

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205223Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 1 of 14  
Clinical Microbiology Review

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Reviewer: Lynette Y. Berkeley

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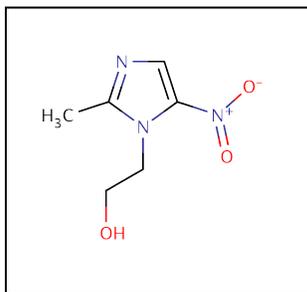
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**DRUG PRODUCT NAME**

Proprietary: Metronidazole Vaginal Gel, 1.3%, Product 55394  
Established: Metronidazole  
Chemical name: 2 – methyl-5-nitroimidazole-1-ethanol

**Chemical Structure**



Molecular formula: C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>  
Molecular weight : 171.16 Da

**PROPOSED INDICATION**

Treatment of bacterial vaginosis in non-pregnant women

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 2 of 14  
Clinical Microbiology Review

**PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION  
AND DURATION OF TREATMENT**

Dosage form: Gel  
Route of Administration: Topical  
Dosage: 5 gm gel (65 mg of metronidazole)  
Strength: 1.3%  
Duration: One day

**DISPENSED**

Rx.

**RELATED DOCUMENTS**

IND 107,484  
NDA 20,208

**REMARKS**

This review is related to a 505 (b) (1) NDA submission. The applicant refers to the IND 107, 484 submission containing a Phase III study of 1.3 % metronidazole and cross references non clinical studies in NDA 20,208 for MetroGel 0.75%. The applicant states that the studies from NDA 20,208 will not be resubmitted for the 1.3% submission.

**EXECUTIVE SUMMARY**

This NDA refers to a (505) (b) (1) submission for MetroGel 1.3% for the treatment of bacterial vaginosis in non-pregnant females. A formulation of MetroGel-Vaginal (0.75 %, once or twice daily for 5 days), was approved in 1992. The applicant makes reference to studies conducted for 0.75% formulation in this NDA submission and also cross references information obtained for NDA 20,208.

Summaries of two studies GW05-0904 Phase 2 and STUDY MP1601-01 the Phase 3 study are presented. The Phase 2 study is a multi-center, randomized investigator-blinded, Phase 2, dose-ranging study of Metronidazole Vaginal Gel in the Treatment of Bacterial Vaginosis. The 255 subjects were randomized (1:1:1:1) in the following arms MetroGel-Vaginal 0.75% QD x 5 days: Metronidazole Vaginal Gel 1.3%, QD x 1 day: Metronidazole Vaginal Gel 1.3% QD x 3 days: or Metronidazole Vaginal Gel 1.3% QD x 5 days. Five grams of study medication was applied intravaginally QD at bedtime according to the assigned dosing schedule.

The cure rate of a single dose of Metronidazole Vaginal Gel 1.3% was higher than that observed for MetroGel-Vaginal 0.75% for 5 days. However, the bacteriological cure rate with a single dose of Metronidazole Vaginal Gel 1.3% was lower than that observed for MetroGel-Vaginal 0.75% for 5 days.

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 3 of 14  
Clinical Microbiology Review

MP-1601-01 was a Phase 3, multi-center, randomized, double-blind, parallel group, vehicle-controlled study conducted at 41 sites to evaluate the safety and efficacy of a single intravaginal dose of Metronidazole Vaginal Gel 1.3% compared with a single intravaginal dose of Vehicle Gel in treating subjects with BV

The primary endpoint was clinical cure at Day 21. At Day 21 the subjects receiving a single dose of intravaginal Metronidazole Vaginal Gel 1.3% had a statistically significantly greater response compared to subjects receiving Vehicle Gel (37.2% and 26.6%, respectively;  $p = 0.010$ ).

In conclusion, this phase 3 study demonstrated that a single dose of Metronidazole Gel 1.3% is effective for the treatment of bacterial vaginosis.

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 4 of 14  
Clinical Microbiology Review

**TABLE OF CONTENTS**

<b>REMARKS</b> .....	2
<b>EXECUTIVE SUMMARY</b> .....	2
<b>1.0 INTRODUCTION</b> .....	5
<b>2.0 NON-CLINICAL INFORMATION</b> .....	5
2.1 ANTIMICROBIAL SPECTRUM OF ACTIVITY .....	5
2.2 MECHANISM(S) OF ACTION.....	5
2.3 MECHANISM(S) OF RESISTANCE.....	6
<b>3.0 CLINICAL STUDIES</b> .....	6
3.1 STUDY GW05-0904.....	6
3.2 STUDY MP1601-01.....	8
<b>4.0 PHARMACODYNAMIC DRUG INTERACTIONS</b> .....	12
4.1 PHARMACOKINETICS .....	12
<b>5.0 PROVISIONAL INTERPRETIVE CRITERIA</b> .....	13
<b>6.0 CORRELATION OF PROVISIONAL INTERPRETIVE CRITERIA WITH CLINICAL OUTCOME</b> .....	13
<b>7.0 LABEL</b> .....	13
7.1 SPONSOR'S VERSION .....	13
7.2 AGENCY VERSION .....	13
<b>8.0 REFERENCES</b> .....	14

# Division of Anti-Infective Products

## Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 5 of 14  
Clinical Microbiology Review

### 1.0 INTRODUCTION

The subject of this IND is a 1.3% concentration of metronidazole formulated as a gel. The drug will be used as treatment for bacterial vaginosis (BV) in non pregnant females and will be administered once intravaginally. MetroGel-Vaginal (0.75 %, once or twice daily for 5 days), was approved in 1992 also for the treatment of bacterial vaginosis. A 1% MetroGel concentration was approved for the topical treatment of inflammatory lesions of rosacea in 1963.

### 2.0 NON-CLINICAL INFORMATION

Nonclinical studies previously conducted to support the clinical use of MetroGel-Vaginal 0.75% (NDA 20,208) are included in microbiology studies to assess efficacy against a number of organisms associated with bacterial vaginosis.

#### 2.1 ANTIMICROBIAL SPECTRUM OF ACTIVITY

Metronidazole is active *in vitro* against many anaerobic bacteria with MIC (mcg/mL)  $\leq 8$  Susceptible (S), 16 Intermediate (I),  $\geq 32$  Resistant (R).

Against parasites the *in vitro* minimal inhibitory concentration (MIC) for most strains of these organisms is 1 mcg/mL or less.

Metronidazole is active against isolates of the following microorganisms:

#### **Bacteria**

Anaerobic gram-negative bacilli, including:

*Bacteroides* species including the *Bacteroides fragilis* group (*B. fragilis*,  
*B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*)  
*Fusobacterium spp.*

Anaerobic gram-positive bacilli, including:

*Clostridium* species and susceptible strains of *Eubacterium spp.*

Anaerobic gram-positive cocci, including:

*Peptococcus niger*  
*Peptostreptococcus spp.*

#### **Protozoal parasites:**

*Entamoeba histolytica*  
*Trichomonas vaginalis*  
*Giardia lamblia*

#### 2.2 MECHANISM(S) OF ACTION

Metronidazole, an imidazole, is an approved antimicrobial agent with activity primarily against selected protozoa and obligate anaerobic bacteria. This low molecular weight molecule diffuses into the bacterial cell. The selectivity of metronidazole in an un-ionized state for anaerobic bacteria results from the ability of these bacteria to reduce the nitro

# Division of Anti-Infective Products

## Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 6 of 14  
Clinical Microbiology Review

group on the metronidazole molecule to its active state by the bacterial nitro-reductase enzyme located in the cytoplasm. This reduction results in the production of cytotoxic compounds that disrupt the helical structure of bacterial DNA thereby inhibiting bacterial nucleic acid synthesis which leads to cell death.

### 2.3 MECHANISM(S) OF RESISTANCE

Resistance of protozoa to metronidazole has not been clearly defined. Bacterial resistance to metronidazole is rare. There is some indication that resistance is related to reduced uptake of the drug and /or a lower level of reduction of the nitro group. Five genes *NimA*, *B*, *C*, *D*, and *E* have been implicated in resistance of strains of *Bacteroides* species to metronidazole. Many non-spore forming gram – positive anaerobic rods are resistant to metronidazole.

Sobel 2009 has shown that topical antimicrobials administered via the vaginal route achieve extremely high local concentrations, far in excess of common minimum inhibitory concentrations.

Studies by Beigi, 2004 and Austin, 2005 have shown that resistance to metronidazole is not significant in intravaginally administered drug. Resistance to metronidazole by anaerobic bacteria is rare and the level is usually low (Rasmussen, 1997). *Atopobium vaginae* is resistant to metronidazole. Gal 2004 reported both intermediate and high level resistance to metronidazole by *Bacteroides spp.* and the facultative anaerobe *Gardnerella vaginalis* which has shown an increased frequency of resistance to this drug.

## 3.0 CLINICAL STUDIES

### 3.1 STUDY GW05-0904

Details of Study GW05-0904 Phase 2 are covered in IND 107,484, SDN 020 dated 02/11/2013. It is a multi-center, randomized investigator-blinded, Phase 2, dose-ranging study of Metronidazole Vaginal Gel in the treatment of bacterial vaginosis (BV).

A total of 255 subjects were randomized and assigned to study treatment. This included approximately 240 otherwise healthy female subjects 18 years or older (average age 35.1 ± 9.93 years) who were clinically diagnosed as having BV by meeting all four of the Amsel criteria (1) off-white (milky or gray), thin, homogeneous discharge; (2) the presence of “clue” cells ≥ 20% of the total epithelial cells on microscopic examination of the saline wet mount; (3) pH of vaginal fluid ≥ 4.7; and (4) a positive 10% potassium hydroxide (KOH) whiff test. The majority of subjects (62.7%) reported no previous episode of BV

Eligible subjects were randomly assigned (1:1:1:1) to one of the following treatment groups: MetroGel-Vaginal 0.75% QD x 5 days: Metronidazole Vaginal Gel 1.3%, QD x 1 day: Metronidazole Vaginal Gel 1.3% QD x 3 days: or Metronidazole Vaginal Gel 1.3% QD x 5 days. Five grams of study medication was applied intravaginally QD at bedtime according to the assigned dosing schedule.

A Test of Cure (TOC) visit was conducted between Day 21 and Day 30. At all visits the investigator performed gynecological examinations and collected vaginal fluid specimens

# Division of Anti-Infective Products

## Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 7 of 14  
Clinical Microbiology Review

for the following tests: saline microscopy ("wet mount") for clue cells, fungal elements, and *T. vaginalis*; 10% KOH amine test ("whiff test"); pH; and Gram stain for Nugent Scoring. Table 1 shows a summary of the population by subject classification and treatment group - the number of subjects in each class were equal across treatment arms.

Table 1: Summary of Subject Populations in GW05-0904

	Metronidazole				Overall (N=255) n (%)
	0.75% QD x 5 Days (N = 66) n (%)	1.3% QD x 1 Day (N = 65) n (%)	1.3% QD x 3 Days (N = 60) n (%)	1.3% QD x 5 Days (N = 64) n (%)	
Randomized subjects	66 (100.0)	65 (100.0)	60 (100.0)	64 (100.0)	255 (100.0)
Safety population <sup>a</sup>	65 (98.5)	65 (100.0)	60 (100.0)	64 (100.0)	254 (99.6)
MITT population	59 (89.4)	59 (90.8)	54 (90.0)	56 (87.5)	228 (89.4)
PP population	49 (74.2)	43 (66.2)	48 (80.0)	49 (76.6)	189 (74.1)

Abbreviation: MITT = Modified Intent-to-Treat; PP = Per Protocol.

a. Includes all randomized subjects who applied any amount of study medication. This may differ from the number of subjects randomized in those cases where the treatment received was not the same as the treatment assigned.

Note: Column percentages calculated using the number of subjects randomized in the treatment group as the denominator.

### Endpoints

The primary efficacy endpoint was the proportion of subjects with therapeutic cure at the test of cure (TOC) / end of study (EOS) visit.

The secondary efficacy criteria of relevance to microbiology were:

- The proportion of subjects with clinical cure at the EOS/TOC visit;
- The proportion of subjects with bacteriological cure at EOS/TOC visit;
- The time to resolution of symptoms (abnormal discharge and odor), defined as the time interval (in days) from randomization to the day indicating resolution of symptoms in the subject's diary;

### Results

Therapeutic cure was the primary efficacy endpoint. The therapeutic cure rate was higher in all Metronidazole Vaginal Gel 1.3% groups in comparison to the MetroGel-Vaginal 0.75% group. In the per-protocol (PP) population, the greatest percentage of therapeutic cure was achieved by subjects in the Metronidazole Vaginal Gel 1.3% x 5 day group. Importantly, the therapeutic cure rate with a single dose of Metronidazole Vaginal Gel 1.3% was greater than that observed for MetroGel-Vaginal 0.75% for 5 days. Table 2 shows these results.

# Division of Anti-Infective Products

## Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 8 of 14  
Clinical Microbiology Review

Table 2: Summary of Therapeutic Cure Rate at Test of Cure/End of Study: Per-Protocol Population - GW05-0904

	Metronidazole			
	0.75% QD x 5 Days (N=49)	1.3% QD x 1 Day (N=43)	1.3% QD x 3 Days (N=48)	1.3% QD x 5 Days (N=49)
Therapeutic cure				
Cured, n (%)	10 (20.4)	13 (30.2)	12 (25.0)	16 (32.7)
Failed, n (%)	39 (79.6)	30 (69.8)	36 (75.0)	33 (67.3)
95% CI for cure rate	(10.2, 34.3)	(17.2, 46.1)	(13.6, 39.6)	(19.9, 47.5)

Abbreviation: CI = confidence interval; QD = once daily

The secondary endpoints of clinical cure and bacteriological cure at TOC also demonstrated that response rates were higher in all Metronidazole Vaginal Gel 1.3% groups in comparison to the MetroGel-Vaginal 0.75% group. Although the cure rate of a single dose of Metronidazole Vaginal Gel 1.3% was higher than that observed for MetroGel-Vaginal 0.75% for 5 days, the bacteriological cure rate with a single dose of Metronidazole Vaginal Gel 1.3% was lower than that observed for MetroGel-Vaginal 0.75% for 5 days (Table 3).

Table 3: Summary of Cure Rates for Secondary Endpoints at Test of Cure/End of Study: Per-Protocol Population – GW05-0904

	Metronidazole			
	0.75% QD x 5 Days (N=49)	1.3% QD x 1 Day (N=43)	1.3% QD x 3 Days (N=48)	1.3% QD x 5 Days (N=49)
Clinical cure				
Cured, n (%)	14 (28.6)	16 (37.2)	17 (35.4)	22 (44.9)
Failed, n (%)	35 (71.4)	27 (62.8)	31 (64.6)	27 (55.1)
95% CI for cure rate	(16.6, 43.3)	(23.0, 53.3)	(22.2, 50.5)	(30.7, 59.8)
Bacteriological cure				
Cured, n (%)	15 (30.6)	13 (30.2)	17 (35.4)	23 (46.9)
Failed, n (%)	34 (69.4)	30 (69.8)	31 (64.6)	26 (53.1)
95% CI for cure rate	(18.3, 45.4)	(17.2, 46.1)	(22.2, 50.5)	(32.5, 61.7)

Abbreviation: CI = confidence interval; OD = once daily

### Conclusion

The objective of this study was to evaluate the efficacy and safety of a new metronidazole formulation in treatment regimens that would enhance compliance and patient acceptability. Results from the study determined the new formulation, Metronidazole Vaginal Gel 1.3% given QD x 1, 3, or 5 days is at least as efficacious as MetroGel-Vaginal 0.75% QD x 5 days

The single dose of Metronidazole Vaginal Gel 1.3% dose provided only slightly lower bacteriological cure rate than MetroGel-Vaginal 0.75% daily for 5 days.

### 3.2 STUDY MP1601-01

MP-1601-01 was a Phase 3, multi-center, randomized, double-blind, parallel group, vehicle-controlled study conducted at 41 sites to evaluate the safety and efficacy of a single

## Division of Anti-Infective Products Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 9 of 14  
Clinical Microbiology Review

intravaginal dose of Metronidazole Vaginal Gel 1.3% compared with a single intravaginal dose of Vehicle Gel in treating subjects with BV.

The study population included 650 healthy females 18 years or older who had a clinical diagnosis of BV meeting all four of the Amsel criteria:

- Off-white (milky or gray), thin, homogeneous discharge;
- the presence of “clue cells”  $\geq 20\%$  of the total epithelial cells on microscopic examination of the saline “wet mount;”
- pH of vaginal fluid  $\geq 4.7$ ; and
- a positive 10% KOH “whiff test.”

The average age of study subjects in the MP-1601-01 study was  $33.4 \pm 9.68$  years. The majority of subjects (68.4%) reported no previous episode of BV. Table 4 shows the demographics of the study populations for MP-1601-01 and GW05-0904

Table 4: Demographics of the Study Populations for MP-1601-01 and GW05-0904

	<b>MP-1601-01 Metronidazole Vaginal Gel 1.3%</b>	<b>GW05-0904 Metronidazole Vaginal Gel 1.3% x 1 Day</b>	<b>MP-1601-01 Vehicle Gel</b>
	<b>(N = 321)</b>	<b>(N = 65)</b>	<b>(N = 316)</b>
Age (years)			
Mean $\pm$ SD	$32.2 \pm 9.14$	$35.0 \pm 10.13$	$34.6 \pm 10.08$
Range	18 to 63	19 to 66	18 to 67
Race			
Asian	2 (0.6%)	0 (0%)	1 (0.3%)
Black or African American	187 (58.3%)	32 (49.2%)	188 (59.5%)
White	126 (39.3%)	33 (50.8%)	121 (38.3%)
Other	6 (1.9%)	0 (0%)	6 (1.9%)

Subjects were evaluated at three time points (a screening/baseline visit, a Day 7 visit, and a Day 21 test of cure visit). The total study duration was up to 30 days for a subject.

Eligible subjects were randomly assigned (1:1) to following treatment groups:

Metronidazole Vaginal Gel 1.3% or Vehicle Vaginal Gel.

One pre-filled applicator (5 grams) of Metronidazole Vaginal Gel 1.3% (65 mg metronidazole) or 5 grams of Vehicle Gel was to be applied intravaginally as a single dose at bedtime on the day of randomization.

The subjects returned to clinic on Day 7 (-0/+2 days) to assess therapeutic response. A “test of cure” (TOC) visit was conducted at Day 21 (-0/+9 days) or at the end of study (EOS) visit. At all visits the investigator performed gynecological examinations and collected vaginal fluid specimens for the following tests: saline microscopy (“wet mount”) for clue cells, fungal elements, and *Trichomonas vaginalis*; 10% KOH amine test (“whiff test”); pH; and Gram stain for Nugent Scoring.

The Modified Intent-To-Treat (MITT) population included all randomized patients who had both a negative test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* at Visit 1,

## Division of Anti-Infective Products Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 10 of 14  
Clinical Microbiology Review

and a Gram stain slide Nugent Score  $\geq 4$  at Visit 1. Under the original protocol, the primary endpoint was to be assessed using the MITT population.

### Endpoints

The primary endpoint for the study was clinical cure at Day 21. Clinical cure was defined as :

1. Return of normal physiological discharge as confirmed by the investigator;
2. Negative 10% KOH “whiff test”;
3. Clue cells < 20% of the total epithelial cells in saline wet mount.

The secondary efficacy endpoints were:

1. Proportion of subjects with bacteriological cure at the TOC/EOS visit. Bacteriological cure was defined as a Nugent score < 4;
2. Proportion of subjects with therapeutic cure at the TOC/EOS visit. Therapeutic cure was defined as both a clinical cure and bacteriological cure;
3. Proportion of subjects with bacteriological cure at the Day 7 visit;
4. Proportion of subjects with clinical cure at the Day 7 visit; and
5. Time to resolution of symptoms as reported by the subject at the Day 7 visit.

### Results

The primary endpoint of the study was met (Table 5, 6, 7) in the primary modified intent-to-treat (PMITT), modified intent-to-treat (MITT) and (per protocol) PP populations respectively. Clinical cure at Day 21 demonstrated that subjects receiving a single dose of intravaginal Metronidazole Vaginal Gel 1.3% had a statistically significantly greater response compared to subjects receiving Vehicle Gel (37.2% and 26.6%, respectively;  $p = 0.010$ ).

Table 5: Analysis of Clinical Cure at Day 21 (Test-of-Cure Visit) (PMITT Population)

	<b>Metronidazole Vaginal Gel 1.3%</b> (N=250)	<b>Vehicle Gel</b> (N=237)	<b>P-Value<sup>a</sup></b>
Clinical Cure <sup>b</sup>			
No	157 (62.8%)	174 (73.4%)	
Yes	93 (37.2%)	63 (26.6%)	0.010
95% Exact Confidence Interval	[31.2%, 43.5%]	[21.1%, 32.7%]	
Difference from Vehicle Gel for Yes	10.6%		
95% Exact Confidence Interval <sup>c</sup>	[2.4%, 18.8%]		

<sup>a</sup> P-value for the difference between treatment groups from a CMH general association test stratified by analysis center.

<sup>b</sup> Clinical cure: Return of normal physiological discharge as confirmed by the investigator, negative 10% KOH “whiff test”, and clue cells < 20% of the total epithelial cells in saline wet mount.

<sup>c</sup> Confidence interval based on binomial distribution.

# Division of Anti-Infective Products

## Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 11 of 14  
Clinical Microbiology Review

Table 6: Sensitivity Analysis for the Primary Efficacy Endpoint: Analysis of Clinical Cure at Day 21 (Test-of-Cure Visit) (MITT Population)

	<b>Metronidazole Vaginal Gel 1.3% (N=292)</b>	<b>Vehicle Gel (N=285)</b>	<b>P-Value<sup>a</sup></b>
Clinical Cure <sup>b</sup>			
No	184 (63.0%)	209 (73.3%)	
Yes	108 (37.0%)	76 (26.7%)	0.007
95% Exact Confidence Interval	[31.4%, 42.8%]	[21.6%, 32.2%]	
Difference from Vehicle Gel for Yes	10.3%		
95% Exact Confidence Interval <sup>c</sup>	[2.8%, 17.9%]		

<sup>a</sup> P-value for the difference between treatment groups from a CMH general association test stratified by analysis center.

<sup>b</sup> Clinical cure:

- Return of normal physiological discharge as confirmed by the investigator OR vaginal discharge = "Absent"
- Negative 10% KOH "whiff test"
- Clue cells < 20% of the total epithelial cells in saline wet mount

Table 7: Primary Efficacy Endpoint: Analysis of Clinical Cure at Day 21 (Test-of-Cure Visit) (Per-Protocol Population)

	<b>Metronidazole Vaginal Gel 1.3% (N=214)</b>	<b>Vehicle Gel (N=204)</b>	<b>P-Value<sup>a</sup></b>
Clinical Cure <sup>b</sup>			
No	127 (59.3%)	143 (70.1%)	
Yes	87 ( 40.7%)	61 ( 29.9%)	0.007
95% Exact Confidence Interval	[34.0%, 47.6%]	[23.7%, 36.7%]	
Difference from Vehicle Gel for Yes	10.8%		
95% Exact Confidence Interval <sup>c</sup>	[1.7%, 19.9%]		

<sup>a</sup> P-value for the difference between treatment groups from a CMH general association test stratified by analysis center.

<sup>b</sup> Clinical cure: Return of normal physiological discharge as confirmed by the investigator, negative 10% KOH "whiff test", and clue cells < 20% of the total epithelial cells in saline wet mount.

The secondary endpoints also demonstrated that a single dose of Metronidazole Vaginal Gel 1.3% was highly effective in treating subjects with BV

- Bacteriological cure at Day 21 was achieved by a statistically significantly greater proportion of subjects in the Metronidazole Vaginal Gel 1.3% group compared to subjects in the Vehicle Gel group (18.8% vs. 8.0%;  $p < 0.001$ )
- Therapeutic cure at Day 21 was achieved by a statistically significantly greater proportion of subjects in the Metronidazole Vaginal Gel 1.3% group compared to subjects in the Vehicle Gel group (16.8% vs. 7.2%;  $p = 0.001$ )
- Bacteriological cure at Day 7 was achieved by a statistically significantly greater proportion of subjects in the Metronidazole Vaginal Gel 1.3% group compared to subjects in the Vehicle Gel group (32.7% vs. 6.3%;  $p < 0.001$ )
- Clinical cure at Day 7 was achieved by a statistically significantly greater proportion

# Division of Anti-Infective Products

## Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 12 of 14  
Clinical Microbiology Review

of subjects in the Metronidazole Vaginal Gel 1.3% group compared to subjects in the Vehicle Gel group (46.0% vs. 20.0%;  $p < 0.001$ )

- The median number of days for time to resolution of symptoms was 6 days for subjects receiving Metronidazole Vaginal Gel 1.3%. The median was not reached for subjects receiving Vehicle Gel. The difference between the treatment groups was highly statistically significant ( $p < 0.001$ )

### Conclusion

The primary endpoint analysis at Day 21 demonstrated that Metronidazole Vaginal Gel 1.3% was statistically significantly more effective than Vehicle Gel ( $p = 0.01$ ) in producing a clinical cure.

The secondary endpoints of bacteriological cure and therapeutic cure at Day 21 also showed highly statistically significant greater efficacy for Metronidazole Vaginal Gel 1.3% than Vehicle Gel ( $p \leq 0.001$ ). Moreover, the secondary endpoints of bacteriological cure and clinical cure assessed at Day 7 were also highly statistically significant ( $p < 0.001$ ) demonstrating that Metronidazole Vaginal Gel 1.3% acts rapidly to cure BV. This rapid activity was also shown by results for the Kaplan-Meier analysis of time to resolution of symptoms with a median time to resolution for subjects treated with Metronidazole Vaginal Gel 1.3% of 6.0 days, while fewer than 50% of subjects using Vehicle Gel had a resolution of symptoms by Day 7 ( $p < 0.001$ ).

In conclusion, this phase 3 study demonstrated that a single dose of Metronidazole Gel 1.3% is effective for the treatment of bacterial vaginosis.

### 4.0 PHARMACODYNAMIC DRUG INTERACTIONS

No pharmacodynamic drug interaction studies have been conducted with the Metronidazole Vaginal Gel 1.3% formulation.

#### 4.1 PHARMACOKINETICS

Pharmacokinetic studies were conducted with the 0.75% gel for NDA 20,208 and 1.3% gel in IND107,484.

An additional study - an in vitro permeation study was conducted with 1.3% gel. The results of the study suggest that the Metronidazole Vaginal Gel 1.3% formulation would result in more metronidazole remaining on the vaginal mucosal surface that is the target treatment site for BV than the 0.75% formulation.

After a single, intravaginal 5 gm dose of 1.3% metronidazole vaginal gel (equivalent to approximately 65 mg of metronidazole) was administered to 20 healthy female subjects a mean maximum serum metronidazole concentration of 238.95 ng/mL was reported (range of 113.93 mg/mL to 428.44 ng/mL). The average maximum time to achieve the  $C_{max}$  was 7.31 hours (range of 3.92 hours to 18.00 hours) after dosing with 1.3% metronidazole vaginal gel. The average half-life of metronidazole was 9.65 hours. These results are comparable to the results obtained from, single, intravaginal 5 gm dose of metronidazole vaginal gel 0.75% (equivalent to 37.5 mg of metronidazole) in healthy subjects. had a mean maximum serum metronidazole concentration of 237 ng/mL (range: 152 to 368 ng/mL).

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 13 of 14  
Clinical Microbiology Review

**5.0 PROVISIONAL INTERPRETIVE CRITERIA**

In bacterial vaginosis this is related to the Nugent score.

**6.0 CORRELATION OF PROVISIONAL INTERPRETIVE CRITERIA WITH CLINICAL OUTCOME**

Studies have shown that when the balance of the bacterial flora in the vagina returns to normal the clinical outcome is positive.

**7.0 LABEL**

MICROBIOLOGY SECTION

7.1 SPONSOR'S VERSION

**12.4 Microbiology**

***Mechanism of Action:***

(b) (4)

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. [see *Clinical Studies (14)*]

Metronidazole is (b) (4) active *in vitro* against most (b) (4) of the following organisms that have been reported to be associated with bacterial vaginosis:

*Bacteroides* spp.

*Gardnerella vaginalis*

*Mobiluncus* spp.

*Peptostreptococcus* spp

7.2 AGENCY VERSION

**Mechanism of Action**

*Metronidazole, is a nitro-imidazole antimicrobial agent that acts primarily against anaerobic bacteria and selected protozoa. The 5-nitro group on the metronidazole molecule is reduced by metabolically active anaerobes to its active state by the bacterial nitro-reductase enzyme after it diffuses into the bacterial cell. This results in the production of cytotoxic compounds that disrupt the helical structure of bacterial DNA thereby inhibiting bacterial nucleic acid synthesis which leads to cell death.*

*Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. [see *Clinical Studies (14)*]*

*Metronidazole is active in vitro against most isolates of the following organisms that have been reported to be associated with bacterial vaginosis:*

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205223  
Date Review Completed: 01/02/2014

Page 14 of 14  
Clinical Microbiology Review

*Bacteroides spp.*

*Gardnerella vaginalis*

*Mobiluncus spp.*

*Peptostreptococcus spp*

## 8.0 REFERENCES

1. Aroutcheva, A., J. Simoes, K. Behbakht, and S. Faro. (2001): *Gardnerella vaginalis* isolated from patients with bacterial vaginosis and from patients with healthy vaginal ecosystems. *Clin. Infect Dis* 33: 1022 – 1027.
2. Austin, M., R. Beigi, L. Meyn L, and S. Hillier. (2005): Microbiologic response to treatment of bacterial vaginosis with topical clindamycin or metronidazole. *J Clinical Microbiology* 43: 4492 - 4497
3. Beigi, R., M. Austin, L. Meyn, et al. (2004) : Antimicrobial resistance associated with treatment of bacterial vaginosis. *Am J Obstet Gynecol* 191: 1124 – 1129.
4. Gal, M. and J. Brazier. (2004): Metronidazole resistance in *Bacteroides spp.* carrying nim genes and the selection of slow-growing metronidazole-resistant mutants. *J Antimicrobial Chemotherapeutics* 54: 109 – 116.
5. Rasmussen, B., K. Bush, and P. Tally. (1997): Antimicrobial resistance in anaerobes. *Clin. Infect. Dis.* 24 (Suppl.1): S110 - S120.
6. Sobel, J. (2009): Antibiotic consideration in bacterial vaginosis. *Current Infectious DiseaseReports.* 11: 471 – 475.

Lynette Y. Berkeley, Ph. D., M.T. (ASCP),  
Microbiologist, DAIP  
01/07/2014

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/s/  
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LYNETTE Y BERKELEY  
01/07/2014

KERRY SNOW  
01/07/2014

## MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

**NDA Number: NDA 205223    Applicant: Valeant  
Pharmaceuticals**

**Stamp Date: May 24, 2013**

**Drug Name: Metronidazole    NDA Type:505(b)1  
vaginal gel 1.3%**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X		
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	X		
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcome?	X		
8	Has the applicant <u>submitted</u> draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?	X		
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in an appropriate/standardized format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?	X		
10	Has the applicant used standardized or nonstandardized			

## MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?			
11	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
12	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

**IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

NA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**There are no potential review issues**

Lynette Y. Berkeley Ph.D., M.T. (A.S.C.P.)

07/17/2013

Reviewing Microbiologist

Date

Kerry Snow, MS

07/17/2013

Acting Microbiology Team Leader

Date

File name: 5\_Microbiology Filing Checklist for a NDA or Supplement 010908

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/s/  
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LYNETTE Y BERKELEY  
07/18/2013

KERRY SNOW  
07/18/2013

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**DATE:** 20 June 2013

**TO:** NDA 205223

**FROM:** Bryan S. Riley, Ph.D.  
Team Leader (Acting)  
OPS/New Drug Microbiology Staff

**THROUGH:** Stephen E. Langille, Ph.D.  
Senior Review Microbiologist  
OPS/New Drug Microbiology Staff

**cc:** Jane A. Dean, RN, MSN  
Regulatory Project Manager  
OND/DAIP

**SUBJECT:** Product Quality Microbiology assessment of Microbial Limits for  
Metronidazole Gel 1.3% [Submission Date: 24 May 2013]

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**The Microbial Limits specification for Metronidazole Gel 1.3% is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

Metronidazole Gel 1.3% is packaged in a single-dose container for vaginal administration.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and Chapter <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

# MEMORANDUM

**Table 1 - Microbial Limits Specification**

Test	Method	Acceptance Criteria
Total Aerobic Microbial Count	USP <61>	NMT (b) (4) CFU/g
Total Yeast and Mold Count	USP <61>	NMT (b) (4) FU/g
<i>Staphylococcus aureus</i>	USP <62>	(b) (4)
<i>Pseudomonas aeruginosa</i>	USP <62>	(b) (4)
<i>Candida albicans</i>	USP <62>	(b) (4)

Although the drug product is in a single-dose container it was also tested for antimicrobial effectiveness as part of the stability studies using USP Chapter <51> (Antimicrobial Effectiveness Testing) and met the acceptance criteria. The drug product contains methylparaben (b) (4), propylparaben (b) (4) and benzyl alcohol (b) (4). The active (Metronidazole, 1.3%) is also an anti-microbial.

**Reviewer Comments – The drug product batches that were tested for antimicrobial effectiveness were stability batches and were not formulated at or below the minimum acceptable preservative content as is typical for this type of preservative efficacy study. However, since the drug product is not in a multiple dose container, this is acceptable from a product quality microbiology perspective.**

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability protocol.

**ADEQUATE**

**Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol.**

**END**

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/s/  
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BRYAN S RILEY  
06/21/2013

STEPHEN E LANGILLE  
06/21/2013