CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205223Orig1s000

SUMMARY REVIEW

Deputy Division Director Decisional Memo

Date	(electronic stamp)
From	Katherine Laessig, MD
Subject	Deputy Division Director Decisional Memo
NDA #	205-223
Applicant Name	Valeant Pharmaceuticals North America LLC
Date of Submission	May 24, 2013
PDUFA Goal Date	March 24, 2014
Established (USAN) Name	Metronidazole Vaginal Gel 1.3%
Dosage Forms / Strength	Vaginal Gel
Approved Indications	Treatment of bacterial vaginosis in nonpregnant women
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package including:	**Names of discipline reviewers**
Medical Officer Review	Hala Shamsuddin
Statistical Review	Cheryl Dixon
Pharmacology Toxicology Review	Owen McMaster
Chemistry, Manufacturing, and Controls Review	Lin Qi
Product Quality Reviews	Bryan Riley
Microbiology Review	Lynette Berkeley
Clinical Pharmacology Reviews	Seong Jang
CDTL Review	Thomas Smith
Labeling Reviews	Aleksander Winiarski, Christine Corser, Sharon Williams

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

1.0 Background

Valeant has submitted NDA 205-223 in support of a new formulation of metronidazole vaginal gel, 1.3%, in a pre-filled applicator that delivers approximately 5 g of gel containing 65 mg of metronidazole. The proposed indication is the treatment of bacterial vaginosis (BV) in nonpregnant women. The proposed dose and route of administration is a single dose administered once intravaginally at bedtime. The clinical program included one phase 1 study, one phase 2 study, and one phase 3 study. Metronidazole vaginal gel, 0.75%, (MetroGel-Vaginal, also owned by Valeant) is currently approved for the treatment of BV at a dose of one applicator (approximately 5 g, containing approximately 37.5 mg metronidazole) once or twice

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daily for five days. Vandazole (0.75% metronidazole vaginal cream), clindamycin 2% vaginal cream, and extended release oral metronidazole and oral tinidazole are also FDA approved for the treatment of BV. While other formulations of metronidazole are not FDA-approved for the treatment of BV, they are CDC-recommended as first line treatment.

This memo will summarize important findings and conclusions by review discipline. For further details, please refer to the discipline specific reviews and the CDTL memo by Thomas Smith, MD.

2.0 Product Quality

The adequacy of the chemistry, manufacturing, and control information contained in this application has been reviewed by the product quality reviewer, Lin Qi, and the product quality microbiology reviewer, Bryan Riley. They have concluded that the CMC information is sufficient to assure the identity, strength, purity, and quality of the drug product and that the microbiological quality is controlled by a suitable testing protocol and therefore have recommended approval. The Office of Compliance has made a final recommendation of acceptable for the manufacturing facilities filed in this NDA on February 4, 2014.

The drug substance is a (b) (4) and is manufactured, controlled, and tested at (b) (4), while a DMF (b) (4) is referenced for detailed chemistry, manufacturing, and controls information. The DMF was found to be adequate to support the current NDA from a review dated January 30, 2014.

The drug product is an aqueous, slightly opaque, yellow gel supplied in 5 g pre-filled applicators. The product is formulated at a pH of 4 to be compatible with the pH of the vaginal fluid. The gel formulation contains 1.3% w/w of metronidazole (b) (4) in a gel (b) (4) containing Polyethylene Glycol 400, Propylene Glycol, Benzyl Alcohol, Methylparaben, Propylparaben, Purified Water, and Polycarbophil. All excipients are compendial grade and within levels used in other approved vaginal drug products. There were no significant drug product changes in description, assays, impurities, package integrity, pH, weight loss, and viscosity observed in the three registration lots through 36 months under longterm storage at 25ºC/65% RH and 6 months storage at 40ºC/75% RH. The available stability data support the proposed expiry period of 36 months when stored under USP controlled room temperature conditions of 20ºC to 25ºC (68ºF to 77ºF) with allowed excursions between 15ºC to 30ºC.

3.0 Pharmacology/Toxicology

The nonclinical reviewer, Owen McMaster, found no nonclinical pharmacology or toxicology issues that preclude approval of metronidazole vaginal gel, 1.3%. The NDA is largely supported by the nonclinical pharmacology and toxicology information for NDA 20-208 for Metrogel-Vaginal 0.75% which was approved in August 1992. The applicant for NDA 20-208 was

Medicis Pharmaceutical Corporation, which was acquired by Valeant in 2012.

The current formulation was evaluated in an intravaginal study in rabbits, titled "Metronidazole Gel: 10 Day Vaginal Irritation Study in Rabbits." After 10 days, treated rabbits showed mild vaginal irritation, but this was similar to that seen with vehicle or with the marketed Metrogel-Vaginal 0.75% product.

There are no impurity concerns with the components of metronidazole vaginal gel 1.3% as they are all either USP or National Formulary.

The prescribing information describes safety issues specific to metronidazole products including mutagenicity, carcinogenicity, and distribution to breast milk.

4.0 Clinical Microbiology

The clinical microbiology reviewer, Lynette Berkeley, concludes that the efficacy of the metronidazole 1.3% gel has been demonstrated by the results of the phase 2 (GW05-0904) and phase 3 (MP-1601-01) studies, and recommends approval. Metronidazole has activity against obligate anaerobic bacteria and select protozoa. The selectivity of metronidazole in an un-ionized state for anaerobic bacteria results from the ability of these bacteria to reduce the nitro group on the metronidazole molecule to its active state by the bacterial nitro-reductase enzyme located in the cytoplasm. This results in the production of cytotoxic compounds that disrupt the helical structure of the bacterial DNA, thereby inhibiting bacterial nucleic acid synthesis, which results in cell death. From the phase 2 study results, Dr. Berkeley noted that the cure rate of a single dose of metronidazole vaginal gel 1.3% was higher than that observed for MetroGel-Vaginal 0.75% for five days. However, the bacteriological cure rate was lower with the 1.3% gel compared to the 0.75% gel. In the phase 3 study, subjects treated with the 1.3 % gel had a statistically significantly higher rate of clinical cure at Day 21 compared to those receiving the vehicle gel. Clinical cure was defined as return of normal physiological vaginal discharge as confirmed by the investigator, negative 10% KOH whiff test, and clue cells <20% of the total epithelial cells in a saline wet mount. These trials will be discussed in greater detail in the clinical efficacy section below.

5.0 Clinical Pharmacology

The clinical pharmacology reviewer, Zhixia (Grace) Yan, finds that from a clinical pharmacology perspective, the data provided are acceptable to recommend approval. A phase 1, single-dose pharmacokinetic (PK) study of metronidazole 1.3% vaginal gel was conducted in healthy, non-pregnant women between the ages of 18 and 40 years (MP-1601-02). Following a single intravaginal application of the 1.3% gel to 20 healthy women, the mean C_{max} of metronidazole was 239 ng/mL (range of 114 to 428 ng/mL). The mean $AUC_{0-\infty}$ was 5434 ng•h/mL (range of 1382 to 12744 ng•h/mL). The average T_{max} was 7.3 hours (range of 3.9 to 18

hours) with an average half-life of 9.65 hours. These results are comparable to the marketed product, MetroGel-Vaginal 0.75%. In addition, the C_{max} and AUC following a single application of the 1.3% gel is approximately 2% and 4%, respectively, of those reported in healthy subjects administered a single oral dose of 500 mg of metronidazole.

6.0 Clinical Efficacy

The statistical reviewer, Cheryl Dixon, medical officer, Hala Shamsuddin, and CDTL, Thomas Smith, have all concluded that the applicant has provided substantial evidence for the efficacy of metronidazole 1.3% vaginal gel for the treatment of BV.

Primary support for the efficacy of metronidazole 1.3% gel is provided by the phase 3 trial, MP-1601-01. This trial was a randomized, multicenter, double-blind study to evaluate the safety and efficacy of a single intravaginal dose of metronidazole 1.3% gel compared to a single dose of vehicle gel in treating women with BV. Supportive evidence comes from the phase 2 dose-ranging study, GW05-0904. GW05-0904 evaluated the safety and efficacy of metronidazole vaginal gel 1.3% administered once daily for one, three, or five days compared with MetroGel-Vaginal 0.75% administered once daily for five days.

MP-1601-01 was conducted at 37 centers in the U.S. and enrolled 651 subjects with a diagnosis of BV, randomized 1:1 to metronidazole 1.3% vaginal gel or vehicle gel. A clinical diagnosis of BV was defined as presence of off-white, thin, homogeneous discharge, presence of clue cells of $\geq$ 20%, vaginal pH $\geq$ 4.7, and a positive KOH whiff test. Subjects were to have a Nugent score of $\geq$ 4. However, the results of Gram stain were not known at the time of screening. Additionally, subjects with a known or suspected other cause of vulvovaginitis were to be excluded. Treatment was to be applied intravaginally at bedtime on Day 0. Subjects returned to clinic on Day 7 to assess initial therapeutic response. The test-of-cure (TOC) visit was conducted at Day 21. The primary endpoint was clinical cure at TOC, defined as return of normal physiological vaginal discharge as confirmed by the investigator, negative 10% KOH whiff test, and clue cells <20% of the total epithelial cells in a saline wet mount. Bacteriologic cure was defined as Nugent score < 4. Therapeutic cure was defined as a clinical and bacteriologic cure. The primary analysis population was the primary modified intent-to-treat (PMITT). Note that the PMITT population was a change from the originally specified primary analysis population (and a protocol amendment) due to confusion regarding capture of ”presence” or “absence” of discharge on the CRFs. Some investigators were recording normal physiologic discharge as “present”. Therefore, the CRF was modified to ask “has the original discharge characteristic of bacterial vaginosis returned to a normal physiologic discharge?” For the PMITT population, significantly more metronidazole gel 1.3% subjects experienced at clinical cure at TOC compared to vehicle gel subjects (93/250 vs. 63/237, p-value 0.010). The results for the per protocol (PP) and microbiological intent to treat populations (MITT) were similar to those for the PMITT. Eighteen percent of subjects in the PMITT population treated

with the metronidazole 1.3% vaginal gel had a bacteriologic cure at TOC compared to eight percent of the vehicle treated subjects (p-value <0.001), while 16.8% of metronidazole 1.3% gel treated subjects had a therapeutic cure at TOC compared to 7.2% of the vehicle gel treated subjects (p-value < 0.001).

Study GW05-0904 was a phase 2, multicenter, randomized, investigator-blind, dose-ranging efficacy and safety study of metronidazole 1.3% vaginal gel (qd x 1d, qd x 3d, and qd x 5d) compared to five days of daily metronidazole vaginal gel 0.75%. The study was conducted at 20 centers in the U.S. and enrolled 255 women with a clinical diagnosis of BV who were randomized 1:1:1:1. Treatment was to be applied vaginally at bedtime. The primary efficacy endpoint was therapeutic cure at TOC (Day 21-30). Therapeutic cure required both clinical and bacteriologic cure. No formal statistical testing was performed to compare treatment groups. Sample size was based on providing a precise estimate of therapeutic cure. Assuming a therapeutic cure rate of 51.6%, a sample of 45 subjects would provide an estimate of therapeutic cure with a 95% confidence interval width of 15%.

Therapeutic and clinical cure rates were numerically higher for all the metronidazole 1.3% vaginal gel groups compared to the 0.75% vaginal gel group for both the PP and MITT populations, as shown in Table 1. Bacteriological cure rates were either higher or numerically similar.

Table 1. Summary of Cure Rates at TOC

Analysis Population	Cure	1.3% x 1d n/N (%)	1.3% x 3d n/N (%)	1.3% x 5d n/N (%)	0.75% x 5d n/N (%)
PP	Therapeutic	13/43 (30.2)	12/48 (25.0)	16/49 (32.7)	10/49 (20.4)
	Clinical	16/43 (37.2)	17/48 (35.4)	22/49 (44.9)	14/49 (28.6)
	Bacteriologic	13/43 (30.2)	17/48 (35.4)	23/49 (46.9)	15/49 (30.6)
MITT	Therapeutic	15/59 (25.4)	12/54 (22.2)	17/56 (30.4)	12/59 (20.3)
	Clinical	18/59 (30.5)	17/54 (31.5)	23/56 (41.1)	17/59 (30.6)
	Bacteriologic	18/59 (30.5)	18/54 (33.3)	26/56 (46.4)	18/59 (30.5)

Source: FDA Statistical Review

The results of this phase 2 study are generally consistent with those of the phase 3 study and support the finding of efficacy.

7.0 Clinical Safety

The medical officer, Hala Shamsuddin, concluded that adequate evidence of safety for metronidazole 1.3 % vaginal gel for the treatment of BV has been provided. She reviewed safety results for all BV subjects who received any dose of 1.3% gel. One hundred eighty-nine subjects received at least one dose in the phase 2 study while an additional 321 received a dose in the phase 3 study. Adverse events noted in ≥ 1% of subjects who received any regimen of metronidazole 1.3% vaginal gel included abdominal pain, diarrhea, nausea, vulvovaginal candidiasis (VVC), nasopharyngitis, headache, dysmenorrhea, vulvo-vaginal burning, and vulvo-vaginal pruritus. Adverse events noted more frequently in the 1.3% gel recipients included abdominal pain, headache, VVC, nasopharyngitis, dysmenorrhea, vulvo-vaginal burning and pruritus. In the phase 2 trial, there was one SAE of hypoglycemia and no deaths. In the phase 3 trial, there were no deaths or SAEs.

8.0 Pediatrics

Valeant requested a partial waiver of studies in premenarcheal pediatric patients and the initial NDA proposed (b) (4) Subsequently, Valeant submitted a plan to evaluate the safety and tolerability of metronidazole 1.3% vaginal gel 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 younger 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.

9.0 Other Regulatory Issues

This application was not presented to the Anti-infective Drugs Advisory Committee as there were no issues requiring AC input.

10.0 Recommended Regulatory Action

I concur with the recommendations of the review team that the application should be approved as the applicant has provided substantial evidence of the safety and efficacy of metronidazole 1.3% vaginal gel for the treatment of BV in non-pregnant women. There is one post-marketing PREA requirement to which the applicant has agreed, as follows:

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

Katherine A. Laessig, MD

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/s/

KATHERINE A LAESSIG
03/24/2014