazole at a concentration of 13 mg/g. The gel also contains benzyl alcohol, methylparaben, polycarbophil, polyethylene glycol 400, propylene glycol, propylparaben, and purified water. It will be available in cartons containing one single-dose, prefilled disposable applicator delivering 5 g of vaginal gel containing approximately 65 mg of metronidazole. The drug product specifications include tests for description, identification, pH, minimum fill, package integrity, viscosity, assay, impurities, and microbial enumeration, and are acceptable. The drug substance is stable within the drug product, and the recommended expiry period for the drug product is 36 months when stored under USP controlled room temperature conditions of 20° C to 25° C, with allowed excursions between 15° C to 30° C.

All facilities inspections have been completed, and the Office of Compliance has determined these facilities to be acceptable.

Dr. Qi concluded that the CMC information is sufficient to assure the identity, strength, purity, and quality of metronidazole vaginal gel, 1.3%, and recommended approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

Owen McMaster, Ph.D., was the pharmacology/toxicology reviewer for this application. Dr. McMaster's findings and recommendations are summarized below.

This NDA is supported by nonclinical pharmacology and toxicology studies conducted under NDA 20208 for metronidazole vaginal gel, 0.75%. Valeant Pharmaceuticals acquired Medicis Pharmaceutical, the holder of NDA 20208, in 2012.

A 10-day vaginal irritation study was performed in rabbits with the 1.3% metronidazole formulation. Treated rabbits had mild vaginal irritation similar to that observed with vehicle or the marketed 0.75% metronidazole gel after 10 days.

Metronidazole has shown mutagenic activity in the Ames assay. It has shown evidence of carcinogenic activity following chronic oral administration in mice and rats. Pulmonary tumors and malignant lymphoma were reported in mouse studies, and mammary tumors and hepatic adenomas and carcinomas were reported in rats. Metronidazole vaginal gel could have direct effects on vaginal tissues. Carcinogenicity studies have not been conducted with metronidazole vaginal gel, 1.3%.

Following oral administration of metronidazole in women, concentrations in breast milk are similar to those in plasma. Some systemic absorption occurs following vaginal administration of metronidazole, so excretion in human milk is possible. Nursing mothers should be advised that they may consider discontinuing breast milk feeding or pump and discard milk for 24 hours after treatment.

Dr. McMaster concluded that there were no nonclinical pharmacology or toxicology data that would preclude approval of metronidazole vaginal gel, 1.3%.

5. Clinical Pharmacology/Biopharmaceutics

Zhixia Yan, Ph.D., was the clinical pharmacology reviewer for this application. Dr. Yan's findings and recommendations are summarized below.

Metronidazole vaginal gel, 1.3%, will be supplied in a single-dose applicator that delivers 5 g of vaginal gel containing approximately 65 mg of metronidazole. Following a single intravaginal dose of 5 g of 1.3% metronidazole gel to 20 healthy female subjects, the mean maximum concentration (C_{max}) of metronidazole was 239 ng/mL. The average time to achieve C_{max} was 7.3 hours (range, 4 to 18 hours), and the average half-life was 9.65 hours. The extent of exposure (area under the curve, $AUC_{0-\infty}$) was 5434 ng·hr/mL. The C_{max} and the $AUC_{0-\infty}$ are approximately 2% and 4%, respectively, of the C_{max} and $AUC_{0-\infty}$ in healthy subjects administered a single oral 500 mg dose of metronidazole tablets (mean C_{max} , 12,785 ng/mL; mean $AUC_{0-\infty}$, approximately 125,000 ng·hr/mL). These values are similar to those observed with a 5 g intravaginal dose (approximately 37.5 mg) of the marketed metronidazole vaginal gel, 0.75%.

Dr. Yan concluded that this NDA was acceptable from a clinical pharmacology perspective.

6. Clinical Microbiology

Lynette Berkeley, Ph.D., was the clinical microbiology reviewer for this application. Dr. Berkeley's findings are summarized below.

This NDA is supported by microbiology studies conducted under NDA 20208 for metronidazole vaginal gel, 0.75%.

Metronidazole acts primarily against anaerobic bacteria and selected protozoa. Anaerobes reduce the 5-nitro group on the metronidazole molecule to its active state after the drug diffuses into the bacterial cell, producing cytotoxic compounds that disrupt the helical structure of bacterial DNA. Inhibition of bacterial DNA synthesis leads to cell death. Topical antimicrobials administered vaginally achieve local concentrations far above common minimal inhibitory concentrations. Metronidazole is active *in vitro* against the following organisms that have been reported to be associated with BV: *Bacteroides* spp., *G. vaginalis*, *Mobiluncus* spp., and *Peptostreptococcus* spp.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of BV. The Nugent scoring system uses Gram stain criteria to evaluate the relative concentration of lactobacilli, *Gardnerella* and *Bacteroides* spp. morphotypes, and curved Gram-variable rods characteristic of BV. Total scores range from 0 to 10: 0 to 3 is considered normal, 4 to 6 is intermediate, and 7 or more is consistent with BV.

Dr. Berkeley concluded that metronidazole vaginal gel, 1.3%, was more effective than vehicle gel for the primary endpoint of clinical cure at Day 21 and for the secondary endpoints of clinical cure at Day 7 and bacteriologic cure at Days 7 and 21. The trial is presented in more detail in the next section.

7. Clinical/Statistical- Efficacy

Hala Shamsuddin, MD, was the clinical reviewer, and Cheryl Dixon, PhD, was the statistical reviewer for this submission. At the end-of-phase 2 meeting in August, 2010, DSPTP recommended that a placebo-controlled phase 3 trial be performed and stated that in view of the known safety and efficacy of the approved metronidazole 0.75% formulation, a single phase 3 study could potentially support approval of the 1.3% formulation. The phase 3 protocol was submitted for special protocol assessment. DAIP issued a non-agreement letter because of a change in the recommendation for primary endpoint assessment. A revised protocol was submitted which incorporated the Division's recommendations; special protocol assessment was not requested. Valeant submitted reports of one phase 2 trial, Study GW05-904, and one phase 3 trial, Study MP-1601-01, to support this NDA.

Study GW05-904

The phase 2 trial was a multicenter, randomized, investigator-blind dose ranging trial that compared three dosing regimens of metronidazole vaginal gel, 1.3%, with the approved regimen of metronidazole vaginal gel, 0.75%, in the treatment of BV. Nonpregnant women 18 years and above with a clinical diagnosis of BV were randomized 1:1:1:1 to receive metronidazole vaginal gel, 1.3%, administered once daily for 1, 3, or 5 days or metronidazole vaginal gel, 0.75%, administered once daily for 5 days. The diagnosis of BV required the presence of all four Amsel criteria: off-white, thin, homogeneous vaginal discharge; presence of clue cells in $\geq 20\%$ of the total epithelial cells on microscopic examination of a saline wet mount; vaginal fluid pH ≥ 4.7 ; and a positive 10% KOH “whiff test.” A vaginal fluid specimen for Gram stain for Nugent scoring was also obtained at enrollment. The primary endpoint was therapeutic cure, defined as clinical cure and bacteriologic cure at the test of cure (TOC) visit at study day 21-30. Clinical cure was defined as resolution of the Amsel criteria present at enrollment. Bacteriologic cure was defined as a Nugent score < 4 . The intent-to-treat (ITT) population included all randomized patients. The modified ITT (MITT) population included all randomized patients who received study medication, returned for at least one post-baseline assessment, had a Nugent score ≥ 4 at enrollment, and had negative tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* at enrollment. The per protocol (PP) population included all patients in the MITT population who satisfied all inclusion and exclusion criteria, had no protocol violations, started study medication within 2 days of randomization, were compliant with study medication, had no antimicrobial drug use during the study period (other than allowed by protocol), used no intravaginal products during the study period, and had a TOC Nugent score result. The PP population was the primary analysis population.

Total enrollment was 255 patients. Table 1 shows cure rates in the PP population.

Table 1. Study GW-05-0904: Cure Rates at TOC Visit (Per Protocol)

	1.3% 1 day (n = 43)	1.3% 3 days (n = 48)	1.3% 5 days (n = 49)	0.75% 5 days (n = 49)
Therapeutic cure	13 (30.2)	12 (25.0)	16 (32.7)	10 (20.4)
Clinical cure	16 (37.2)	17 (35.4)	22 (44.9)	14 (28.6)
Bacteriologic cure	13 (30.2)	17 (35.4)	23 (46.9)	15 (30.6)

Adapted from GW-05-0904 study report, Table 11-4

No formal statistical testing was performed. Dr. Dixon stated that no treatment comparisons were statistically significant in an exploratory analysis. According to the applicant, the single-dose regimen appeared to have the highest patient acceptability and was therefore selected for the phase 3 trial.

Study MP-1601-01

The phase 3 trial was a multicenter, randomized, double-blind, vehicle-controlled trial. Nonpregnant women 18 years and above with a clinical diagnosis of BV were randomized 1:1 to receive a single dose of metronidazole vaginal gel, 1.3%, or vehicle gel. The diagnosis of BV required the presence of all four Amsel criteria. A vaginal fluid specimen for Gram stain for Nugent scoring was also obtained at enrollment. Patients returned for follow-up on study

day 7. The primary endpoint was clinical cure at the TOC visit on study day 21-30. Clinical cure was defined as return of normal physiologic discharge as confirmed by the investigator, negative 10% KOH “whiff test,” and presence of clue cells in <20% of the total epithelial cells on microscopic examination of a saline wet mount. Bacteriologic cure was defined as a Nugent score <4. Therapeutic cure was defined as clinical cure and bacteriologic cure. The safety population included all randomized patients who applied any amount of study drug. The MITT population included all randomized patients who had a Nugent score ≥ 4 at enrollment and had negative tests for *C. trachomatis* and *N. gonorrhoeae* at enrollment. The PP population included all patients in the MITT population who satisfied all inclusion and exclusion criteria, had no protocol violations, started study drug within 2 days of randomization, were compliant with study drug, had no antimicrobial drug use during the study period (other than allowed by protocol), used no intravaginal products during the study period, and had a TOC Nugent score result.

There was one protocol amendment. (b) (4)

[Redacted]

To eliminate confusion and improve the accuracy of this outcome determination, the case report form was modified to assess vaginal discharge with the question, “Has the original discharge characteristic of bacterial vaginosis returned to a normal physiologic discharge?” A primary MITT (PMITT) population was added and defined as the subset of MITT patients who were evaluated at study day 21 using the modified assessment question. The PMITT population was defined as the primary analysis population, and the total sample size of the trial was revised accordingly. For secondary analyses, the day 7 population was defined as the subset of the PMITT population that was evaluated using the modified assessment question.

There were 651 patients randomized: 325 to metronidazole vaginal gel and 326 to vehicle gel. The median age of the patients in the PMITT population was 32 years, and the median Nugent score was 8. Vaginal itching, irritation, and inflammation were absent in most patients and, when present, were usually mild. Table 2 shows cure rates at the TOC visit. Cure rates were statistically significantly greater in patients treated with metronidazole gel than in patients treated with vehicle gel.

Table 2. Study MP-1601-01: Clinical Cure Rates at TOC Visit

Analysis population	Metronidazole gel	Vehicle gel	Difference (95% CI)	p-value
	1.3% n/N (%)	n/N (%)		
PMITT	93/250 (37.2)	63/237 (26.6)	10.6 (2.4, 18.8)	0.010
MITT	108/292 (37.0)	76/285 (26.7)	10.3 (2.8, 17.9)	0.007
PP	87/214 (40.7)	61/204 (29.9)	10.8 (1.7, 19.9)	0.007

Adapted from statistical review

Table 3 shows results for secondary endpoint analyses. In all analyses, success rates were statistically significantly greater in patients treated with metronidazole gel than in patients treated with vehicle gel.

Table 3. Study MP-1601-01: Secondary Endpoint Analyses

	Metronidazole gel 1.3%	Vehicle gel	Difference (95% CI)	p-value
	n/N (%)	n/N (%)		
TOC visit				
Bacteriologic cure				
PMITT	47/250 (18.8)	19/237 (8.0)	10.8 (4.8, 16.7)	<0.001
MITT	57/292 (19.5)	22/285 (7.7)	11.8 (6.3, 17.3)	<0.001
PP	44/214 (20.6)	14/204 (6.9)	13.7 (7.0, 20.4)	<0.001
Therapeutic cure				
PMITT	42/250 (16.8)	17/237 (7.2)	9.6 (3.9, 15.3)	0.001
MITT	49/292 (16.8)	18/285 (6.3)	10.5 (5.3, 15.6)	<0.001
PP	39/214 (18.2)	15/204 (7.4)	10.8 (4.7, 16.9)	<0.001
Day 7 visit				
Clinical cure				
Day 7 population	93/202 (46.0)	41/205 (20.0)	26.0 (17.3, 34.8)	<0.001
MITT	120/292 (41.1)	57/285 (20.0)	21.1 (13.8, 28.4)	<0.001
Bacteriologic cure				
Day 7 population	66/202 (32.7)	13/205 (6.3)	26.3 (19.1, 33.6)	<0.001
MITT	99/292 (33.9)	18/285 (6.3)	27.6 (21.5, 33.7)	<0.001

Adapted from clinical and statistical reviews

Comment: For comparison purposes, the Clinical Studies section of the currently approved Metrogel-Vaginal (metronidazole vaginal gel, 0.75%) label states that clinical cure rates for evaluable patients 4 weeks after completion of therapy were 98/185 (53%) for the qd regimen and 109/190 (57%) for the bid regimen; treatment was for 5 days. The Clinical Studies section of the Vandazole (metronidazole vaginal gel, 0.75%) label provides results from an active-control trial which had Metrogel-Vaginal as the comparator; treatments were administered qd for 5 days. The primary endpoint was therapeutic cure in the MITT population (defined as patients who received study medication and had a Nugent score of ≥ 4) at the test of cure visit on study day 22-31. For 229 patients receiving Vandazole, the therapeutic cure rate was 42.8%, the clinical cure rate was 52.4%, and the Nugent score cure rate was 52.0%; for 243 patients receiving Metrogel, the respective cure rates were 30.9%, 45.3%, and 41.1%.

The Clinical Studies section of the label for Clindesse (clindamycin vaginal cream, 2%) describes a placebo-controlled trial of 144 patients with BV. Clindamycin vaginal cream was administered as a single dose. The primary endpoint was therapeutic cure in the MITT population (defined as patients who received study medication and had a Nugent score of ≥ 4) at the test of cure visit on study day 21-30. For 78 patients receiving Clindesse, the therapeutic cure rate was 29.5%, the clinical cure rate was 41.0%, and the Nugent score cure rate was 44.9%; for 66 patients receiving placebo, the respective cure rates were 3.0%, 19.7%, and 6.1%.

Study MP-1601-01 demonstrated that metronidazole vaginal gel, 1.3%, administered as a single dose is superior to vehicle gel in the treatment of BV. The clinical and statistical reviewers concluded that metronidazole vaginal gel, 1.3%, is effective in the treatment of BV.

8. Safety

Hala Shamsuddin, MD, reviewed the safety data for this submission. The trials summarized in the Clinical/Statistical – Efficacy section above included 510 patients who received at least one dose of metronidazole vaginal gel, 1.3%: 321 in Study MP-1601-01 and 189 in Study GW-05-0904.

There were no deaths and one serious adverse event that was considered unrelated to study therapy: hypoglycemia that developed in an insulin-dependent diabetic patient one week following treatment.

Adverse events that occurred more frequently in patients treated with metronidazole vaginal gel, 1.3%, than in vehicle gel recipients included vulvovaginal candidiasis, headache, and dysmenorrhea.

The safety profile of metronidazole vaginal gel, 1.3%, is similar to that of the other topical metronidazole products for BV.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Valeant requested a partial waiver of studies in premenarcheal pediatric patients. The initial NDA submission (b) (4) (b) (4). Valeant submitted a plan to evaluate the safety and tolerability of metronidazole vaginal gel, 1.3%, in approximately 48 adolescent patients with BV. The pediatric plan was discussed with the Pediatric Review Committee (PeRC) on December 4, 2013. PeRC modified the partial waiver subpopulation to females less than 12 years of age and agreed with the plan for partial deferral of study in female patients 12 years to less than 18 years of age.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

The labeling for metronidazole vaginal gel, 1.3%, will be similar to that of Vandazole (metronidazole vaginal gel, 0.75%), with the major exception of the Pediatric Use section, which will state that safety and efficacy in pediatric patients below the age of 18 have not been established.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the recommendation of the review team that metronidazole vaginal gel, 1.3%, be approved for the treatment of BV.

- Risk Benefit Assessment

The benefits of therapy of BV with metronidazole vaginal gel, 1.3%, outweigh the risks. Metronidazole vaginal gel, 1.3%, administered as a single dose is superior to vehicle gel in the treatment of BV. Although the clinical cure rate is unimpressive, it is in the same range as the cure rates for other topical products for BV. The adverse event profile is similar to that of the other topical metronidazole products for BV, and this product offers the advantage of single-dose therapy.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Routine postmarketing safety monitoring is sufficient.

- Recommendation for Other Postmarketing Requirements and Commitments

The following PREA requirement is recommended:

2123-001 A study to evaluate the safety of metronidazole gel 1.3% single dose in the treatment of bacterial vaginosis in females 12 to less than 18 years of age

The timetable the applicant submitted on February 6, 2014, states that they will conduct this study according to the following schedule:

Final Protocol Submission:	August, 2014
Study Completion:	December, 2015
Final Report Submission:	June, 2016

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/s/

THOMAS D SMITH
02/12/2014