CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-806

MEDICAL REVIEW

Team Leader Review

Application Type	NDA
Submission Number	NDA 21-806
Submission Code	N
Letter Date	July 19, 2004
Stamp Date	September 18, 2004
PDUFA Goal Date	May 20, 2005
Established Name	Metronidazole Gel, 0.75% w/w Vaginal
(Proposed) Trade Name	Metronidazole Gel, 0.75% w/w Vaginal
Therapeutic Class	vaginal antibacterial
Applicant	TEVA Pharmaceuticals USA
Priority Designation	S
Formulation	intravaginal
Dosing Regimen	on applicatorful (5gm containing 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days
Indication	treatment of bacterial vaginosis
Intended Population	adult women

Recommendation:

The Division recommends approval of metronidazole vaginal gel 0.75% vaginal gel once daily at bedtime for 3 days for the treatment of bacterial vaginosis. The review team has determined that the product is both safe and effective at the recommended dose regimen for this indication based on the review of a single randomized double-blind study demonstrating that metronidazole vaginal gel is not inferior to the reference listed drug Metronidazole vaginal gel 0.75% (MetroGel Vaginal®). There are no phase IV commitments. Pediatric studies for post-menarchal patients have been fulfilled with the conduct of this study (extrapolate findings of safety and efficacy from adult women to postmenarchal females) and studies for pre-menarchal patients are waived for this indication.

Background:

This NDA consists of one pivotal study entitled "A Multi-center, Double-blind, Parallel-Group study Comparing the Bioequivalence of TEVA Pharmaceuticals USA's Generic Formulation of Metronidazole Vaginal Gel, 0.75% and MetroGel Vaginal® Metronidazole Vaginal Gel, 0.75% in the Treatment of Bacterial Vaginosis." This study was originally designed to fulfill the Office of Generics Drug's requirement for the determination of bioequivalence of the candidate drug product to the RLD Metronidazole vaginal gel 0.75% (MetroGel Vaginal®) based on a 90% confidence interval around the difference in proportions of therapeutic cure of the two active study treatments. The study drug is virtually identical to the comparator agent, except for a higher pH for the study drug, and a substitution of one inactive ingredient.

The applicant had originally submitted this application with the Office of Generic Drugs (OGD) as a 505(j) on 2/26/02. On 4/8/02, the OGD refused to file the application because their reviewer determined that clinical bioequivalence of the candidate product to the RLD was not established in the pivotal study. The OGD's bioequivalence conclusion is based on the finding that the 90% confidence interval around the difference in successful outcomes (symptom resolution and a negative KOH AND a negative culture) in the Per Protocol population exceeded the prespecified interval of -20 to +20 percentage points. The applicant received a second refuse to receive letter from OGD on 6/20/02 and further received a request to withdraw letter on 10 20/03, following which their ANDA was withdrawn on 11/5/03. After negotiations with OGD disclosed that the application could not be filed as a 505(j), it was submitted as a 505(b)(2) application to the Division of Special Pathogen and Immunologic Drug Products as an alternate route to market.

There are several drugs available to treat bacterial vaginosis, although few have been approved following the implementation of the 1998 FDA draft Guidance for Industry, "Bacterial Vaginosis- Developing Antimicrobial Drugs for Treatment". The primary endpoint for evaluation of drug efficacy under the draft guidance is a composite endpoint (therapeutic cure) which recommends an outcome of cure for both clinical (Amsel) and gram stain criteria (Nugent score). Clinical cure is defined as resolution of all Amsel criteria (pH, "whiff test", clue cells and appearance of vaginal discharge) used in diagnosis of BV. A Nugent score cure is defined as a Nugent score of 0-3 (normal) after

treatment. Cure rates for products approved under this draft guidance cannot be compared to cure rates for products marketed pre-guidance, because the Nugent score was not included as part of the definition for cure. Recent assessment of outcomes based on the composite endpoint show that point estimates of efficacy appear to be lower when both Amsel and Nugent (gram stain) criteria are used than when only Amsel criteria as used (please see the MO review of NDA 50-793 for additional detail)

Study Overview and Conclusions:

Dr. Joette Meyer's clinical review of this application finds that the candidate drug product metronidazole vaginal gel 0.75% vaginal gel (TEVA Pharmaceuticals USA) is not inferior in efficacy to the reference listed drug MetroGel Vaginal® (3M pharmaceuticals) as therapy for the treatment of bacterial vaginosis. This conclusion is based on HFD 590's finding that the difference in proportion of therapeutic cures (clinical cure and Nugent score of 0-3 at test of cure) on day 22-31 exceeded the 95% confidence interval threshold required to conclude that the products are therapeutically noninferior (1998 Draft Guidance for Industry_ Bacterial Vaginosis). In the primary analysis in the Per Protocol population, the therapeutic cure rate was 55% (86/155) for the test group and 40% (63/159) for the reference group; (95% confidence interval on the 15 percentage point difference in therapeutic cure rate: 6.1%, 25.7%) at Visit 3 (Day 22-31). The supportive analysis in the MITT population was consistent with the findings in the per protocol population, with efficacy rates that were generally lower for both study arms. The safety analysis was favorable, with no serious drug related adverse events and no unanticipated adverse events identified.

			Therapeutic Cures			
Analytic population/ Timing of evaluation/ Analytic outcome			Metronidazole vaginal gel 0.75% (TEVA) n/N (%)	MetroGel Vaginal® (3M) n/N (%)	Difference	95% CI
FDA Primary efficacy analysis						
PP	Visit 3	Therapeutic cure	86/155 (55%)	**63/159 (40%)**	15%	4.31, 27.41
FDA Supportive analyses						
MITT	Visit 3	Therapeutic cure	113/229 (49%)	94/243 (39%)	10%	1.33, 20.00
PP	Visit 2	Therapeutic cure	100/155 (65%)	78/159 (49%)	16%	3.91, 27.23
MITT	Visit 2	Therapeutic cure	137/229 (60%)	117/243 (48%)	12%	2.32, 21.03

Safety Outcomes			
Adverse event category (AE)	Metronidazole vaginal gel 0.75% (TEVA) n/N (%)	MetroGel Vaginal® (3M) n/N (%)	p value
Any AE	92/220 (41.8%)	117/239 (49.6%)	0.125
Drug related AE	25/220 (11.4%)	41/239 (17.2%)	0.077
Severe AE	7/220 (8.0%) abdominal pain (2) headache (3) vomiting pyelonephritis	6/239 (5%) abdominal pain, asthenia, fever, diarrhea, nausea dysmenorrhea, pharyngitis leukorrhea	-

Serious AE	2 bronchospasm, ovarian cyst	0	-	

Sponsor's Additional Analyses

		VISIT 2			VISIT 3		
	Assessment of Vaginal Fluid parameters	Metronidazole vaginal gel 0.75% (TEVA) PP N=155 MITT N=229 (%)	MetroGel Vaginal® (3M) PP N=159 MITT N=243 (%)	Difference*	Metronidazole vaginal gel 0.75% (TEVA) PP N=155 MITT N=229 (%)	MetroGel Vaginal® (3M) PP N=159 MITT N=243 (%)	Difference*
PP	No Discharge	134 (86%)	136 (86%)	0	123 (79%)	117 (74%)	5
MITT		180 (87%)	188 (87%)	0	164 (80%)	161 (75%)	5
PP	No clue cells	128 (83%)	131 (82%)	1	111 (72%)	104 (65%)	7
MITT		173 (84%)	183 (85%)	-1	146 (71%)	148 (69%)	2
PP	Negative KOH	133 (86%)	138 (87%)	-1	119 (77%)	120 (75%)	2
MITT		178 (86%)	189 (88%)	-2	156 (76%)	163 (76%)	0
PP	pH <4.7	128 (83%)	125 (79%)	4	108 (70%)	103 (65%)	5
MITT		173 (84%)	175 (81%)	3	145 (70%)	145 (67%)	3
PP	Nugent <4	108 (70%)	93 (58%)	12	103 (66%)	91 (57%)	9
MITT		143 (69%)	129 (60%)	9	134 (65%)	123 (57%)	8
PP	No need for additional treatment	130 (84%)	133 (84%)	0	118 (76%)	116 (73%)	3
MITT		176 (85%)	185 (86%)	-1	156 (76%)	160 (74%)	2

*Metronidazole (TEVA)- MetroGel (3M)

Notable in this submission is the higher proportion of favorable Nugent score responses on week 2 compared to week 3 (see shaded boxes). There is limited information regarding the time it takes to repopulate the natural vaginal flora following treatment for BV and the published literature suggests that the Nugent score may need to be evaluated at a more remote endpoint than clinical symptoms. This study finds that the Nugent score resolution paralleled the clinical response at both time points, although investigator assessment of the need for additional therapy more closely approximated the traditional Amsel criteria. An analysis of the Amsel parameters indicates that numerical point estimates for the individual vaginal fluid criteria were generally more favorable for the study drug relative to the comparator, at the visit 3 time point. Interestingly, for either treatment arm, the Visit 2 success rates were generally higher than the values obtained for each individual parameter obtained at Visit 3, including the Nugent score rates, although the difference in point estimates appear to be narrower for the Nugent score endpoint than for the other vaginal fluid parameters. Another interesting observation was that the investigators assessment of the need for additional treatment more closely approximated the outcomes of vaginal discharge, presence of clue cells, KOH, and pH than it did the Nugent score.

As discussed in Dr. Meyer's review, the Agency evaluated the discordant outcomes between the clinical and bacteriologic outcomes, particularly for the subset of clinical cures and Nugent failures at Visit 2 who transition to clinical failures and Nugent cures on visit 3. Two of the clinical failures at the late time point were attributed to a fungal infection, whereas in 7, clinical failure could not be explained in the face of a Nugent cure, and there were too few discordant cases to evaluate the correlation of individual clinical criteria to the Nugent score outcomes.

There appear to be no baseline differences that could account for the consistent superior outcomes for the study drug over the comparator. TEVA's metronidazole vaginal gel 0.75% is identical to the innovator's product in the active ingredient, strength, dosage and route of administration, except for one inert ingredient carbomer, which replaces the hypomellose in the comparator formulation, and the final pH, which is higher for the study drug. Drs. Meyer and Dixon evaluated efficacy by center, by severity strata, by lot of drug evaluated and found no differences that would provide a plausible explanation for the difference in outcomes. The statistical superiority is demonstrated whether the review team evaluated the outcomes based on OGD's definition of bioequivalence (90% CI) or HFD 590's parameters for non-inferiority (95% CI). Although the results of this study show the product to be statistically superior, it cannot be concluded that the product is clinically superior based on only one clinical study, and on the background of uncertainty regarding the Nugent score findings. However, the outcomes based on the Amsel criteria are consistent with previous finding of safety and efficacy regarding other metronidazole vaginal products, and are sufficient to conclude that there is adequate evidence of efficacy and safety to support approval of this 505(b)(2) application. As noted above, the drug product is as safe as the metronidazole vaginal gel 0.75% vaginal gel RLD despite the numerical advantage in efficacy. The review uncovered no adverse events of concern. One case of serious bronchospasm and hypoxia occurred in a patient who received the study drug. This adverse event was unlikely to be drug related hypersensitivity as it occurred 7 days post treatment.

Summary:
The study provides convincing evidence that the metronidazole gel 0.75% vaginal gel drug formulation is safe and efficacious in the treatment of bacterial vaginosis and the review team recommends approval of this application. Several modification are proposed for the product label, as outlined in Dr. Meyer' review.

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Through:
Yon Yu, PM
NDA 21-735

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/s/

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NDA 21-806

CLINICAL REVIEW

Application Type	21-806
Submission Number	000
Submission Code	N
Letter Date	July 19, 2004
Stamp Date	September 18, 2004
PDUFA Goal Date	May 20, 2005
Reviewer Name	Joette M. Meyer, Pharm.D.
Review Completion Date	May 17, 2005
Proposed Trade Name	Metronidazole Gel USP, 0.75% w/w Vaginal
Final Trade Name	Metronidazole Vaginal Gel, 0.75%
Therapeutic Class	Vaginal Antibacterial
Applicant	TEVA Pharmaceuticals USA
Priority Designation	S
Formulation	0.75% w/w Vaginal Gel
Dosing Regimen	one applicator full (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days.
Indication	Treatment of Bacterial Vaginosis
Intended Population	Adult Women

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

MetroGel-Vaginal® 0.75%, a metronidazole vaginal gel to treat women with bacterial vaginosis was approved on August 17, 1992 (NDA 20-208). TEVA Pharmaceuticals developed a similar vaginal formulation of metronidazole gel that they initially intended to submit as an abbreviated new drug application (ANDA) to the Office of Generic Drugs (OGD). Based on the advice of OGD, TEVA performed an *in vivo* pharmacokinetic study and a clinical equivalence study. Clinical equivalence in OGD is defined as: confidence bounds of a two-sided 90% confidence interval about the treatment difference within the limits ± 20%. The results of the clinical study, demonstrated TEVA's product to be clinically inequivalent (slightly superior) to the referenced product (MetroGel-Vaginal® 0.75%). Therefore, TEVA's product was considered ineligible for a 505(j) submission.

On July 15, 2003, TEVA contacted the Division to express their interest in submitting a 505(b)2 new drug application (NDA) for Metronidazole Vaginal Gel, 0.75%. A Pre-NDA meeting was held on November 3, 2003. The applicant submitted the current application as a 505(b)2 submission on July 19, 2004.

The Division reviewed the clinical study and determined, according to criteria for efficacy used in the Office of New Drugs, that metronidazole vaginal gel, 0.75% was non-inferior to MetroGel-Vaginal® 0.75% for the treatment of bacterial vaginosis in non-pregnant women. Although the results of the primary endpoint, therapeutic cure, show statistical significance of metronidazole vaginal gel compared to MetroGel-Vaginal, a claim of clinical superiority would require a second clinical study for confirmation of effect. Adverse events were similar in the two treatment groups.

In summary, metronidazole vaginal gel, 0.75% was determined to be safe and effective for the treatment of bacterial vaginosis in adult, non-pregnant women.

1.2 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity or Phase 4 studies at this time.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

A single Phase 3 randomized, double-blind, active controlled study was performed which compared TEVA's metronidazole vaginal gel 0.75% w/w to the approved product (MetroGel-Vaginal® 0.75%). Study medication was applied once daily at bedtime for 5 nights. The primary efficacy endpoint was therapeutic cure (clinical cure plus bacteriological cure) at the Day 22-31 follow-up visit (Visit 3).

The determination of therapeutic response in this study is in agreement with the July 1998 Draft Guidance for Industry "Bacterial Vaginosis – Developing Antimicrobial Drugs for Treatment".

Although the protocol stated that therapeutic equivalence (non-inferiority) would be concluded if the 90% confidence interval about the difference of the therapeutic cure rates is contained within the range of -20% to 20%, the Division used a 95% confidence interval for a determination of non-inferiority.

1.3.2 Efficacy

A total of 579 subjects received study medication. Of these, 229 metronidazole and 243 MetroGel subjects were included in the FDA-defined Modified Intent to Treat (MITT) population. The Per Protocol (PP) population consisted of 155 metronidazole and 159 MetroGel subjects. In the PP analysis, the therapeutic cure rates at Visit 3 were 51.6% (80/155) for the metronidazole group and 36.5% (58/159) for the MetroGel group (95% confidence interval of the treatment different [3.6%, 26.6%]). In the FDA MITT analysis, the therapeutic cure rates were 42.8% (98/229) for the metronidazole group and 30.9% (75/243) for the MetroGel group (95% confidence interval of the treatment difference [2.8%, 21.0%)]. In both analyses, metronidazole was shown to be non-inferior MetroGel, as the lower bound of the 95% confidence interval around the treatment difference was above -20%.

In summary, metronidazole vaginal gel, 0.75% was determined to be non-inferior to MetroGel-Vaginal® 0.75% for the treatment of bacterial vaginosis in non-pregnant women. Although the results of the primary endpoint, therapeutic cure, show statistical significance of metronidazole vaginal gel, 0.75% compared to MetroGel-Vaginal® 0.75%, as defined by a lower bound of the 95% confidence interval around the treatment difference above zero, a claim of clinical superiority would require a second clinical study for confirmation of effect.

1.3.3 Safety

No deaths were reported during the study. Two serious adverse events were reported (both in the MetroGel group). Both were related to pre-study conditions (severe asthma requiring hospitalization and ovarian cyst requiring hospitalization), and were considered not related to study medication. Eleven subjects discontinued due to adverse events, 5 in the metronidazole vaginal gel group (yeast infection – 2 subjects; pyelonephritis – 2 subjects; vaginal itching/discharge) and 6 in the MetroGel group (Bartholins cyst requiring antibiotics; urinary tract infection – 2 subjects; cervicitis; vaginal irritation; and ovarian cyst).

A total of 42% (92/220) of subjects in the metronidazole group and 49% (117/239) of subjects in the MetroGel group experienced an adverse event during the study. Individual adverse events were similar between the two treatment groups. The adverse events that occurred in > 5% of subjects were abdominal pain (4.5% metronidazole group, 7.5% MetroGel group), headache (6.8%, 7.9%, respectively), fungal infection (12.3% and 17.6%), and pruritus (5.5% and 4.2%).

Events occurring in ≥ 1% of subjects treated with metronidazole vaginal gel included: fungal infection (12.3%), headache (6.8%), pruritus (5.5%), abdominal pain (4.5%), nausea (3.2%), dysmenorrhea (2.7%), pharyngitis (1.8%), rash (1.4%), infection (1.4%), diarrhea (1.4%), breast pain (1.4%), and metrorrhagia (1.4%).

The adverse events that were considered definitely or probably related to study medication in ≥1% of subjects in a treatment group were fungal infections (20 [9%] in the metronidazole group and 32 [13%] in the MetroGel group). Symptomatic vaginal candidiasis is a recognized adverse event that occurs in approximately 10% of women during or immediately after antibacterial therapy for BV.

In summary, metronidazole vaginal gel 0.75% was found to be safe for the treatment of bacterial vaginosis in adult, non-pregnant women.

1.3.4 Dosing Regimen and Administration

The recommended dose is one applicator full of metronidazole gel, vaginal (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days. For once a day dosing, metronidazole vaginal gel should be administered at bedtime.

In the sponsor's Phase 3 clinical study, study medication was supplied as a single 70 gram tube of metronidazole vaginal gel 0.75% w/w and five vaginal applicators. Subjects were instructed to apply the medication intravaginally once a day at bedtime using the supplied 5-gram vaginal applicator (approximately 37.5 mg of metronidazole). The treatment period was 5 days.

Clinical Reviewer's Comment: Although metronidazole vaginal gel 0.75% w/w was not studied as a twice a day regimen, the product labeling for MetroGel-Vaginal® 0.75% (the approved referenced product for this 505(b)2 NDA) states the product may be used in this way. Therefore, the product labeling for metronidazole vaginal gel 0.75% w/w, which has been shown to be non-

inferior to MetroGel, will state the product may be used one or twice daily, and will be marketed in a 70 gram tube, which provides enough product to allow a subject using twice daily administration to complete a full course of therapy.

Subjects were also given instructions on how to administer the product:

1. To prepare the medication for application, first remove the cap from the tube and puncture the tamperproof seal with the sharp end of the tube cap. Screw on one of the supplied plastic applicators with the plunger in the down position. Fill the applicator by squeezing the tube until the applicator is full. Unscrew the applicator from the tube.
2. Insert the applicator into the vagina and depress the applicator plunger to apply the medication. This may be most easily done while lying on your back. The applicator should then be discarded.

Additional instructions on avoiding alcohol and vaginal intercourse were also provided:

> You should not drink alcohol during the five day treatment period and for one day afterward. Alcohol taken with oral metronidazole can cause nausea and vomiting. While blood levels are significantly lower with metronidazole vaginal gel than with usual doses of oral metronidazole, a possible interaction with alcohol cannot be excluded.
>
> You should not engage in vaginal intercourse throughout the first 7 days of the study.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies with metronidazole vaginal gel were not performed. Significant systemic drug-drug interactions would not be expected with intravaginal administration of metronidazole due to low systemic absorption. Metronidazole vaginal gel is less likely to produce the adverse events seen with oral metronidazole dosing, due to lower levels of systemic exposure; however, the possibility of adverse events, cannot be excluded. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available.

Drug-drug interactions known to occur with oral metronidazole that cannot be excluded with metronidazole vaginal gel:

- Disulfiram-like reaction to alcohol
- Potentiation of the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time.
- Elevation of serum lithium levels and, in a few cases, signs of lithium toxicity.
- Use of cimetidine with oral metronidazole may prolong the half-life and decrease plasma clearance of metronidazole.

1.3.6 Special Populations

Metronidazole gel was not studied in subjects with renal or hepatic insufficiency. Dose modification for these populations should not be necessary given the low systemic absorption of metronidazole from intravaginal preparations. Metronidazole gel was not studied in women under age 18; however, the data presented in these studies can be reasonably extrapolated to include all postmenarchal females because of the similar expected safety profile of the drug and similar pathophysiology of BV in younger women.

Pregnant women were not included in the clinical trial of metronidazole vaginal gel, nor were they studied in clinical trials of MetroGel. Following oral metronidazole administration, the drug crosses the placental barrier, enters the fetal circulation, and is also secreted into human breast milk in concentrations similar to those found in plasma. Metronidazole has been shown to be mutagenic in a number of in vitro assay systems, although mammalian studies have failed to demonstrate a potential for genetic damage. In rodents, metronidazole is a carcinogen, causing various neoplasms, particularly mammary and hepatic tumors. Therefore, it is recommended that metronidazole vaginal gel should only be used in pregnant and nursing women if the benefit to the mother clearly outweighs the risk to the fetus.

Due to the limited number of subjects $\geq$ 65 years old enrolled the Phase 3 trial conducted with metronidazole gel, no conclusions can be drawn regarding the safety and efficacy of metronidazole gel in the geriatric population.

All subjects were female so no gender analysis of safety or efficacy was performed.

There was no significant difference in therapeutic cure rates by race when compared to the overall study population. Differences, if any, in the incidence of adverse events between subjects of white and black races in the two treatment groups are not considered to be clinically relevant.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	Metronidazole Vaginal Gel, 0.75%
Applicant's Proposed Trade Name	Metronidazole Gel, USP, 0.75% w/w Vaginal
Final Trade Name	Metronidazole Vaginal Gel, 0.75%

Therapeutic Class	Vaginal Antibacterial
Applicant	TEVA Pharmaceuticals USA

Formulation	0.75% w/w Vaginal Gel
Dosing Regimen	one applicator full (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days.

Indication	Treatment of Bacterial Vaginosis

Intended Population	Adult Women

2.2 Currently Available Treatment for Indication

Active Ingredient	Trade Name	Treatment Regimen	Comments
Clindamycin	Cleocin 2% cream (100 mg)	QHS x 3 days QHS x 7 days	7-day treatment is the only therapy approved for use in the 2nd and 3rd trimesters of pregnancy
	Cleocin 100 mg vaginal ovule	QHS x 3 days	
	Clindesse 100 mg vaginal cream	Single dose	Approved November 30, 2004
Metronidazole	MetroGel Vaginal 0.75% gel	QD or BID x 5 days	
	Flagyl ER 750 mg oral tablet	PO QD x 7 days	Oral therapy
	Flagyl 750 mg oral tablet	QD x 7 days	Oral therapy
Sulfanilamide	AVC 15% cream	BID x 30 days	
	AVC cream and suppository (1.05 grams)	Cream BID and suppository BID x 30 days	

The triple sulfa products, Sultrin® cream and tablets (each containing 3.42% sulfathiazole; 2.86% sulfacetamide, and 3.7% sulfabenzamide), were once FDA-approved for twice daily use for 4-6 days or 10 days, respectively, but the applicant withdrew the NDA on August 4, 2004.

3M's MetroGel-Vaginal® (metronidazole vaginal gel, 0.75%) has been approved since August 17, 1992.

2.3 Availability of Proposed Active Ingredient in the United States

The following is a qualitative and quantitative comparison of the reference-listed drug (MetroGel-Vaginal® 0.75%) and TEVA's proposed metronidazole vaginal gel, 0.75% formulation:

Reference-listed Drug Formulation (MetroGel-Vaginal® 0.75%)		Teva Product Formulation (Metronidazole Vaginal Gel, 0.75%)	
Ingredient	**Percentage (%)**	**Ingredient**	**Percentage (%)**
Metronidazole, USP	0.75	Metronidazole, USP	0.75
Carbomer 934, NF		Hypromellose, USP	
Edetate Disodium, USP		Edetate Disodium, USP	
Methylparaben, NF		Methylparaben, NF	
Propylene Glycol, USP		Propylene Glycol, USP	
Propylparaben, NF		Propylparaben, NF	
Sodium Hydroxide, NF		Sodium Hydroxide, NF	
Purified Water, USP		Purified Water, USP	

*Solution used to adjust pH

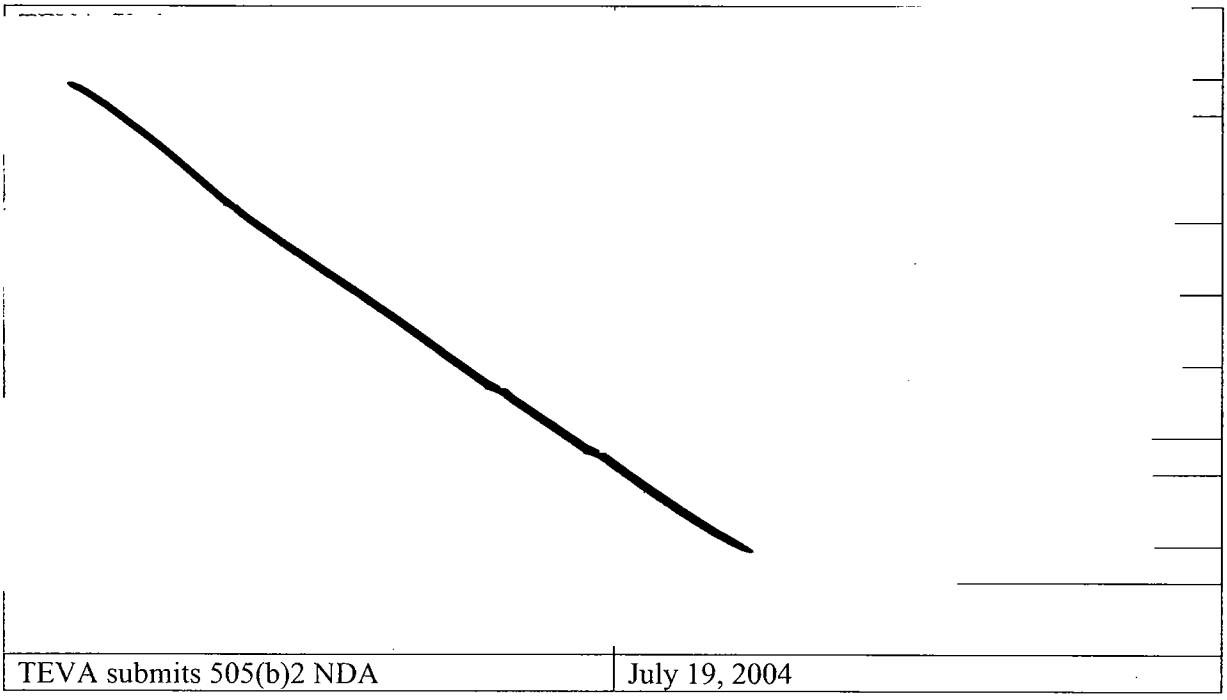
2.4 Important Issues With Pharmacologically Related Products

Metronidazole is known to be mutagenic in *in vitro* assay systems (although in vivo mammalian studies have failed to demonstrate a potential for genetic damage) and is carcinogenic in rodents. Therefore, the drug should not be used in pregnant or nursing mothers, unless the benefit to the mother clearly outweighs the risk to the fetus.

2.5 Presubmission Regulatory Activity

However, the results of the clinical study, demonstrated TEVA's product as not clinically equivalent (slightly superior) to the referenced product (MetroGel-Vaginal®, 0.75%; NDA 20-208). On July 15, 2003, TEVA Pharmaceuticals contacted the Division to express their interest in submitting a 505(b)2 new drug application (NDA) for metronidazole vaginal gel, 0.75%. The timeline of events is summarized below.

Timeline of Events



TEVA submits 505(b)2 NDA	July 19, 2004

The meeting minutes from the Pre-NDA teleconference (PIND 67,025) are included below:

MEETING SUMMARY:
The principal topics discussed during the meeting are as follows:
- The adequacy of the completed studies to support the indication
- The adequacy of the completed studies to support the superiority claim
- The acceptability of the sponsor's proposal regarding [redacted] identification test and room temperature stability data
- The safety of the excipient hypromellose in the proposed level

QUESTIONS FOR DISCUSSION WITH THE AGENCY'S RESPONSES:
(The sponsor's questions as well as any follow-up responses are reproduced in italicized type below.)
1. Are the PK and comparative clinical efficacy studies performed to date sufficient to support approval of a 505(b)(2) NDA?
On the surface the data submitted in the briefing package appear sufficient to support an NDA submission by the sponsor. The determination as to whether the data is sufficient to support approval can only be made after full review of the application. One clinical trial is sufficient for the proposed indication, specifically because the therapeutic agent is metronidazole, a product for which there is substantially clinical experience with respect to this indication.

2. Are the comparative clinical efficacy study results sufficient to support a claim of clinical superiority to MetroGel in our labeling? If not, what additional studies would be required to support such a claim?
Generally speaking, in order to make a claim of superiority, two clinical trials are needed. In this circumstance another clinical trial that replicated the results reported in the first trial would be required for a superiority claim.

3 [redacted]

[redacted]

Is this acceptable to the Agency?
This proposal is acceptable.

4
[redacted]

ADDITIONAL COMMENTS:
• The sponsor's proposed formulation contains an excipient hypromellose [redacted] at a level above that currently listed for vaginal dosage forms in the Agency's Inactive Ingredient Database. Teva intends to rely on published literature studies to support the safety of the proposed level. The Division is reserving comments on the safety until a full review of the literature.
• The Division stated that statistical comments will be provided to Teva following the teleconference.

For a qualitative and quantitative comparison of the reference-listed drug and TEVA's proposed formulation see Section 3.1 "CMC" in this review.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The application is approvable from the Chemistry, Manufacturing, and Controls (CMC) perspective. Below are the conclusions from the CMC review.

Clinical Reviewer's Comment: For more information, see the complete CMC Review by Dorota Matecka, Ph.D. filed with this NDA.

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Metronidazole Vaginal Gel, 0.75%. During the review several minor issues, including the following were resolved.

The specification of the drug product, Metronidazole Vaginal Gel, 0.75%, was revised to include the viscosity analytical procedure and acceptance criteria. Also, the proposed description of the gel was revised to describe more accurately the color of the gel. In addition, the quantitative color analytical procedure and acceptance criteria were added to the drug product specification to provide a better control of the color changes on storage. As mentioned above, the metronidazole drug substance complies with the USP monograph for metronidazole. In addition, the HPLC analytical procedure and acceptance criteria were added to the drug substance specification.

The stability data submitted in the application (including the 27-Apr-2005 amendment) support the proposed expiration dating of 24 months for the drug product. It should be noted that the expiration dating for the original metronidazole vaginal gel (MetroGel-Vaginal®, 0.75%) is 36 months.

No trade name was proposed for this product. The originally proposed established name for the drug product as "Metronidazole Gel USP, 0.75% w/w Vaginal" was consulted with the Labeling and Nomenclature Committee (LNC) and was eventually changed to "Metronidazole Vaginal Gel". The drug product complies with most of the requirements of the USP monograph for metronidazole gel. However, several tests in the specification of the current product are new or different from those listed in the monograph. For example, the TEVA's drug product specification uses a UV, instead of TLC, as one of the identification tests. The HPLC analytical procedure for assay and impurities is also different than that of the USP monograph. Therefore, the USP designation should not be used for this product, and, instead, the name will contain "vaginal" to indicate the route of administration for this product.

3.2 Animal Pharmacology/Toxicology

The application is approvable from the Pharmacology/Toxicology perspective. Below are the conclusions from the Pharmacology/Toxicology review.

Clinical Reviewer's Comment: For more information, see the complete Pharmacology/Toxicology Review by Owen McMaster, Ph.D. filed with this NDA.

No preclinical toxicology studies were performed in support of this NDA. Metronidazole Vaginal Gel, 0.75 % is almost identical to a registered product MetroGel-Vaginal® 0.75%. The preclinical toxicology data that has been included in the label for metronidazole vaginal gel, 0.75% can be found in the label of other metronidazole drug products.

The oral LD_{50} values were 1 to 5 g/kg in rats and mice. Metronidazole administration at very high doses has been associated with testicular dystrophy and prostiatrophy, ataxia, muscular atrophy and tremors. At 500 mg/kg, pulmonary tumors were recorded in mice.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Phase 3 clinical study (Study TCR-03) and Phase I pharmacokinetic study conducted by the sponsor, along with the package insert for MetroGel were the sources of data used in this review.

The study report and the datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\Cdsesub1\N21806\N_000\2004-10-05.

4.2 Tables of Clinical Studies

The two studies conducted by the sponsor are listed in the Table below.

Study	Number of Patients/Subjects Enrolled	Study Design	Number of Subjects Completed	Results
PK Study	38	Single-dose, cross-over study to evaluate relative bioavailability of metronidazole vaginal gel vs. MetroGel-Vaginal®	37 (one withdrew for personal reasons)	90% CI for all PK parameters within 80% to 120%
Phase III Study (TCR-03)	579	Multi-center, double-blind, randomized study of metronidazole vaginal gel vs. MetroGel-Vaginal® for 7 days	459 (ITT); 421 (MITT); 314 (PP)	Therapeutic cure at TOC of metronidazole vaginal gel was clinically equivalent (slightly superior) to MetroGel-Vaginal®

4.3 Review Strategy

The single Phase 3 study's efficacy results were reviewed overall and by center to determine robustness and validity. In addition, safety results were compared between the two formulations to look for clinically relevant differences.

4.4 Data Quality and Integrity

DSI inspections were not conducted for this NDA. Metronidazole is not a NME, has been studied previously for bacterial vaginosis and a variety of systemic infections, and has a well-characterized safety profile. In addition, no discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

A 10% random sample of subjects (N=57) enrolled in Study TCR-03 was generated by the FDA Statistical Reviewer. The applicant was requested to submit the CRFs for these subjects for review. The FDA Clinical Reviewer examined the CRFs for inclusion/exclusion criteria, dates of visits, clinical signs and symptoms, concomitant medications and indications, microbiology

findings, and evaluability determinations. The data in the CRFs was compared to the electronic datasets generated by the applicant. The Reviewer found agreement between the random sample of CRFs and the electronic datasets in all instances.

4.5 Compliance with Good Clinical Practices

The Phase 3 study was conducted in compliance with GCP.

4.6 Financial Disclosures

The applicant obtained certification from each investigator and sub-investigator who enrolled subjects in the Phase 3 study (Study TCR-03). No investigator had any disclosable information to reveal.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The application is approvable from the Clinical Pharmacology/Biopharmaceutics perspective. Below are the conclusions from the Clinical Pharmacology/Biopharmaceutics review.

Clinical Reviewer's Comment: For more information, see the complete Clinical Pharmacology/Biopharmaceutics Review by Gerlie Gieser, Ph.D. filed with this NDA.

In the relative bioavailability study, the plasma Cmax of metronidazole from the sponsor's vaginal gel was statistically significantly higher than that from the reference vaginal gel. Likewise, the plasma metronidazole AUCo-inf from the sponsor's vaginal gel product was numerically larger but the difference from that of the reference product was not statistically significant. Although the Cmax of metronidazole from the applicant's formulation was significantly higher than that achieved from the innovator's product, the difference in peak concentrations is not expected to exert a clinical safety concern because the Cmax of metronidazole after intravaginal administration is only 2% of the mean plasma Cmax typically seen following a single dose of metronidazole 500 mg oral tablet. To treat BV in nonpregnant adults and adolescent females, the Center for Disease Control (CDC) recommends an oral dosage regimen of either 2 grams metronidazole as a single dose, or 500 mg twice daily for 7 days.

The 90% confidence interval of the log transformed Cmax and AUC of metronidazole from the test formulation was within the 80-125% acceptance range, thereby making the sponsor's vaginal product systemically bioequivalent to the RLD.

Age, bodyweight, body surface area, race, and smoking did not appear to significantly influence the relative bioavailability findings. In addition, race did not appear to significantly influence the therapeutic bioequivalency findings of the clinical trial, i.e., there was a comparable percentage

of White and Black female BV patients with bacteriologic cure (expressed as % patients with Nugent scores 0 to 3 at the Test-of-Cure Visit and the Post-Treatment Visit) following therapy with either the sponsor's metronidazole vaginal gel or the MetroGel-Vaginal ® product.

5.2 Pharmacodynamics

Not applicable. No information on pharmacodynamics was included in the NDA submission.

5.3 Exposure-Response Relationships

Not applicable. No information on exposure-response was included in the NDA submission.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Treatment of bacterial vaginosis in adult, non-pregnant women.

6.1.1 Methods

The applicant conducted a single, Phase 3 study (Study TCR-03) that was considered a pivotal efficacy study.

6.1.2 General Discussion of Endpoints

The primary endpoint determined in Study TCR-03 was therapeutic outcome. The therapeutic outcome was derived from the clinical and bacteriological (Nugent score) outcome at the Test-of-Cure Visit.

The determination of therapeutic response in this study is in agreement with the July 1998 Draft Guidance for Industry "Bacterial Vaginosis – Developing Antimicrobial Drugs for Treatment". The following table is reproduced from the draft Guidance.

Determination of Therapeutic Response by TOC visit (summarized)		
If the clinical outcome is...	And the Nugent score result is...	then the overall therapeutic outcome is...
cure	0-3	cure
cure	> 3	failure
failure	0-3	failure
failure	> 3	failure
cure	NE	NE
NE	0-3	NE
NE	> 3	NE

NE = non-evaluable

6.1.3 Study Design

For a complete description of the study design and efficacy data obtained from Study TCR-03, see Appendix, Section 10.1 "Review of Individual Study Report".

Study TCR-03 was a double-blind, randomized, parallel-group, multicenter study in subjects with bacterial vaginosis. Non-pregnant female subjects 18 years of age or older with a confirmed clinical diagnosis of bacterial vaginosis and a Nugent score of ≥ 4 were eligible for enrollment. Subjects were free of other known or suspected infectious causes of vulvovaginitis.

A clinical diagnosis of BV was defined as having the presence of clue cells ≥ 20%; an off-white (milky or gray), thin, homogeneous discharge; a pH of vaginal fluid ≥ 4.7; and a positive 10% KOH whiff test.

Subjects were randomized in a 1:1 ratio to one of two treatment groups (metronidazole vaginal gel, 0.75% or 3M Pharmaceuticals' MetroGel-Vaginal® (metronidazole vaginal gel, 0.75%). Subjects inserted one applicator full of metronidazole vaginal gel (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once daily at bedtime for 5 days. Subjects returned for clinical evaluations at Day 8 to 15 and Day 22 to 31.

The study included 3 visits: a baseline (Day 1) visit and follow-up visits at Day 8-15 (Visit 2) and Day 22-31 (Visit 3). At each visit, the investigator performed a gynecological exam and collected specimens for the following tests: saline wet mount to check for the presence of clue cell and *Trichomonas vaginalis*; 10% KOH whiff test; vaginal fluid pH, and Gram's stain for Nugent scoring.

The primary efficacy endpoint was the proportion of subjects with therapeutic cure at Visit 3 (Day 22-31). A subject was considered a therapeutic cure if they were a clinical cure and a bacteriological cure.

A subject was considered a clinical cure if all of the following were satisfied:

- The original discharge characteristic of BV returned to a normal physiological
- discharge
- The 10% KOH whiff test was negative
- The saline wet mount was negative for clue cells
- The vaginal fluid pH was < 4.7
- The investigator indicated that the subject did not require additional therapy for BV.

A subject was considered a bacteriological cure if she had a Nugent score < 4.

Enrollment was planned for approximately 542 subjects (271 subjects in each of the treatment groups) in order to complete 380 per-protocol subjects. A total of 579 subjects were actually enrolled.

6.1.4 Efficacy Findings

The primary efficacy endpoint in Study TCR-03 was the proportion of subjects with a therapeutic cure at Visit 3. A total of 579 subjects received study medication. Of these, 229 metronidazole and 243 MetroGel subjects were included in the FDA-defined Modified Intent to Treat (MITT) population. The Per Protocol (PP) population consisted of 155 metronidazole and 159 MetroGel subjects.

As shown in the table below, in the PP analysis, the therapeutic cure rates at Visit 3 were 51.6% (80/155) for the metronidazole group and 36.5% (58/159) for the MetroGel group (95% confidence interval of the treatment different [3.6%, 26.6%]). In the FDA MITT analysis, the therapeutic cure rates were 42.8% (98/229) for the metronidazole group and 30.9% (75/243) for the MetroGel group (95% confidence interval of the treatment difference [2.8%, 21.0%)]. In both analyses, metronidazole was shown to be non-inferior MetroGel, as the lower bound of the 95% confidence interval around the treatment difference was above -20%. Although the results of the primary endpoint, therapeutic cure, show statistical superiority of metronidazole vaginal gel compared to MetroGel-Vaginal (as defined by a lower bound of the 95% confidence interval around the treatment difference above zero), a claim of clinical superiority would require a second clinical study for confirmation of effect.

FDA's Analysis of Primary Efficacy Endpoint

Efficacy Endpoint	Subjects	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	95% Confidence Interval
Primary Efficacy: Therapeutic Cure Rate At Visit 3	Per-Protocol	(N=155)	(N=159)	
		80 (51.6%)	58 (36.5%)	(3.6%, 26.6%)
	Modified Intent-to-Treat	(N=229)	(N=243)	
		98 (42.8%)	75 (30.9%)	(2.8%, 21.0%)

6.1.5 Clinical Microbiology

The application is approvable from the Microbiology perspective. Below are the conclusions from the Microbiology review.

Clinical Reviewer's Comment: For more information, see the complete Microbiology Review by Kalavati Suvarna, Ph.D. filed with this NDA.

In vitro, metronidazole is active against most strains of *Gardnerella vaginalis*, *Bacteroides* sp., *Mobiluncus* sp., and *Peptostreptococcus* sp., which are associated with BV. At concentrations of 1000 – 4000 µg/ml, metronidazole partially inhibited the growth of vaginal *Lactobacillus* isolates. At higher concentrations (> 5000 µg/ml) of metronidazole, 86-92% inhibition of growth was observed at 24 hours. However, in a study that evaluated the effect of metronidazole on

vaginal lactobacilli colonization, an improvement in lactobacilli colonization was observed at EOT and at 3 weeks after discontinuation of therapy.

In the clinical study TCR-03, the efficacy of metronidazole vaginal gel was greater (64%) than MetroGel-Vaginal® (46%) in the treatment of bacterial vaginosis. The study only provided information on the Nugent scores using vaginal swabs at baseline and post-treatment. No information was available on the species of bacteria at baseline and post-treatment in patients enrolled in the clinical studies. Therefore, the activity of metronidazole against the bacterial species associated with BV could not be analyzed in the clinical study. The cure by Nugent score suggests that there was an increase in *Lactobacillus* morphotypes and decrease in the *Gardnerella, Bacteroides* and *Mobiluncus* morphotypes in 74% patients at 16 to 25 days after discontinuation of therapy with metronidazole vaginal gel compared to 61% in patients treated with MetroGel-Vaginal®. Approximately 10% of patients in the metronidazole vaginal gel arm developed a vaginal yeast infection compared to 17% in the MetroGel-Vaginal® arm.

6.1.6 Efficacy Conclusions

Metronidazole vaginal gel 0.75% was shown to be non-inferior to MetroGel-Vaginal® (metronidazole vaginal gel, 0.75%) for the treatment of bacterial vaginosis in non-pregnant adult women.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

For a complete description of the safety data obtained from Study TCR-03, see Appendix, Section 10.1 "Review of Individual Study Report".

7.1.1 Deaths

No deaths were reported during the clinical study.

7.1.2 Other Serious Adverse Events

Two serious adverse events (SAEs) were reported. Both occurred in the MetroGel group. Both SAEs were hospitalizations for pre-study conditions (severe asthma requiring hospitalization and ovarian cyst requiring hospitalization), and were considered not related to study medication.

7.1.3 Dropouts and Other Significant Adverse Events

Eleven subjects discontinued due to adverse events, 5 in the metronidazole group (yeast infection – 2 subjects; pyelonephritis – 2 subjects; vaginal itching/discharge) and 6 in the MetroGel group

(Bartholins cyst requiring antibiotics; urinary tract infection – 2 subjects; cervicitis; vaginal irritation; and ovarian cyst).

7.1.4 Other Search Strategies

Due to the limited number of subjects ≥ 65 years old enrolled the Phase 3 trial, no conclusions can be drawn regarding the safety and efficacy of metronidazole gel in the geriatric population.

All subjects were female so no gender analysis of safety or efficacy was performed.

The incidence of adverse events by treatment group was evaluated based on race (Whites and Blacks). There were too few subjects of other racial backgrounds for meaningful comparisons. Differences, if any, in the incidence of particular adverse events between white and black subjects in the two treatment groups are not considered to be clinically relevant.

Summary of Treatment-Emergent Adverse Events for Subjects of White Race

		Metronidazole Vaginal Gel, 0.75% (N=71)	MetroGel® Vaginal Gel, 0.75% (N=80)
Body System	COSTART Term	N (%)	N (%)
	Number Of Subjects With At Least One AE	30 (42.3%)	43 (53.8%)
BODY AS A WHOLE	ABDOMINAL PAIN	3 (4.2%)	9 (11.3%)
	ACCIDENTAL INJURY	--	1 (1.3%)
	ASTHENIA	--	1 (1.3%)
	CYST	--	1 (1.3%)
	FEVER	--	1 (1.3%)
	FLU SYNDROME	--	2 (2.5%)
	HEADACHE	6 (8.5%)	9 (11.3%)
	INFECTION	--	1 (1.3%)
	INFECTION FUNGAL	4 (5.6%)	8 (10.0%)
	MUCOUS MEMBRANE DISORDER	1 (1.4%)	--
	BODY SYSTEM TOTAL	13 (18.3%)	30 (37.5%)
DIGESTIVE SYSTEM	ANOREXIA	2 (2.8%)	--
	DIARRHEA	2 (2.8%)	2 (2.5%)
	DYSPEPSIA	1 (1.4%)	1 (1.3%)
	FLATULENCE	--	1 (1.3%)
	GINGIVITIS	1 (1.4%)	--

		Metronidazole Vaginal Gel, 0.75% (N=71)	MetroGel® Vaginal Gel, 0.75% (N=80)
Body System	COSTART Term	N (%)	N (%)
	NAUSEA	3 (4.2%)	3 (3.8%)
	VOMITING	1 (1.4%)	--
	BODY SYSTEM TOTAL	8 (11.3%)	5 (6.3%)
NERVOUS SYSTEM	DIZZINESS	2 (2.8%)	1 (1.3%)
	NERVOUSNESS	--	1 (1.3%)
	BODY SYSTEM TOTAL	2 (2.8%)	2 (2.5%)
RESPIRATORY SYSTEM	COUGH INCREASED	--	1 (1.3%)
	HICCUP	--	1 (1.3%)
	PHARYNGITIS	1 (1.4%)	4 (5.0%)
	RHINITIS	1 (1.4%)	2 (2.5%)
	SINUSITIS	--	2 (2.5%)
	BODY SYSTEM TOTAL	2 (2.8%)	9 (11.3%)
SKIN AND APPENDAGES	PRURITUS	4 (5.6%)	2 (2.5%)
	RASH	1 (1.4%)	--
	SWEATING	1 (1.4%)	--
	URTICARIA	1 (1.4%)	--
	BODY SYSTEM TOTAL	7 (9.9%)	2 (2.5%)
UROGENITAL SYSTEM	CERVICITIS	--	1 (1.3%)

		Metronidazole Vaginal Gel, 0.75% (N=71)	MetroGel® Vaginal Gel, 0.75% (N=80)
Body System	COSTART Term	N (%)	N (%)
	CERVIX DISORDER	--	1 (1.3%)
	DYSMENORRHEA	2 (2.8%)	2 (2.5%)
	LEUKORRHEA	2 (2.8%)	5 (6.3%)
	METRORRHAGIA	2 (2.8%)	3 (3.8%)
	PYELONEPHRITIS	2 (2.8%)	--
	URINARY FREQUENCY	--	1 (1.3%)
	URINARY TRACT INFECTION	--	3 (3.8%)
	VAGINITIS	1 (1.4%)	1 (1.3%)
	VULVOVAGINAL DISORDER	--	5 (6.3%)
	BODY SYSTEM TOTAL	9 (12.7%)	20 (25.0%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system.
At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
Source: Table 8.1 in the applicant's submission dated May 17, 2005

Summary of Treatment-Emergent Adverse Events for Subjects of Black Race

		Metronidazole Vaginal Gel, 0.75% (N=143)	MetroGel® Vaginal Gel, 0.75% (N=153)
Body System	COSTART Term	N (%)	N (%)
	Number Of Subjects With At Least One AE	59 (41.3%)	70 (45.8%)
BODY AS A WHOLE	ABDOMINAL PAIN	7 (4.9%)	7 (4.6%)
	ALLERGIC REACTION	2 (1.4%)	--
	ASTHENIA	--	1 (0.7%)
	BACK PAIN	2 (1.4%)	--
	CYST	--	1 (0.7%)
	FLU SYNDROME	1 (0.7%)	--
	HEADACHE	7 (4.9%)	8 (5.2%)
	INFECTION	2 (1.4%)	2 (1.3%)
	INFECTION FUNGAL	22 (15.4%)	33 (21.6%)
	PAIN	1 (0.7%)	1 (0.7%)
	VIRAL INFECTION	--	1 (0.7%)
	BODY SYSTEM TOTAL	41 (28.7%)	49 (32.0%)
CARDIOVASCULAR SYSTEM	HYPERTENSION	--	1 (0.7%)
	TACHYCARDIA	--	1 (0.7%)
	BODY SYSTEM TOTAL	--	2 (1.3%)
DIGESTIVE SYSTEM	ANOREXIA	--	2 (1.3%)
	CONSTIPATION	1 (0.7%)	1 (0.7%)

		Metronidazole Vaginal Gel, 0.75% (N=143)	MetroGel® Vaginal Gel, 0.75% (N=153)
Body System	COSTART Term	N (%)	N (%)
	DIARRHEA	1 (0.7%)	4 (2.6%)
	DYSPEPSIA	--	2 (1.3%)
	ESOPHAGITIS	--	1 (0.7%)
	FLATULENCE	2 (1.4%)	--
	GASTROINTESTINAL DISORDER	--	2 (1.3%)
	NAUSEA	4 (2.8%)	1 (0.7%)
	BODY SYSTEM TOTAL	8 (5.6%)	11 (7.2%)
NERVOUS SYSTEM	DEPRESSION	1 (0.7%)	--
	DIZZINESS	--	3 (2.0%)
	HALLUCINATIONS	--	1 (0.7%)
	INSOMNIA	1 (0.7%)	--
	SOMNOLENCE	--	1 (0.7%)
	BODY SYSTEM TOTAL	2 (1.4%)	3 (2.0%)
RESPIRATORY SYSTEM	ASTHMA	1 (0.7%)	1 (0.7%)
	BRONCHITIS	--	1 (0.7%)
	COUGH INCREASED	--	1 (0.7%)
	DYSPNEA	--	1 (0.7%)
	PHARYNGITIS	2 (1.4%)	1 (0.7%)
	RHINITIS	1 (0.7%)	--

		Metronidazole Vaginal Gel, 0.75% (N=143)	MetroGel® Vaginal Gel, 0.75% (N=153)
Body System	COSTART Term	N (%)	N (%)
	BODY SYSTEM TOTAL	3 (2.1%)	5 (3.3%)
SKIN AND APPENDAGES	ACNE	2 (1.4%)	--
	MACULOPAPULAR RASH	--	1 (0.7%)
	PRURITUS	8 (5.6%)	8 (5.2%)
	RASH	1 (0.7%)	2 (1.3%)
	BODY SYSTEM TOTAL	9 (6.3%)	10 (6.5%)
SPECIAL SENSES	TASTE PERVERSION	--	1 (0.7%)
	BODY SYSTEM TOTAL	--	1 (0.7%)
UROGENITAL SYSTEM	AMENORRHEA	--	1 (0.7%)
	BREAST ENLARGEMENT	1 (0.7%)	--
	BREAST PAIN	3 (2.1%)	1 (0.7%)
	CERVIX DISORDER	--	1 (0.7%)
	DYSMENORRHEA	3 (2.1%)	1 (0.7%)
	DYSURIA	1 (0.7%)	1 (0.7%)
	FEMALE LACTATION	1 (0.7%)	--
	LABIAL EDEMA	1 (0.7%)	--
	LEUKORRHEA	--	4 (2.6%)
	MENORRHAGIA	1 (0.7%)	--
	METRORRHAGIA	1 (0.7%)	--

		Metronidazole Vaginal Gel, 0.75% (N=143)	MetroGel® Vaginal Gel, 0.75% (N=153)
Body System	COSTART Term	N (%)	N (%)
	SALPINGITIS	2 (1.4%)	--
	URINARY FREQUENCY	1 (0.7%)	--
	URINARY TRACT INFECTION	1 (0.7%)	2 (1.3%)
	VAGINITIS	--	1 (0.7%)
	VULVOVAGINAL DISORDER	2 (1.4%)	3 (2.0%)
	BODY SYSTEM TOTAL	16 (11.2%)	13 (8.5%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system.
At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
Source: Table 8.2 in the applicant's submission dated May 17, 2005

7.1.5 Common Adverse Events

The adverse events (AEs) that occurred in more than 5% of subjects were abdominal pain (4.5% metronidazole group, 7.5% MetroGel group), headache (6.8%, 7.9%, respectively), fungal infection (12.3% and 17.6%), and pruritus (5.5% and 4.2%).

7.1.6 Laboratory Findings

Routine laboratory testing was not performed during the study.

7.1.7 Vital Signs

Routine testing of vital signs was not performed during the study.

7.1.8 Electrocardiograms (ECGs)

Electrocardiograms were not obtained during the study

7.1.9 Immunogenicity

Not applicable. No data on immunogenicity was included in the NDA submission.

7.1.10 Human Carcinogenicity

Not applicable. No data regarding human carcinogenicity was included in the NDA submission.

7.1.11 Special Safety Studies

Not applicable. There have been no special safety issues identified with this product.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This product does not have the potential for dependence or abuse.

7.1.13 Human Reproduction and Pregnancy Data

Metronidazole vaginal gel is in Pregnancy Category B. Metronidazole crosses the placental barrier, enters the fetal circulation, and is also secreted into human breast milk in concentrations similar to those found in plasma following oral metronidazole administration. Metronidazole has been shown to be mutagenic in a number of in vitro assay systems, although mammalian studies have failed to demonstrate a potential for genetic damage. In rodents, metronidazole is a carcinogen, causing various neoplasms, particularly mammary and hepatic tumors. Therefore, it is recommended that metronidazole vaginal gel should only be used in pregnant and nursing women if the benefit to the mother clearly outweighs the risk to the fetus.

7.1.14 Assessment of Effect on Growth

Not applicable. This product does not have the potential for growth suppression.

7.1.15 Overdose Experience

Not applicable. This product does not have the potential for overdose.

7.1.16 Postmarketing Experience

MetroGel-Vaginal® (metronidazole vaginal gel, 0.75%) has been approved since August 17, 1992. No post-marketing issues have been identified to date.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Study TCR-03 was the primary source of clinical data. A total of 579 subjects were enrolled (293 in the metronidazole group and 286 in the MetroGel group) and 334 completed the study (166 and 168, respectively). Reasons for discontinuation included failure of vaginosis symptoms to resolve, presence of *Neisseria gonorrhoea* or *Chlamydia trachomatis* or a Nugent score < 4 at screening, or adverse event (5 subjects and 6 subjects, respectively).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable. Secondary clinical data sources were not used in this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The AEs that were considered definitely or probably related to study medication in more than 5% of subjects in a treatment group were fungal infections (20 [9%] in the metronidazole group and 32 [13%] in the MetroGel group).

A review of the concomitant medications dataset revealed 66 subjects who received treatment for a yeast infection (assumed, vaginal candidiasis) during the study (23 [10%] subjects in the metronidazole group and 43 [18%] in the MetroGel group).

Clinical Reviewer's Comment: As noted in the MetroGel package insert: known or previously unrecognized vaginal candidiasis may present in approximately 6 to 10% of subjects during therapy with metronidazole vaginal gel.

In the applicant's study 10% in the metronidazole vaginal gel group and 18% in the MetroGel group developed symptomatic vaginal candidiasis during or immediately after therapy, which is consistent with previous data.

In conclusion, the treatment-emergent adverse events, regardless of relationship to study medication, reported for metronidazole were similar to MetroGel and consistent with what is known about the drug.

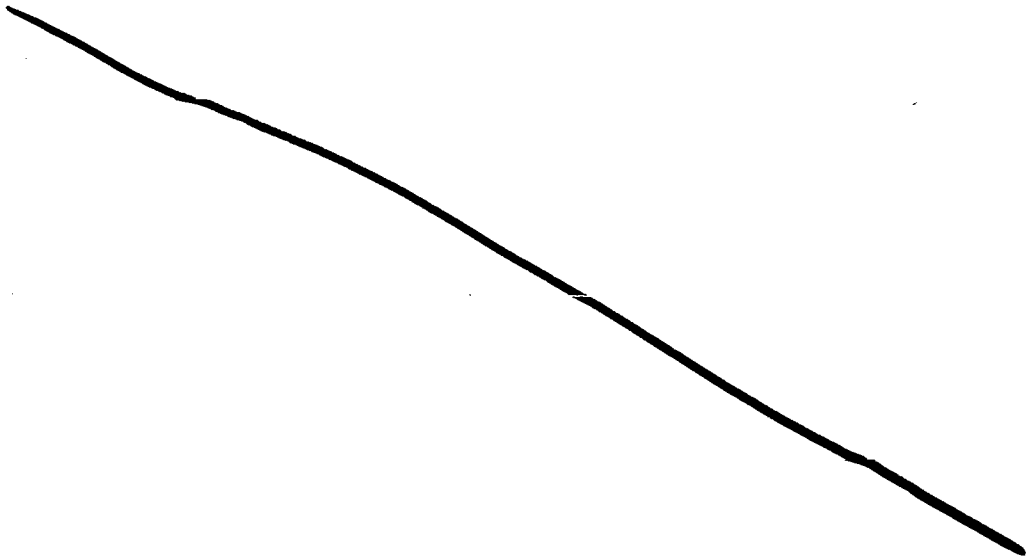
7.4 General Methodology

Not applicable. Only one clinical study was performed, therefore no pooling of data across studies was performed.

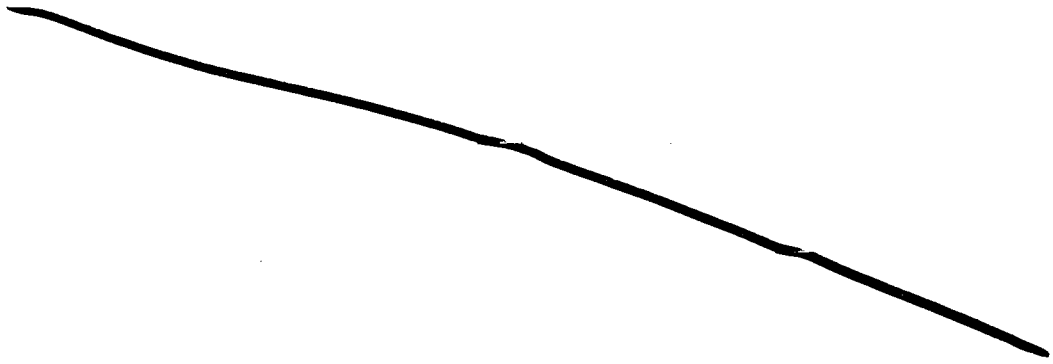
8 ADDITIONAL CLINICAL ISSUES

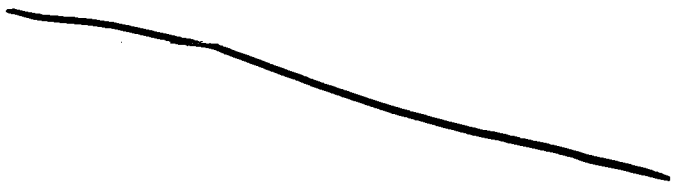
8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions



8.3 Special Populations





8.4 Pediatrics

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was held.

8.6 Literature Review

Not applicable.

8.7 Post-marketing Risk Management Plan

No post-marketing risk management plan is planned.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Metronidazole vaginal gel was found to be safe and effective for the treatment of bacterial vaginosis in adult, non-pregnant women.

9.2 Recommendation on Regulatory Action

Metronidazole vaginal gel should be approved for the treatment of bacterial vaginosis in non-pregnant women. The recommended dose is one applicator full of metronidazole vaginal gel

(approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days. For once daily dosing, metronidazole vaginal gel should be administered at bedtime.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity or Phase 4 studies at this time.

9.3.1 Risk Management Activity

None.

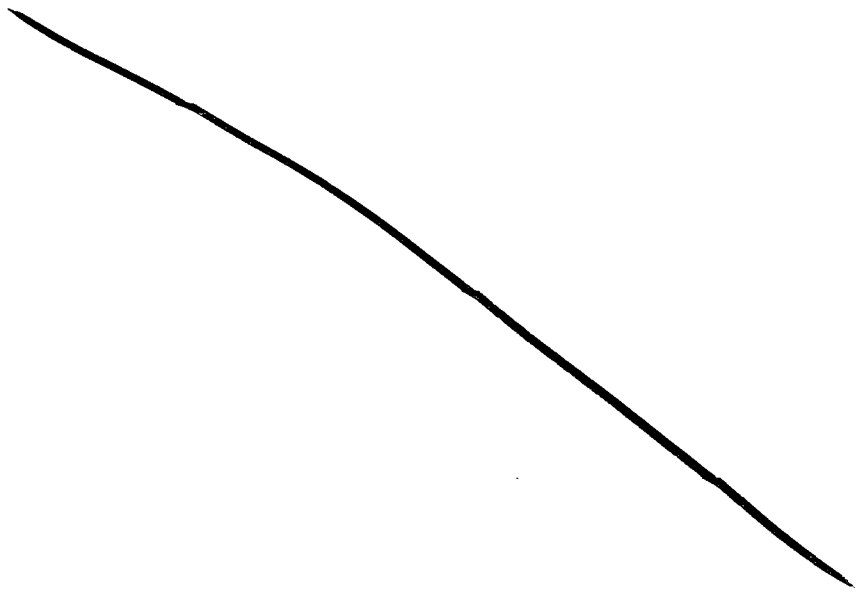
9.3.2 Required Phase 4 Commitments

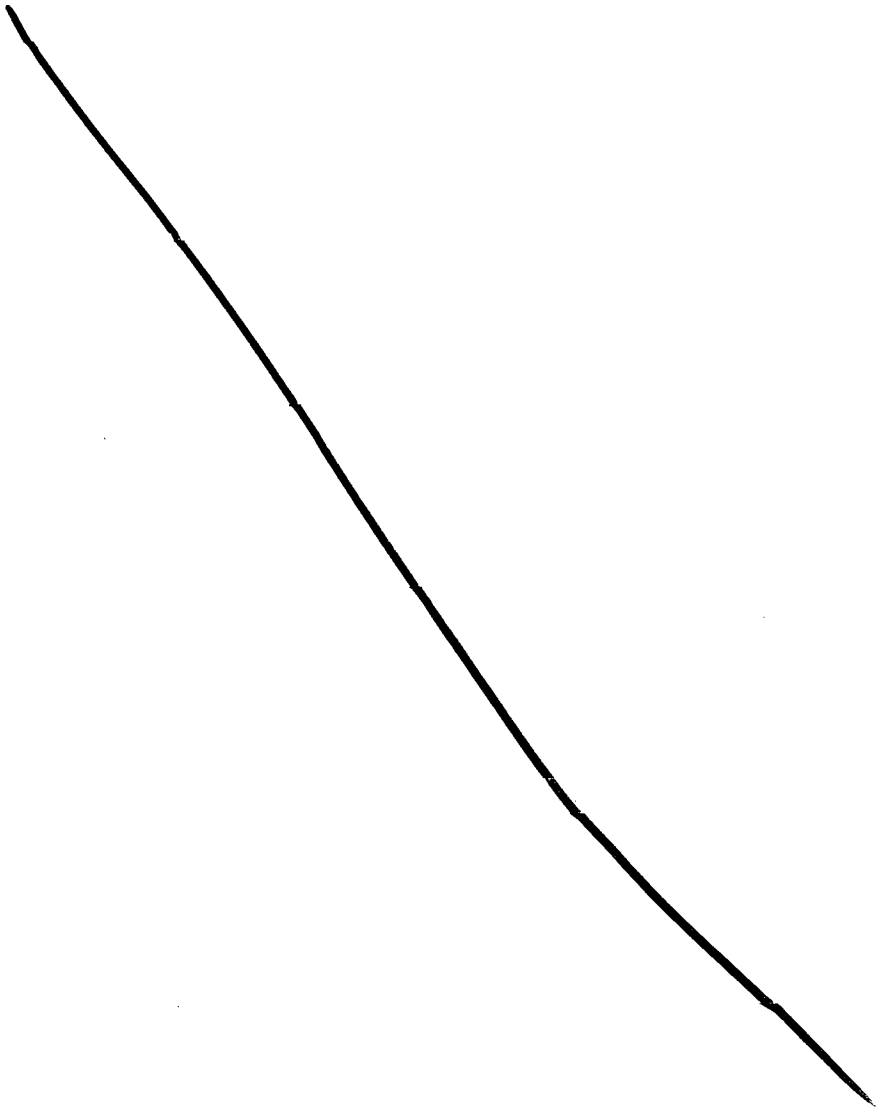
None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review





9.5 Comments to Applicant

None.

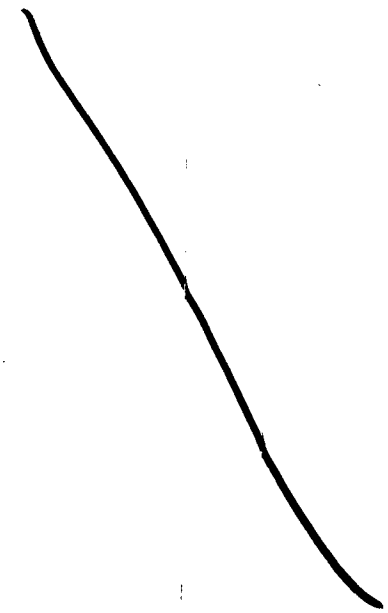
10 APPENDICES

10.1 Review of Individual Study Reports

A Multi-Center, Double-Blind, Parallel Group Study Comparing the Bioequivalence of TEVA Pharmaceuticals USA's Generic Formulation of Metronidazole Vaginal Gel, 0.75% and MetroGel-Vaginal. Metronidazole Vaginal Gel, 0.75% in the Treatment of Bacterial Vaginosis

Protocol: TCR-03
Date of Inclusion of First Patient: January 11, 2002
Date of Completion of Last Subject: March 17, 2003
Date of Study Report: May 16, 2003

Investigators: The study was performed by 20 investigators at 20 US sites



The sponsor of the study is TEVA Pharmaceuticals USA (TEVA). TEVA supplied the investigational treatments (metronidazole vaginal gel, 0.75%; and 3M Pharmaceuticals' MetroGel-Vaginal® 0.75%. Study monitoring, regulatory compliance, quality assurance, maintenance of clinical trial authorization, and safety reporting to regulatory authorities were performed by [redacted]. Data management, biostatistical

analysis, and preparation of integrated clinical/statistical reports were performed by [redacted]

10.1.1 Study Objectives

The purpose of this study was to demonstrate comparable efficacy, safety, and tolerability of TEVA Pharmaceuticals USA's generic formulation of metronidazole vaginal gel, 0.75% with 3M Pharmaceuticals' MetroGel-Vaginal® 0.75% in the treatment of bacterial vaginosis.

10.1.2 Overall Design and Plan Description

The study schedule is depicted in Table 1. This was a randomized, double-blind, parallel group study comparing TEVA Pharmaceuticals USA's metronidazole vaginal gel, 0.75% (test product) and MetroGel-Vaginal® 0.75% (reference product). This study was a comparison of the marketed product MetroGel-Vaginal® against the test product, TEVA's metronidazole vaginal gel, 0.75%.

At the Baseline Visit (Day 1) the investigator performed a medical history and pelvic exam. Subjects were randomly assigned in a 1:1 ratio (metronidazole vaginal gel:MetroGel-Vaginal®) to either one of the two study formulations. Approximately 271 subjects were to receive TEVA Pharmaceuticals USA's metronidazole vaginal gel, 0.75% and approximately 271 subjects were to receive 3M Pharmaceuticals' MetroGel-Vaginal® 0.75%. The site designated an individual not performing any other study-related procedures to dispense/collect the study medication.

The medication was applied intravaginally once daily at bedtime for five consecutive days using the supplied 5-gram vaginal applicators (for sites that gave written Subject Instructions, a sample is provided in Protocol Appendix II). Subjects returned for follow-up evaluation 7 to 14 days after the first day of treatment. The investigator performed a gynecological exam and collected specimens for the following tests:

- Saline "wet mount" to check for the presence of clue cells and *Trichomonas vaginalis*
- 10% KOH "whiff test"
- Vaginal fluid pH
- Gram's stain (for Nugent scoring)

The treatment period was five days. The final Test of Cure study visit occurred 21-30 days after the first day of treatment. Subjects who in the investigator's opinion appeared to be worsening could be discontinued at the investigator's discretion at any time during the study. An unscheduled visit could be performed for this purpose.

Enrollment was initiated at all sites under the protocol dated December 4, 2001.

There were no amendments to the protocol.

TABLE 1
Study Schedule

	Baseline Visit (Day 1)	Post-Treatment Visit (Day 8 to 15)	Test of Cure Visit (Day 22 to 31) or Early Termination
Screening/Consent	X		
Demographics	X		
Inclusion/Exclusion	X		
Medical History	X		
Vaginosis History	X		
Pelvic Examination	X	X	X
Laboratory Testing	X[1]	X[2]	X[3]
Concomitant Medications	X	X	X
Adverse Events		X	X
Clinical Response		X	X
Drug Dispensing/ Accountability[4]	X	X	
End of Study Form[5]			X
Study Diary Dispensing	X		
Study Diary Collection		X	

[1] Laboratory testing at Visit 1 consisted of wet mount to check for clue cells and *Trichonomas vaginalis*, a 10% KOH whiff test, vaginal fluid pH, Gram's stain for Nugent Scoring, a urine pregnancy test, and LCx assays for *Chlamydia trachomatis* and *Neisseria gonorrhoeae.* PAP smear was performed at Visit 1 if no results were available for the previous 12 months.
[2] Laboratory testing at the Post-Treatment Visit consisted of wet mount to check for clue cells and *Trichonomas vaginalis*, a 10% KOH whiff test, vaginal fluid pH, Gram's stain for Nugent Scoring.
[3] Laboratory testing at the Test of Cure Visit consisted of wet mount to check for clue cells and *Trichonomas vaginalis*, a 10% KOH whiff test, vaginal fluid pH, Gram's stain for Nugent Scoring, and a urine pregnancy test.
[4] The site designated an individual not performing any other study-related procedures to dispense/collect the study medication.
[5] For subjects completing the study, the End of Study form was completed at Visit 3 (Day 22 to 31). The form was completed at an unscheduled visit or at Visit 2 if the subject discontinued early.
Source: Table 9.1 in the applicant's NDA submission

10.1.3 Inclusion Criteria

1. Subjects must provide written informed consent prior to any study related procedures being performed.
2. Female subjects must have a clinical diagnosis of bacterial vaginosis, defined as having the presence of "clue cells"* 20% of the total epithelial cells on microscopic examination of the saline "wet mount," and have all of the following criteria:

    - Off-white (milky or gray), thin, homogeneous discharge

- pH of vaginal fluid ≥ 4.7
- a positive 10% KOH "whiff test"

*Diagnostic "clue cells" should have *Gardnerella* like organisms (small, non-motile, coccobacilli) covering not only the surface of the squamous epithelial cells, but also spreading out past cell boundaries, obscuring the cytoplasmic margins and thus creating a "shaggy" appearance. The entire cell need not be covered with bacteria, but cells with organisms simply sticking to the surface without extending past the cytoplasmic margins should not be considered "clue cells."

3. Subjects must be 18 years of age or older with no known medical conditions that, in the investigator's opinion, may interfere with study participation.
4. Women of childbearing potential must have a negative urine pregnancy test result upon entry into the study.
5. Subjects must agree to abstain from sexual intercourse throughout the first seven days of the study. Following the first 7 days, subjects must agree to use a non-lubricated condom when engaging in sexual intercourse.
6. Subjects must be willing to abstain from alcohol ingestion during the five-day treatment period and for one day afterward.
7. Subjects must agree to refrain from the use of intra-vaginal products throughout the study (e.g., douches, feminine deodorant sprays, spermicides, lubricated condoms, tampons, and diaphragms).

10.1.4 Exclusion Criteria

1. Subjects with known or suspected other infectious causes of vulvovaginitis (e.g., candidiasis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, active herpes simplex, or human papilloma virus) or any other vaginal or vulvar condition that in the investigator's opinion would confound the interpretation of clinical response.
2. Subjects with a Gram's stain slide Nugent score < 4 (see Table 2).
3. Subjects who received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days of randomization.
4. Subjects who have taken disulfuram within the last 14 days.
5. Subjects who have demonstrated a previous hypersensitivity reaction to metronidazole, either orally or topically administered, or any form of parabens.
6. Subjects with primary or secondary immunodeficiency.
7. Women who will be under treatment during the study period for cervical intraepithelial neoplasia (CIN) or cervical carcinoma.
8. Subjects who are pregnant, breast feeding, or planning a pregnancy.
9. Subjects who are menstruating at the time of diagnosis.
10. Subjects with intrauterine devices.
11. Concurrent anticoagulation therapy with coumadin or warfarin.
12. Concurrent use of systemic corticosteroids or systemic antibiotics.
13. Subjects with clinically significant unstable medical disorders, life-threatening diseases, or current malignancies.
14. Subjects previously enrolled in this study.

15. Subjects who have participated in another clinical trial or have taken an experimental drug within the past 30 days.
16. Subjects who are unwilling or unable to comply with the requirements of the protocol.

TABLE 2
Nugent Scoring System for Gram Stained Vaginal Smears

SCORE*	*Lactobacillus* morphotypes	*Gardnerella/Bacteriodes* spp. morphotypes	Curved Gram-variable rods
0	4+ **	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	--
4	0	4+	--

* Morphotypes are scored as the average number seen per oil immersion field (minimum of 10-20 fields should be examined). Each morphotype is then given a score from the left hand column. The total score is calculated by adding the individual morphotype scores + Lactobacillus + Gardnerella/Bacteroides + Curved Gram-negative rods.
** Quantification scale: 0 = no morphotypes seen; 1+ = less than 1 morphotype per filed; 2+ = 1 to 4 morphotypes; 3+ = 5 to 30 morphotypes; 4+ = more than 30 morphotypes per field.
Source: Study Protocol and July 1998 Draft Guidance for Industry "Bacterial Vaginosis – Developing Antimicrobial Drugs for Treatment

10.1.5 Treatments Administered

Subjects who met the inclusion/exclusion criteria after the pelvic exam were randomly assigned in a 1:1 ratio (in blocks of 4) to either one of the two study formulations:

- metronidazole vaginal gel, 0.75%, TEVA Pharmaceuticals USA, lot # 1189-064
- MetroGel-Vaginal® 0.75%, 3M Pharmaceuticals, lot # RKBN00, exp. September 1, 2004

Study medication was supplied to subjects in a single 70 gram tube. Each subject was also given five vaginal applicators. The subject was instructed to apply the medication intravaginally once a day at bedtime using the supplied 5-gram vaginal applicator (approximately 37.5 mg of metronidazole). Subjects were given subject instructions (see below) and diary cards to record medication doses. The treatment period was 5 days.

Subject Instructions:

1. To prepare the medication for application, first remove the cap from the tube and puncture the tamperproof seal with the sharp end of the tube cap. Screw on one of the supplied plastic applicators with the plunger in the down position. Fill the applicator by squeezing the tube until the applicator is full. Unscrew the applicator from the tube.
2. Insert the applicator into the vagina and depress the applicator plunger to apply the medication. This may be most easily done while lying on your back. The applicator should then be discarded.
3. You will use the medication once daily at bedtime for 5 days (5 doses).
4. Record all doses taken on the diary card provided.
5. Do not expose the study medication to extremes in temperature and do not attempt to remove the black shrink-wrap from the medication tube.

6. Please discard all applicators, used and unused, and return the study medication at your next study visit.

Precautions:
Metronidazole vaginal gel contains ingredients that may cause burning and irritation of the eye; therefore, contact with the eyes should be avoided. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

You should not drink alcohol during the five day treatment period and for one day afterward. Alcohol taken with oral metronidazole can cause nausea and vomiting. While blood levels are significantly lower with metronidazole vaginal gel than with usual doses of oral metronidazole, a possible interaction with alcohol cannot be excluded.

You should not engage in vaginal intercourse throughout the first 7 days of the study.

10.1.6 Blinding

This was a double-blind study. The investigators, staff at the study sites, study monitors, and data analysis/management personnel were blinded to the subject assignment. In order to ensure that information which could potentially bias handling of data was not disclosed, only three copies of the randomization schedule with drug assignments were generated by the applicant. One copy remained with the clinical packaging records at [redacted], one copy was sent to the Independent Statistician, and the other was sent to TEVA in a sealed envelope and maintained in a locked, fireproof cabinet. In the event of an emergency, the specific subject treatment could have been identified by removing the overlay of the two-part label, which was attached to the CRF label page after dispensing; however, every effort was made to maintain the blind. Tubes were labeled and packaged so that neither the subject nor the investigator could identify the treatment. A black shrink-wrap material concealed the identity of the sample tubes. Due to a slight variation in the reference and test applicators, a person not performing any other study related procedures collected and dispensed the study medication to ensure all applicators were discarded. The individual designated to collect the study medication did not discuss the applicator's appearance. Subjects were assigned to a treatment regimen in a double-blind fashion by assigning treatments in sequential order.

The fixed portion displayed the following information: protocol number, subject number, an investigational use statement, warning statements, and the sponsoring company's name. After dispensing, the tear off section was attached to the label page of the CRF. The tear off portion consisted of a two-part label. One section repeated the information on the fixed portion, and the other contained the blinded portion identifying the product. A two-piece, double blind label consisting of a fixed portion and a tear-off portion was attached to each subject kit.

The applicant reports that the study blind was inadvertently broken for two subjects in the study. Subject 653 (who received the reference product) and Subject 657 (who received the test product) removed the labels from their tubes of study medication. They were returned to the third-party dispenser at the site (Site 11) without unblinding any other site personnel. Both subjects completed the study. The applicant reports no other unblinding occurred during the study.

10.1.7 Primary Efficacy Variable

The efficacy of this study was based on the therapeutic cure rate at Visit 3. A therapeutic cure was a subject who was considered both a clinical cure and a bacteriological cure, where clinical response and bacteriological response were defined as follows, respectively.

Clinical Reviewer's Comment: Therapeutic outcome as determined by the applicant is similar to what is recommended in the July 1998 Draft Guidance for Industry "Bacterial Vaginosis – Developing Antimicrobial Drugs for Treatment". For comparison, the following table is reproduced from the draft Guidance.

Determination of Therapeutic Response by TOC visit (summarized)

If the clinical outcome is...	*And the Nugent score result is...*	*then the overall therapeutic outcome is...*
cure	*0-3*	*cure*
cure	*> 3*	*failure*
failure	*0-3*	*failure*
failure	*> 3*	*failure*
cure	*NE*	*NE*
NE	*0-3*	*NE*
NE	*> 3*	*NE*

NE = non-evaluable

Clinical Response:
Clinical Cure was defined as resolution of the clinical findings from the Baseline Visit. Subjects must have had all the following:

The original discharge characteristic of bacterial vaginosis returned to a normal physiological discharge, which varies in appearance and consistency depending on the menstrual cycle.

- The 10% KOH "whiff test" was negative.
- The saline wet mount was negative for clue cells.
- The vaginal fluid pH was < 4.7.

Clinical Failure was defined as a subject who did not meet the definition of clinical cure, or in the investigator's opinion, required additional treatment for the bacterial vaginosis infection.

Bacteriological Response:
Bacteriological Cure was defined as a Nugent Score < 4.

Bacteriological Failure was defined as a Nugent Score ≥ 4.

Subjects who were classified as clinical failures at Visit 2 were discontinued from the study, and their clinical and bacteriological responses and treatment assessments were carried forward to

Visit 3. The primary efficacy endpoint was the proportion of subjects with a therapeutic cure at Visit 3.

10.1.8 Statistical and Analytical Plan

10.1.8.1 Data Sets Analyzed

Three subject populations were defined, intent-to-treat (ITT), modified intent-to-treat (MITT) and per-protocol (PP). An ITT subject was any individual who received study medication and returned for at least one follow-up visit. A MITT subject was any individual who (a) met inclusion and exclusion criteria, (b) received study medication, (c) returned for at least one follow-up visit, and (d) had a negative test result for *Neisseria gonorrhoeae, Chlamydia trachomatis*, and a Gram's stain slide Nugent Score ≥ 4 at Visit 1.

A PP subject was any individual who (a) met all inclusion/exclusion criteria, (b) was compliant with study medication (received at least 3 consecutive days of therapy and no more than 6 days of therapy), (c) had no study violations which could have altered the effect of, or the accurate assessment of, the applied study treatment, and (d) was assessed for efficacy at Visit 3 (within Day 22 to Day 31) or defined as failure at Visit 2.

Clinical Reviewer's Comment: The applicant also stated in their study report that "subjects who began using study treatment more than 2 days after the Baseline visit were excluded from PP analyses. Subjects were not excluded from PP analyses for using intravaginal products post-treatment." An additional analysis excluding subjects who used intravaginal products post-treatment was also conducted by the applicant, and the results are provided in the Results section of this review.

Subjects with the following protocol deviations, which were felt by the applicant no to alter the effect or assessment of study treatment, were included by the applicant in the PP analyses:

- Presence of vaginal discharge unrelated to bacterial vaginosis
- Menses during a study visit
- pH ≥ 4.7 unrelated to bacterial vaginosis
- Use of intravaginal products post-treatment
- Use of certain concomitant medications
- Removal of shrinkwrap on medication tube

Safety analyses were conducted on the ITT population, and efficacy analyses were conducted on both the PP and the MITT populations. Data for all subjects is included in the subject listings.

10.1.8.2 Windowing Conventions

The following windowing conventions were used for the clinical and bacteriological evaluations including the vaginal fluid discharge and microbiological testing.

Visit Window	
Visit 1	Day 1
Visit 2	Day 8 to Day 15
Visit 3	Day 22 to Day 31

Any observation that fell outside the windows is marked with an asterisk in the listings.

10.1.8.3 Handling of Dropouts or Missing Values

For the analysis of efficacy, a last-observation-carried-forward (LOCF) approach was used for missing efficacy results in the MITT population. For PP subjects who were discontinued from the study at Visit 2 due to clinical failure, clinical and bacteriological responses were carried forward to Visit 3.

Clinical Reviewer's Comment: The Division usually considers a worst-case scenario outcome for subjects with missing data in the MITT analysis and this will be applied in the FDA MITT analysis (see Results section).

10.1.8.4 Efficacy Parameters and Analyses

Primary Efficacy Endpoints and Analyses
The primary efficacy endpoint is the proportion of subjects with therapeutic cure at Visit 3. A therapeutic cure was a subject who was considered both a clinical cure and a bacteriological cure.

A two-sided 90% confidence interval about the difference in therapeutic cure rates between the test and reference products was constructed by the applicant using Wald's method with Yates' continuity correction based on the data of PP subjects pooled from all clinical centers. Bioequivalence of the test product to the reference product was obtained if the confidence bounds of the 90% confidence interval were contained within the limits –0.20 (–20%) to 0.20 (20%).

Clinical Reviewer's Comment: The Office of Generic Drugs (OGD) defines "clinical bioequivalence" as defined above in this study. The difference in therapeutic cure rates between treatment groups for this study (as shown in the Results section) fell outside this interval (90% CI [6.07%, 25.65%]). In the Office of New Drugs, the difference in therapeutic cure rates is based upon a 95% CI of the difference with a delta of ± 20%, which is the standard that the applicant was held to for this study. See Results for further discussion. It should also be noted that recent applications for drugs to treat BV submitted to the Division have used a non-inferiority margin of -15% rather than -20%.

No formal statistical analyses were performed to detect treatment-by-center interactions. Analysis results were summarized by center, and the homogeneity of treatment effects was investigated using descriptive statistics. If a significant treatment-by-center interaction was

observed, the nature and effect of this interaction was examined. A significant effect was defined as a difference in test-to-reference success proportions within a center that was opposite in sign and whose magnitude exceeded the mean difference across all centers by at least three-fold.

The above analyses were also conducted on the MITT population to evaluate the consistency of the PP subject findings.

Secondary Efficacy Endpoints and Analyses
The secondary efficacy endpoint was the proportion of subjects with therapeutic cure at Visit 2.

Similar analyses as described for the primary efficacy endpoint were performed on the secondary efficacy endpoint by the applicant for both the PP and MITT populations.

Tolerability Analysis
Proportions of subjects completing treatment were compared between the test and reference treatment groups for the MITT population. The significance was evaluated by a two-sided continuity-corrected Z-test based on the data pooled from all centers.

10.1.9 Safety Evaluations

Adverse events were monitored throughout the study. Treatment-emergent adverse events are those events with a start date on or after the study drug administration date, or those events with a start date prior to the study drug but continuing and increasing in severity after study drug administration. If the onset date of an adverse event was missing and the end date was missing or was after study drug administration, that event was counted as a treatment-emergent adverse event. If the onset date of an adverse event was the same as the study drug administration date, but the time of onset was missing and the end date was missing or after administration of study drug, that event was counted as a treatment-emergent adverse event. Adverse events were coded using the COSTART dictionary (Coding Symbols for a Thesaurus of Adverse Reaction Terms), 5th edition.

10.1.10 Determination of Sample Size

The treatment contrast of primary interest was a two one-sided test evaluation of the proportions of subjects with therapeutic cure at Visit 3 (the Test of Cure Visit). Sample size was based on information obtained by the applicant about MetroGel®-Vaginal once a day formulation in the NDA "Summary Basis of Approval." The test was constructed as a two-sided 90% Wald's confidence interval with Yates' continuity correction to have a 90% power. For an asymptotically normal 90% continuity-corrected confidence interval about the difference in success proportions between the TEVA (test) and MetroGel-Vaginal (reference) products, covering a maximum allowable difference of 0.20, a minimum of 190 per-protocol subjects per treatment group was required. This was based on an expected therapeutic cure rate of 55%; the calculation allows for the possibility of the true cure rate of the test product ranging from 95% to 105% of the reference product cure rate.

10.1.11 Disposition of Study Subjects

A total of 579 subjects were enrolled into the study, and 334 subjects completed the study. The disposition of subjects is summarized in Table 3.

TABLE 3
Subject Discontinuations by Reason

	Metronidazole Vaginal Gel, 0.75%	**MetroGel® Vaginal Gel, 0.75%**
Number Randomized	**293**	**286**
Number Completed Study	**166 (57%)**	**168 (59%)**
Reason Discontinued	127 (43%)	118 (41%)
Vaginosis symptoms failed to show improvement or worsened	29 (10%)	34 (12%)
A positive LCx assay for the presence of either *Neisseria gonorrhoeae* or *Chlamydia trachomatis* or a Nugent score < 4 at screening	60 (20%)	44 (15%)
Adverse event	5 (2%)	6 (2%)
Serious adverse event	0 (0%)	0 (0%)
Pregnancy	0 (0%)	0 (0%)
Protocol violation	7 (2%)	2 (1%)
Subject refused continued participation/withdrew consent	9 (3%)	6 (2%)
Lost to follow-up	15 (5%)	23 (8%)
Other	2 (1%)	3 (1%)

Source: Table 10.1 in the applicant's study report

10.1.12 Efficacy Evaluability

Three subject populations were defined by the applicant: intent-to-treat (ITT), modified intent-to-treat (MITT) and per-protocol (PP). By the applicant's definition, an ITT subject was any individual who received study medication and returned for at least one follow-up visit. A MITT subject was any individual who (a) met inclusion and exclusion criteria, (b) received study medication, (c) returned for at least one follow-up visit, and (d) had a negative test result for *Neisseria gonorrhoeae, Chlamydia trachomatis*, and a Gram's stain slide Nugent Score ≥ 4 at Visit 1. A PP subject was any individual who (a) met all inclusion/exclusion criteria, (b) was compliant with study medication (received at least 3 consecutive days of therapy and no more than 6 days of therapy), (c) had no study violations which could have altered the effect of, or the accurate assessment of, the applied study treatment, and (d) was assessed for efficacy at Visit 3 (within Day 22 to Day 31) or defined as failure at Visit 2.

Safety analyses were conducted by the applicant on the ITT population, and efficacy analyses were conducted on both the PP and the MITT populations.

Table 4 summarizes the total enrollment and eligibility for the applicant's analysis of all subjects enrolled into the study. The subjects who used study medication comprised the Intent-to-Treat population, which was also considered to be the Safety population (220 in the metronidazole group and 239 in the MetroGel group).

TABLE 4
Subject Evaluability

	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%
Subjects Enrolled	293	286
Subjects Excluded from Intent-to-Treat Analysis	73 (25%)	47 (16%)
Subjects Included in Intent-to-Treat Analysis	220 (75%)	239 (84%)
Subjects Excluded from Modified Intent-to-Treat Analysis	87 (30%)	71 (25%)
Subjects Included in Modified Intent-to- Treat Analysis	206 (70%)	215 (75%)
Subjects Excluded from Per-Protocol Analysis	138 (47%)	127 (44%)
Subjects Included in Per-Protocol Analysis	155 (53%)	159 (56%)

Source: Table 11.1 in the applicant's study report

Clinical Reviewer's Comment: A modified Intent-to-Treat (MITT) population should include all randomized subjects who receive at least one dose of study drug and who have bacteriologic evidence of bacterial vaginosis (i.e., Nugent score ≥ 4) at baseline. Post-baseline factor(s) should not result in exclusion from the MITT population. Subjects who have missing data should be considered failures in the MITT analysis. The applicant was asked to populate an evaluability table, accounting for all subjects excluded from each of the three analysis populations (Safety (Intent-to-Treat), MITT and Per Protocol. The applicant was informed that their current definitions of the Safety (Intent-to-Treat) and PP populations are acceptable. In addition, the applicant was asked to indicate the reason for exclusion from the PP population. Only the primary reason for exclusion should be indicated for each subject.

Table 4A was submitted by the applicant in response to the above request.

The applicant also supplied specific information on subjects who used prohibited medications or who violated other exclusion criteria, as requested.

The subjects who used prohibited medications in the metronidazole group used the following medications:
Metronidazole group: prednisone (806), ciprofloxacin (364) minocycline (647), topical miconazole (215), and clotrimazole cream (672)

MetroGel group: macrobid (559 and 206), solumedrol (255), prednisone (420), azithromycin (255 and 638), amoxicillin (302), cefzil (607), monistat (103 and 261), terazole 3 cream (303)

TABLE 4A
FDA Defined Subject Evaluability

	Metronidazole Vaginal Gel, 0.75%	*MetroGel® Vaginal Gel, 0.75%*
Number Randomized	***293***	***286***
Number Included in the Safety Population*	***220***	***239***
Subjects who did not take any study medication or did not return for any post-baseline visit	*73*	*47*
Number Included in the Modified Intent-to-Treat (MITT) Population**	***229***	***243***
Reasons for Exclusion from the MITT Population		
Did not take any study medication	*37*	*22*
Did not meet the bacteriological definition of BV at baseline (Nugent score < 4)	*27*	*21*
Number Included in the Per Protocol (PP) Population	***155***	***159***
Reasons for Exclusion from the PP Population		
Known/suspected infectious causes of vulvovaginitis other than BV	*17*	*20*
Started using study medication later than 2 days after Visit 1	*13*	*9*
Had sexual intercourse /used intra-vaginal products during the first 7 days of the study	*2*	*2*
Received less than 3 consecutive days of therapy or more than 6 days of therapy	*4*	*6*
Use of prohibited medication (list number of subjects by category of drug i.e., systemic antimicrobials, systemic corticosteroids, warfarin, etc.)	*5*	*10*
Other exclusion criteria violation (list specific example)	*0*	*1*
Lost to follow-up	*3*	*10*
Test-of-Cure visit (Visit 3) outside the window	*30*	*26*

** Safety population includes subjects taking at least one dose to study medication and returned for at least one post-baseline visit*

*** MITT population includes subjects taking at least one dose to study medication and who meet the bacteriological definition of bacterial vaginosis (i.e., Nugent score ≥ 4) at baseline.*

Source: applicant's submission dated February 3, 2005

10.1.13 Demographic and Other Baseline Characteristics

Demographic data recorded at baseline are summarized in Table 5 for the ITT population. All subjects were female. Most of the subjects were black (65%). The mean age of the subjects was 33 years with a range of 18 to 77 years.

Table 5
Baseline Characteristics for Intent-to-Treat Population

Characteristic		Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=239)	p-value
Race	White	71 (32%)	80 (33%)	0.956[1]
	Black	143 (65%)	153 (64%)	
	Hispanic	3 (1%)	3 (1%)	
	Asian	2 (1%)	1 (0%)	
	Other	1 (0%)	2 (1%)	
Age (years)	Mean ± Std	32.99 ± 10.74	32.68 ± 10.12	0.732[2]
	Min - Max	18.1 - 71.6	18.2 - 77.5	
History of Urogenital Disorders	*Trichomonas Vaginalis*	24 (11%)	46 (19%)	0.006[1]
	Chlamydia Trachomatis	50 (23%)	53 (22%)	0.774[1]
	Neisseria Gonorrhoeae	18 (8%)	21 (9%)	0.659[1]
	Herpes Simplex	19 (9%)	15 (6%)	0.314[1]
	Active Genital Warts	17 (8%)	12 (5%)	0.157[1]

[1] P-values for treatment comparisons from Cochran-Mantel-Haenszel test adjusting for center.
[2] P-values for treatment comparisons from Friedman's test with treatment and center as fixed effects.
Source: abstracted from Table 11.2.1.A in the applicant's study report

10.1.14 Efficacy Results

10.1.14.1 Primary Endpoint

The primary efficacy endpoint was the proportion of subjects with therapeutic cure at Visit 3.

A two-sided 90% confidence interval about the difference in therapeutic cure rates between the test and reference products was constructed by the applicant using Wald's method with Yates' continuity correction for the PP population. Bioequivalence of the test product to the reference product was concluded if the confidence bounds of the 90% confidence interval were contained within the limits –0.20 (–20%) to +0.20 (20%).

The therapeutic cure rate at Visit 3 is summarized in Table 6. Metronidazole vaginal gel was determined to be non-inferior (slightly superior) to MetroGel, when analyzed using both the PP and MITT populations.

The secondary efficacy endpoint was the proportion of subjects with a therapeutic cure at Visit 2, also shown in Table 6. Again, metronidazole vaginal gel was determined to be non-inferior (slightly superior) to MetroGel, when analyzed using both the PP and MITT populations.

TABLE 6
Analysis of Primary and Secondary Efficacy Endpoints

Efficacy Endpoint	Subjects	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	90% Confidence Interval[1]
Primary Efficacy: Therapeutic Cure Rate At Visit 3	Per-Protocol	(N=155)	(N=159)	
		86 (55%)	63 (40%)	(6.07%, 25.65%)
	Modified Intent-to-Treat[2]	(N=206)	(N=215)	
		111 (54%)	89 (41%)	(4.07%, 20.91%)
Secondary Efficacy: Therapeutic Cure Rate At Visit 2	Per-Protocol	(N=155)	(N=159)	
		100 (65%)	78 (49%)	(5.67%, 25.46%)
	Modified Intent-to-Treat[2]	(N=206)	(N=215)	
		134 (65%)	113 (53%)	(4.19%, 20.79%)

For subjects who were identified as clinical failures and were discontinued or should have been discontinued from the study at Visit 2, clinical and bacteriological responses at Visit 2 were carried forward to Visit 3.
[1]Confidence intervals from Wald's method with Yates' continuity correction.
[2]A last-observation-carried-forward (LOCF) approach was used for missing efficacy results for the mITT subjects.
Source: Table 11.4.1 in the applicant's NDA study report

Clinical Reviewer's Comment: The applicant was informed that clinical non-inferiority in the Office of New Drugs is assessed using a 95% confidence interval about the difference in therapeutic cure rates (primary efficacy endpoint) between the test drug and comparator for both the MITT and PP populations. They were asked to recalculate results using a 95% confidence interval for the primary efficacy analysis, as well as the secondary efficacy endpoints for both the MITT and PP populations.

Table 6A was submitted by the applicant in response to the above request.

TABLE 6A
Applicant's Analysis of Primary and Secondary Efficacy Endpoints

Efficacy Endpoint	Subjects	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	95% Confidence Interval[1]
Primary Efficacy: Therapeutic Cure Rate At Visit 3	Per-Protocol	(N=155)	(N=159)	
		86 (55%)	63 (40%)	(4.31%, 27.41%)
	Modified Intent-to-Treat[2]	(N=229)	(N=243)	
		113 (49%)	94 (39%)	(1.33%, 20.00%)
Secondary Efficacy: Therapeutic Cure Rate At Visit 2	Per-Protocol	(N=155)	(N=159)	
		100 (65%)	78 (49%)	(3.91%, 27.23%)
	Modified Intent-to-Treat[2]	(N=229)	(N=243)	
		137 (60%)	117 (48%)	(2.32%, 21.03%)

For subjects who were identified as clinical failures and were discontinued or should have been discontinued from the study at Visit 2, clinical and bacteriological responses at Visit 2 were carried forward to Visit 3.
[1]Confidence intervals from Wald's method with Yates' continuity correction.
[2]A last-observation-carried-forward (LOCF) approach was used for missing efficacy results for the mITT subjects.
Source: applicant's submission dated February 3, 2005

Clinical Reviewer's Comments: In Table 6A the applicant included 6 metronidazole and 5 MetroGel subjects as successes in the PP population. However, these subjects were determined by the Clinical and Statistical Reviewers not to meet the criteria necessary for clinical success (either for absence of a discharge or pH > 4.7. The applicant attributed these findings to cause(s) other than BV. The Reviewers did not agree with this approach and these subjects were included as failures in the FDA's PP analysis.

Also, in Table 6A the applicant used a last-observation-carried forward approach for the subjects in the MITT population (i.e., subjects with therapeutic cures at Visit 2 were considered cures at Visit 3, if clinical data were missing at Visit 3). The Division traditionally considers subjects with missing data to be failures ("worst-case" scenario) in MITT analyses. Therefore, 15 subjects in the metronidazole PP population and 19 subjects in the MetroGel PP population were re-classified by the Clinical and Statistical Reviewers from therapeutic cures to therapeutic failures at Visit 3.

The FDA's revised analyses using for the PP and MITT populations can be seen in Table 6B for the primary endpoint (therapeutic cure at Visit 3).

TABLE 6B
FDA's Analysis of Primary Efficacy Endpoint

Efficacy Endpoint	Subjects	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	95% Confidence Interval
Primary Efficacy: Therapeutic Cure Rate At Visit 3	Per-Protocol	(N=155)	(N=159)	
		80 (51.6%)	58 (36.5%)	(3.6%, 26.6%)
	Modified Intent-to-Treat	(N=229)	(N=243)	
		98 (42.8%)	75 (30.9%)	(2.8%, 21.0%)

An additional analysis performed by the applicant excluding subjects who used intravaginal products post-treatment is provided in Table 7.

TABLE 7
Analysis of Primary and Secondary Efficacy Endpoints
Excluding Subjects Who Used Other Vaginal Products After Treatment

Efficacy Endpoint	Subjects	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	90% Confidence Interval[1]
Primary Efficacy: Therapeutic Cure Rate At Visit 3	Per-Protocol	(N=150)	(N=158)	
		83 (55%)	63 (40%)	(5.56%, 25.36%)
	Modified Intent-to- Treat[2]	(N=206)	(N=215)	
		111 (54%)	89 (41%)	(4.07%, 20.91%)
Secondary Efficacy: Therapeutic Cure Rate At Visit 2	Per-Protocol	(N=150)	(N=158)	
		96 (64%)	78 (49%)	(4.77%, 24.80%)
	Modified Intent-to- Treat[2]	(N=206)	(N=215)	
		134 (65%)	113 (53%)	(4.19%, 20.79%)

Subjects who used other vaginal products after treatment period with no other protocol violation were excluded from the per-protocol analyses.
For subjects who were identified as clinical failures and were discontinued or should have been discontinued from the study at Visit 2, clinical and bacteriological responses at Visit 2 were carried forward to Visit 3.
[1] Confidence intervals from Wald's method with Yates' continuity correction.
[2] A last-observation-carried-forward (LOCF) approach was used for missing efficacy results for the mITT subjects.
Source: Table 14.3.1 in the applicant's study report

Clinical Reviewer's Comment: A discussion of the Division's approach regarding missing data is warranted here.

The applicant assessed outcome of subjects at two study visits following study drug administration. Clinical and bacteriological outcomes were assessed at both visits and the data from Visit 3 was used to determine therapeutic cure for the purposes of the primary endpoint of the study. If subjects had missing data at Visit 3, and they were not a therapeutic failure at Visit

2, then they were considered indeterminate at Visit 3 and a therapeutic failure in the FDA's analysis of the primary endpoint, as discussed above.

The Clinical and Statistical Reviewers determined that for subjects with missing data at Visit 3, clinical, but not bacteriologic failures, at Visit 2 would be carried forward, for the purpose of determining therapeutic response at Visit 3. Clinical failures at Visit 2 were carried forward as therapeutic failures at Visit 3. However, bacteriologic failures at Visit 2 were not carried forward as therapeutic failures at Visit 3, as long as they achieved clinical cure at Visit 2. The rationale for this approach is that Visit 2 is not required to be a visit in the clinic, as per the draft Guidance, and many sponsors obtain data on clinical symptoms by interviewing the subject over the telephone without performing physical exams in order to obtain a specimen for Nugent scoring. Therefore, we usually only rely on Nugent scores from Visit 3. Also, it is suspected that the Nugent score (bacteriological response) may lag behind symptomatic (clinical) response,[1] which is further support to not rely on bacteriologic information from Visit 2.

In order to assess whether clinical response may reverse from cure to failure between Visits 2 and 3, and thereby make the above assumptions invalid, the Reviewer looked for subjects in the study were clinical cures/bacteriologic failures at Visit 2 and became clinical failures/bacteriologic cures at Visit 3. Nine subjects were identified. Of these subjects, two (86 and 600) developed a yeast infection following study drug (at or before Visit 2).

The individual components of the clinical component for these nine subjects at Visit 2 and Visit 3 are shown below. Table 9 was created by the Reviewer. For the majority of these subjects, ≥ 2 of the 4 clinical components became abnormal at Visit 3, with the exception of Subject 482 (metronidazole group) who only had an abnormal pH reading at Visit 3. The data do not lead to any conclusion regarding why these subjects may have reversed their outcomes from Visit 2 to Visit 3; however, the number of subjects is small and therefore a reversal of clinical outcome is assumed not be clinically significant in this study.

1 Cook RL, et al. Journal of Clinical Microbiology 1992;30:870-7.

TABLE 9
Subjects with a Reversal of Outcome from Visit 2 to Visit 3

Subject #	*Visit #*	*20% Clue Cells*	*Discharge*	*KOH*	*pH of Vaginal Fluid ≥ 4.7*
141/ Metronidazole Gel	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3	*Present*	*Present*	*Positive*	*Yes*
482/ Metronidazole Gel	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3	*Absent*	*Absent*	*Negative*	*Yes*
586/ Metronidazole Gel	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3	*Present*	*Present*	*Positive*	*Yes*
86/ MetroGel[1,3]	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3 (out of window)	*Absent*	*Present*	*Negative*	*Yes*
532/ MetroGel	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3	*Present*	*Absent*	*Positive*	*Yes*
600/ MetroGel[3]	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3	*Present*	*Present*	*Positive*	*Yes*
669/ MetroGel[2]	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3 (out of window)	*Present*	*Present*	*Positive*	*Yes*
693/ MetroGel	*Visit 2*	*Absent*	*Absent*	*Negative*	*No*
	Visit 3	*Present*	*Present*	*Positive*	*No*
783/ MetroGel	*Visit 2*	*Absent*	*Absent*	*Absent*	*No*
	Visit 3	*Present*	*Present*	*Absent*	*No*

[1] *Excluded from PP because Visit 3 was out of window*
[2] *Excluded from PP because study med was started later than 2 days after Visit 1 and Visit 3 was out of window*
[3] *noted to have developed a yeast infection at or before Visit 2*

10.1.14.2 Other Endpoints

Clinical cure rates and Nugent (bacteriological) cure rates, individually, were evaluated by the Division at Visit 3.

Clinical Reviewer's Comment: Table 8 was created by the Clinical and Statistical Reviewers using the MITT and PP populations, as defined in the comment pertaining to Table 6B above.

TABLE 8
FDA's Clinical and Bacteriological (Nugent) Cure Rates at Visit 3

Population	Endpoint	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	Difference (95% CI)
Per Protocol	Clinical Cure	98/155 (63.2)	86/159 (54.1)	9.1 (-2.4, 20.6)
	Nugent Cure	95/155 (61.3)	77/159 (48.4)	12.9 (1.3, 24.4)
Modified Intent To Treat	Clinical Cure	120/229 (52.4)	110/243 (45.3)	7.1 (-2.3, 16.5)
	Nugent Cure	119/229 (52.0)	100/243 (41.1)	10.9 (1.5, 20.3)

An analysis of efficacy results for special populations (age, gender, and race) was performed by the Division. Differences in age could not be assessed, since the majority of the subjects in this study were less than the age of 55 (96%). All subjects were female so no gender analysis was performed. There was no significant difference in therapeutic cure rates by race when compared to the overall study population (data not shown).

10.1.15 Safety Evaluation

The number of subjects reporting one or more treatment-emergent AEs is summarized in Table 10. The two treatment groups were comparable with regard to the incidence of AEs. There was no significant statistical difference between the two treatment groups with regard to the occurrence of AEs (both $p>0.05$).

Table 10
Number of Subjects Reporting Treatment-Emergent Adverse Events

	Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=239)	P-value for Generic vs. MetroGel®
Adverse event(s) regardless of relationship to study medication	92 (41.8%)	117 (49.0%)	0.125[1]
Adverse event(s) probably related or definitely related to study medication	25 (11.4%)	41 (17.2%)	0.077[1]

[1] P-values for treatment comparisons from Pearson's chi-square test for ITT subjects pooled from all study centers.
Source: Table 12.2.1.A in the applicant's study report

Treatment-emergent AEs are summarized by severity and relationship to treatment in Table 11. There was no significant statistical difference between the two treatment groups with regard to severity or relationship to treatment (both $p>0.05$).

The AEs that occurred in more than 5% of subjects in any treatment group were abdominal pain, headache, fungal infection, and pruritus. Most AEs were mild or moderate in severity.

The AEs that were considered definitely or probably related to the study medication that occurred in more than 5% of subjects were fungal infections.

No severe AEs were considered definitely or probably related to the study medication. Two SAEs were reported (both in the MetroGel group). Both SAEs were hospitalizations for pre-study conditions, and were considered not related to study medication. No deaths were reported. Eleven subjects discontinued due to adverse events, 5 in the test group and 6 in the reference group.

Table 11
Treatment-Emergent Adverse Events by Severity and Relationship to Study Drug

Parameter		Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=239)	P-value for Generic vs. MetroGel®
Number (%) of Subjects with At Least One AE		92 (41.8%)	117 (49.0%)	
Severity of Events	Unknown	0 (0%)	1 (1%)	0.105[1]
	Mild	53 (58%)	80 (68%)	
	Moderate	32 (35%)	30 (26%)	
	Severe	7 (8%)	6 (5%)	
Relationship of Events to Study Medication	Not Related	41 (45%)	57 (49%)	0.092[1]
	Possibly Related	26 (28%)	19 (16%)	
	Definitely Related	0 (0%)	3 (3%)	

[1] P-values for treatment comparisons from Mantel-Haenszel test or Fisher's exact test if appropriate, for ITT subjects pooled from all study centers.
Source: Table 12.2.1.B in the applicant's study report

The incidence of treatment-emergent AEs summarized by treatment, COSTART body system, and COSTART preferred term in Table 12. Each AE (preferred term) experienced by at least one subject is listed under the appropriate body system. The AEs that occurred in more than 5% of subjects were abdominal pain (4.5% metronidazole group, 7.5% MetroGel group), headache (6.8%, 7.9%, respectively), fungal infection (12.3% and 17.6%), and pruritus (5.5% and 4.2%).

TABLE 12
Summary of Treatment-Emergent Adverse Events by Treatment

		Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=299)
Body System	COSTART Term	N (%)	N (%)
	Number Of Subjects With At Least One AE	92 (41.8%)	117 (49.0%)
BODY AS A WHOLE	ABDOMINAL PAIN	10 (4.5%)	18 (7.5%)
	ACCIDENTAL INJURY	--	1 (0.4%)
	ALLERGIC REACTION	2 (0.9%)	--
	ASTHENIA	--	2 (0.8%)
	BACK PAIN	2 (0.9%)	--
	CYST	--	2 (0.8%)
	FEVER	--	1 (0.4%)
	FLU SYNDROME	1 (0.5%)	2 (0.8%)
	HEADACHE	15 (6.8%)	19 (7.9%)
	INFECTION	3 (1.4%)	3 (1.3%)
	INFECTION FUNGAL	27 (12.3%)	42 (17.6%)
	MUCOUS MEMBRANE DISORDER	1 (0.5%)	--
	PAIN	1 (0.5%)	1 (0.4%)
	VIRAL INFECTION	--	1 (0.4%)
	BODY SYSTEM TOTAL	57 (25.9%)	83 (34.7%)
CARDIOVASCULAR SYSTEM	HYPERTENSION	--	1 (0.4%)
	TACHYCARDIA	--	1 (0.4%)
	BODY SYSTEM TOTAL	--	2 (0.8%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once.
Source: Table 12.2.2.A in the applicant's study report

TABLE 12 (continued)
Summary of Treatment-Emergent Adverse Events by Treatment

		Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=239)
Body System	COSTART Term	N (%)	N (%)
DIGESTIVE SYSTEM	ANOREXIA	2 (0.9%)	2 (0.8%)
	CONSTIPATION	1 (0.5%)	1 (0.4%)
	DIARRHEA	3 (1.4%)	6 (2.5%)
	DYSPEPSIA	1 (0.5%)	3 (1.3%)
	ESOPHAGITIS	--	1 (0.4%)
	FLATULENCE	2 (0.9%)	1 (0.4%)
	GASTROINTESTINAL DISORDER	--	2 (0.8%)
	GINGIVITIS	1 (0.5%)	--
	NAUSEA	7 (3.2%)	5 (2.1%)
	VOMITING	1 (0.5%)	--
	BODY SYSTEM TOTAL	16 (7.3%)	17 (7.1%)
NERVOUS SYSTEM	DEPRESSION	1 (0.5%)	--
	DIZZINESS	2 (0.9%)	4 (1.7%)
	HALLUCINATIONS	--	1 (0.4%)
	INSOMNIA	1 (0.5%)	--
	NERVOUSNESS	--	1 (0.4%)
	SOMNOLENCE	--	1 (0.4%)
	BODY SYSTEM TOTAL	4 (1.8%)	5 (2.1%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once.
Source: Table 12.2.2.A in the applicant's study report

TABLE 12 (continued)
Summary of Treatment-Emergent Adverse Events by Treatment

		Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=239)
Body System	COSTART Term	N (%)	N (%)
RESPIRATORY SYSTEM	ASTHMA	1 (0.5%)	1 (0.4%)
	BRONCHITIS	--	1 (0.4%)
	COUGH INCREASED	--	2 (0.8%)
	DYSPNEA	--	1 (0.4%)
	HICCUP	--	1 (0.4%)
	PHARYNGITIS	4 (1.8%)	5 (2.1%)
	RHINITIS	2 (0.9%)	2 (0.8%)
	SINUSITIS	--	2 (0.8%)
	BODY SYSTEM TOTAL	6 (2.7%)	14 (5.9%)
SKIN AND APPENDAGES	ACNE	2 (0.9%)	--
	MACULOPAPULAR RASH	--	1 (0.4%)
	PRURITUS	12 (5.5%)	10 (4.2%)
	RASH	3 (1.4%)	2 (0.8%)
	SWEATING	1 (0.5%)	--
	URTICARIA	2 (0.9%)	--
	BODY SYSTEM TOTAL	18 (8.2%)	12 (5.0%)
SPECIAL SENSES	TASTE PERVERSION	--	1 (0.4%)
	BODY SYSTEM TOTAL	--	1 (0.4%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once.
Source: Table 12.2.2.A in the applicant's study report

TABLE 12 (continued)
Summary of Treatment-Emergent Adverse Events by Treatment

		Metronidazole Vaginal Gel, 0.75% (N=220)	MetroGel® Vaginal Gel, 0.75% (N=239)
Body System	COSTART Term	N (%)	N (%)
UROGENITAL SYSTEM	AMENORRHEA	--	1 (0.4%)
	BREAST ENLARGEMENT	1 (0.5%)	--
	BREAST PAIN	3 (1.4%)	1 (0.4%)
	CERVICITIS	--	1 (0.4%)
	CERVIX DISORDER	--	2 (0.8%)
	DYSMENORRHEA	6 (2.7%)	3 (1.3%)
	DYSURIA	1 (0.5%)	1 (0.4%)
	FEMALE LACTATION	1 (0.5%)	--
	LABIAL EDEMA	1 (0.5%)	--
	LEUKORRHEA	2 (0.9%)	9 (3.8%)
	MENORRHAGIA	1 (0.5%)	--
	METRORRHAGIA	3 (1.4%)	3 (1.3%)
	PYELONEPHRITIS	2 (0.9%)	--
	SALPINGITIS	2 (0.9%)	--
	URINARY FREQUENCY	1 (0.5%)	1 (0.4%)
	URINARY TRACT INFECTION	1 (0.5%)	5 (2.1%)
	VAGINITIS	2 (0.9%)	2 (0.8%)
	VULVOVAGINAL DISORDER	2 (0.9%)	8 (3.3%)
	BODY SYSTEM TOTAL	27 (12.3%)	33 (13.8%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once.

Source: Table 12.2.2.A in the applicant's study report

Treatment-emergent adverse events are summarized by severity in Table 13. Most AEs were mild or moderate in severity, and none of the severe AEs were considered definitely or probably related to study medication.

TABLE 13
Summary of Treatment-Emergent Adverse Events by Severity .

		Metronidazole Vaginal Gel, 0.75% (N=220)			MetroGel® Vaginal Gel, 0.75% (N=239)		
Body System	COSTART Term	Mild N (%)	Moderate N (%)	Severe N (%)	Mild N (%)	Moderate N (%)	Severe N (%)
	Number Of Subjects With At Least One AE	53 (24.1%)	32 (14.5%)	7 (3.2%)	80 (33.5%)	30 (12.6%)	6 (2.5%)
BODY AS A WHOLE	ABDOMINAL PAIN	6 (2.7%)	2 (0.9%)	2 (0.9%)	14 (5.9%)	3 (1.3%)	1 (0.4%)
	ACCIDENTAL INJURY	--	--	--	--	1 (0.4%)	--
	ALLERGIC REACTION	2 (0.9%)	--	--	--	--	--
	ASTHENIA	--	--	--	1 (0.4%)	--	1 (0.4%)
	BACK PAIN	2 (0.9%)	--	--	--	--	--
	CYST[1]	--	--	--	--	1 (0.4%)	--
	FEVER	--	--	--	--	--	1 (0.4%)
	FLU SYNDROME	--	1 (0.5%)	--	1 (0.4%)	1 (0.4%)	--
	HEADACHE	9 (4.1%)	3 (1.4%)	3 (1.4%)	15 (6.3%)	4 (1.7%)	--
	INFECTION	2 (0.9%)	1 (0.5%)	--	2 (0.8%)	1 (0.4%)	--
	INFECTION FUNGAL	19 (8.6%)	8 (3.6%)	--	36 (15.1%)	6 (2.5%)	--
	MUCOUS MEMBRANE DISORDER	1 (0.5%)	--	--	--	--	--
	PAIN	1 (0.5%)	--	--	1 (0.4%)	--	--
	VIRAL INFECTION	--	--	--	1 (0.4%)	--	--
	BODY SYSTEM TOTAL	38 (17.3%)	14 (6.4%)	5 (2.3%)	65 (27.2%)	15 (6.3%)	2 (0.8%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
[1] One subject in the MetroGel® group had an event of ovarian cyst with missing severity
Source: Table 12.2.2.B in the applicant's study report

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TABLE 13 (continued)
Summary of Treatment-Emergent Adverse Events by Severity

		Metronidazole Vaginal Gel, 0.75% (N=220)			MetroGel® Vaginal Gel, 0.75% (N=239)		
Body System	COSTART Term	Mild N (%)	Moderate N (%)	Severe N (%)	Mild N (%)	Moderate N (%)	Severe N (%)
	Number Of Subjects With At Least One AE	53 (24.1%)	32 (14.5%)	7 (3.2%)	80 (33.5%)	30 (12.6%)	6 (2.5%)
BODY AS A WHOLE	ABDOMINAL PAIN	6 (2.7%)	2 (0.9%)	2 (0.9%)	14 (5.9%)	3 (1.3%)	1 (0.4%)
	ACCIDENTAL INJURY	--	--	--	--	1 (0.4%)	--
	ALLERGIC REACTION	2 (0.9%)	--	--	--	--	--
	ASTHENIA	--	--	--	1 (0.4%)	--	1 (0.4%)
	BACK PAIN	2 (0.9%)	--	--	--	--	--
	CYST[1]	--	--	--	--	1 (0.4%)	--
	FEVER	--	--	--	--	--	1 (0.4%)
	FLU SYNDROME	--	1 (0.5%)	--	1 (0.4%)	1 (0.4%)	--
	HEADACHE	9 (4.1%)	3 (1.4%)	3 (1.4%)	15 (6.3%)	4 (1.7%)	--
	INFECTION	2 (0.9%)	1 (0.5%)	--	2 (0.8%)	1 (0.4%)	--
	INFECTION FUNGAL	19 (8.6%)	8 (3.6%)	--	36 (15.1%)	6 (2.5%)	--
	MUCOUS MEMBRANE DISORDER	1 (0.5%)	--	--	--	--	--
	PAIN	1 (0.5%)	--	--	1 (0.4%)	--	--
	VIRAL INFECTION	--	--	--	1 (0.4%)	--	--
	BODY SYSTEM TOTAL	38 (17.3%)	14 (6.4%)	5 (2.3%)	65 (27.2%)	15 (6.3%)	2 (0.8%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).

[1] One subject in the MetroGel® group had an event of ovarian cyst with missing severity

Source: Table 12.2.2.B in the applicant's study report

TABLE 13 (continued)
Summary of Treatment-Emergent Adverse Events by Severity

		Metronidazole Vaginal Gel, 0.75% (N=220)			MetroGel® Vaginal Gel, 0.75% (N=239)		
Body System	COSTART Term	Mild N (%)	Moderate N (%)	Severe N (%)	Mild N (%)	Moderate N (%)	Severe N (%)
NERVOUS SYSTEM	DEPRESSION	1 (0.5%)	--	--	--	--	--
	DIZZINESS	2 (0.9%)	--	--	4 (1.7%)	--	--
	HALLUCINATIONS	--	--	--	1 (0.4%)	--	--
	INSOMNIA	--	1 (0.5%)	--	--	--	--
	NERVOUSNESS	--	--	--	1 (0.4%)	--	--
	SOMNOLENCE	--	--	--	1 (0.4%)	--	--
	BODY SYSTEM TOTAL	3 (1.4%)	1 (0.5%)	--	5 (2.1%)	--	--
RESPIRATORY SYSTEM	ASTHMA	--	1 (0.5%)	--	--	--	1 (0.4%)
	BRONCHITIS	--	--	--	--	1 (0.4%)	--
	COUGH INCREASED	--	--	--	2 (0.8%)	--	--
	DYSPNEA	--	--	--	1 (0.4%)	--	--
	HICCUP	--	--	--	1 (0.4%)	--	--
	PHARYNGITIS	1 (0.5%)	3 (1.4%)	--	3 (1.3%)	--	2 (0.8%)
	RHINITIS	1 (0.5%)	1 (0.5%)	--	2 (0.8%)	--	--
	SINUSITIS	--	--	--	1 (0.4%)	1 (0.4%)	--
	BODY SYSTEM TOTAL	2 (0.9%)	4 (1.8%)	--	9 (3.8%)	2 (0.8%)	3 (1.3%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
[1] One subject in the MetroGel® group had an event of ovarian cyst with missing severity
Source: Table 12.2.2.B in the applicant's study report

TABLE 13 (continued)
Summary of Treatment-Emergent Adverse Events by Severity

		Metronidazole Vaginal Gel, 0.75% (N=220)			MetroGel® Vaginal Gel, 0.75% (N=239)		
Body System	COSTART Term	Mild N (%)	Moderate N (%)	Severe N (%)	Mild N (%)	Moderate N (%)	Severe N (%)
SKIN AND APPENDAGES	ACNE	2 (0.9%)	--	--	--	--	--
	MACULOPAPULAR RASH	--	--	--	1 (0.4%)	--	--
	PRURITUS	7 (3.2%)	5 (2.3%)	--	4 (1.7%)	6 (2.5%)	--
	RASH	1 (0.5%)	2 (0.9%)	--	--	2 (0.8%)	--
	SWEATING	1 (0.5%)	--	--	--	--	--
	URTICARIA	2 (0.9%)	--	--	--	--	--
	BODY SYSTEM TOTAL	11 (5.0%)	7 (3.2%)	--	5 (2.1%)	7 (2.9%)	--
SPECIAL SENSES	TASTE PERVERSION	--	--	--	1 (0.4%)	--	--
	BODY SYSTEM TOTAL	--	--	--	1 (0.4%)	--	--
UROGENITAL SYSTEM	AMENORRHEA	--	--	--	--	1 (0.4%)	--
	BREAST ENLARGEMENT	1 (0.5%)	--	--	--	--	--
	BREAST PAIN	1 (0.5%)	2 (0.9%)	--	1 (0.4%)	--	--
	CERVICITIS	--	--	--	--	1 (0.4%)	--
	CERVIX DISORDER	--	--	--	2 (0.8%)	--	--
	DYSMENORRHEA	3 (1.4%)	3 (1.4%)	--	1 (0.4%)	1 (0.4%)	1 (0.4%)
	DYSURIA	1 (0.5%)	--	--	1 (0.4%)	--	--
	FEMALE LACTATION	1 (0.5%)	--	--	--	--	--

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
[1] One subject in the MetroGel® group had an event of ovarian cyst with missing severity
Source: Table 12.2.2.B in the applicant's study report

TABLE 13 (continued)
Summary of Treatment-Emergent Adverse Events by Severity

		Metronidazole Vaginal Gel, 0.75% (N=220)			MetroGel® Vaginal Gel, 0.75% (N=239)		
Body System	COSTART Term	Mild N (%)	Moderate N (%)	Severe N (%)	Mild N (%)	Moderate N (%)	Severe N (%)
UROGENITAL SYSTEM	LABIAL EDEMA	1 (0.5%)	--	--	--	--	--
	LEUKORRHEA	--	2 (0.9%)	--	7 (2.9%)	2 (0.8%)	--
	MENORRHAGIA	1 (0.5%)	--	--	--	--	--
	METRORRHAGIA	2 (0.9%)	1 (0.5%)	--	3 (1.3%)	--	--
	PYELONEPHRITIS	--	1 (0.5%)	1 (0.5%)	--	--	--
	SALPINGITIS	1 (0.5%)	1 (0.5%)	--	--	--	--
	URINARY FREQUENCY	--	1 (0.5%)	--	1 (0.4%)	--	--
	URINARY TRACT INFECTION	--	1 (0.5%)	--	2 (0.8%)	3 (1.3%)	--
	VAGINITIS	--	2 (0.9%)	--	2 (0.8%)	--	--
	VULVOVAGINAL DISORDER	1 (0.5%)	1 (0.5%)	--	8 (3.3%)	--	--
	BODY SYSTEM TOTAL	12 (5.5%)	14 (6.4%)	1 (0.5%)	24 (10.0%)	8 (3.3%)	1 (0.4%)

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
[1] One subject in the MetroGel® group had an event of ovarian cyst with missing severity
Source: Table 12.2.2.B in the applicant's study report

Treatment-emergent adverse events that were considered by the investigator to be definitely or probably related to study medication are summarized by severity in Table 14. The AEs that were considered definitely or probably related to study medication in more than 5% of subjects in a treatment group were fungal infections (20 [7%] in the metronidazole group and 32 [11%] in the MetroGel group).

A review of the concomitant medications dataset revealed 66 subjects who received treatment for a yeast infection (assumed, vaginal candidiasis) during the study (23 [8%] subjects in the metronidazole group and 43 [15%] in the MetroGel group).

Clinical Reviewer's Comment: As noted in the MetroGel package insert: known or previously unrecognized vaginal candidiasis may present in approximately 6 to 10% of subjects during therapy with metronidazole vaginal gel.

In the applicant's study 8% in the metronidazole vaginal gel group and 15% in the MetroGel group developed symptomatic vaginal candidiasis during or immediately after therapy, which is consistent with previous data.

TABLE 14
Summary of Treatment-Emergent Adverse Events Related or Probably Related to Study Medication by Severity

		Metronidazole Vaginal Gel, 0.75% (N=220)			MetroGel® Vaginal Gel, 0.75% (N=239)		
Body System	COSTART Term	Mild N (%)	Moderate N (%)	Severe N (%)	Mild N (%)	Moderate N (%)	Severe N (%)
	Number Of Subjects With At Least One AE	19 (8.6%)	6 (2.7%)	--	37 (15.5%)	4 (1.7%)	--
BODY AS A WHOLE	ABDOMINAL PAIN	--	--	--	4 (1.7%)	--	--
	HEADACHE	--	1 (0.5%)	--	1 (0.4%)	--	--
	INFECTION FUNGAL	17 (7.7%)	3 (1.4%)	--	29 (12.1%)	3 (1.3%)	--
	BODY SYSTEM TOTAL	**17 (7.7%)**	**4 (1.8%)**	--	**34 (14.2%)**	**3 (1.3%)**	--
DIGESTIVE SYSTEM	ANOREXIA	1 (0.5%)	--	--	--	--	--
	NAUSEA	1 (0.5%)	--	--	--	--	--
	BODY SYSTEM TOTAL	1 (0.5%)	--	--	--	--	--
NERVOUS SYSTEM	DIZZINESS	2 (0.9%)	--	--	1 (0.4%)	--	--
	BODY SYSTEM TOTAL	**2 (0.9%)**	--	--	**1 (0.4%)**	--	--
SKIN AND APPENDAGES	PRURITUS	--	1 (0.5%)	--	1 (0.4%)	--	--
	RASH	--	--	--	--	1 (0.4%)	--
	BODY SYSTEM TOTAL	--	1 (0.5%)	--	1 (0.4%)	1 (0.4%)	--
UROGENITAL SYSTEM	DYSMENORRHEA	1 (0.5%)	--	--	1 (0.4%)	--	--
	LEUKORRHEA	--	1 (0.5%)	--	2 (0.8%)	--	--
	VAGINITIS	--	1 (0.5%)	--	--	--	--
	BODY SYSTEM TOTAL	**1 (0.5%)**	**2 (0.9%)**	--	**3 (1.3%)**	--	--

Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or COSTART term), subjects are only counted once (under the greatest reported severity).
Source: Table 12.2.2.C in the applicant's study report

10.1.16 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths were reported during the study.

Two serious adverse events (SAEs) were reported (both in the MetroGel group). Both SAEs were hospitalizations for pre-study conditions, and were considered not related to study medication. Subject 255 had an SAE of severe asthma that required hospitalization. Subject 584 had an SAE of an ovarian cyst that required hospitalization.

Narratives for the two SAEs are included.

Subject Number: 255
Site Number: 6
Event: bronchospasm/hypoxia
COSTART Preferred Term: asthma

Initials: [redacted]
Randomized Therapy: MetroGel-Vaginal® 0.75%
Onset of AE: 7 days post-treatment
Duration: 3 days
Severity: Severe
Outcome: Recovered without Sequelae

Subject 255, [redacted] a 45-year-old Black female, was enrolled into the study on 6/13/2002 with a history of non-cardiac chest pain in March 2001 and bronchitis in April 2002. On [redacted] she presented to her family physician complaining of cough, chills, and headache. She was admitted to the hospital for bronchitis. She was given Zithromax, albuterol, oxygen, and Solu-Medrol. A chest X-ray was done with normal results. She was discharged on [redacted] with good resolution.

She discontinued from the study on 7/1/2002 due to worsening symptoms of bacterial vaginosis.

The SAE was considered by the investigator to be not related to study medication.

Subject Number: 584
Site Number: 21
Event: ovarian cyst
COSTART Preferred Term: cyst
Initials: [redacted]
Randomized Therapy: MetroGel-Vaginal® 0.75%
Onset of AE: unknown
Duration: unknown
Severity: unknown
Outcome: unknown

Subject 584, [redacted], a 32-year-old White female, was enrolled into the study on 6/11/2002 with a history of a left ovarian cyst in 2002. She did not return to the site for any follow-up visits and did not respond to phone calls or certified letters. The site was notified by the subject's sister that the subject was hospitalized for the ovarian cyst. She was lost to follow-up, and was considered discontinued due to the adverse event. The event met the criteria for an SAE. The SAE was considered by the investigator to be not related to study medication.

Clinical Reviewer's Comment: The Reviewer agrees with the investigator's assessments of these SAEs.

10.1.17 Adverse Events Resulting in Discontinuation of Study Drug

Eleven subjects discontinued due to adverse events, 5 in the metronidazole group (yeast infection – 2 subjects; pyleonephritis – 2 subjects; vaginal itching/discharge) and 6 in the MetroGel group (Bartholins cyst requiring antibiotics; urinary tract infection – 2 subjects; cervicitis; vaginal irritation; and ovarian cyst).

10.1.18 Clinical Laboratory Evaluations

Clinical laboratory tests were not performed in this study.

10.1.19 Vital Signs and Physical Findings and Safety Assessments

There were no vital sign assessments, physical examinations, or other safety assessments performed during the study.

10.1.20 Conclusions

The efficacy and safety of metronidazole vaginal gel, 0.75% was compared to MetroGel-Vaginal® 0.75% in a double-blind, randomized, US multicenter study of adult non-pregnant women with a confirmed clinical diagnosis of bacterial vaginosis and a Nugent score of ≥ 4 (bacteriological diagnosis). The primary efficacy endpoint was therapeutic cure (clinical plus bacteriological cure) at Visit 3, which occurred at Day 22-31.

A total of 579 subjects received study medication. Of these, 229 metronidazole and 243 MetroGel subjects were included in the FDA-defined Modified Intent to Treat (MITT) population. The Per Protocol (PP) population consisted of 155 metronidazole and 159 MetroGel subjects. In the PP analysis, the therapeutic cure rates at Visit 3 were 51.6% (80/155) for the metronidazole group and 36.5% (58/159) for the MetroGel group (95% confidence interval of the treatment different [3.6%, 26.6%]). In the FDA MITT analysis, the therapeutic cure rates were 42.8% (98/229) for the metronidazole group and 30.9% (75/243) for the MetroGel group (95% confidence interval of the treatment difference [2.8%, 21.0%)]. In both analyses, metronidazole was shown to be non-inferior MetroGel, as the lower bound of the 95% confidence interval around the treatment difference was above -20%. Although the results of the primary endpoint, therapeutic cure, show statistical significance of metronidazole vaginal gel compared to MetroGel-Vaginal (as defined by a lower bound of the 95% confidence interval around the treatment difference above zero), a claim of clinical superiority would require a second clinical study for confirmation of effect.

No deaths were reported during the study. Two serious adverse events were reported (both in the MetroGel group). Both were related to pre-study conditions (severe asthma requiring hospitalization and ovarian cyst requiring hospitalization), and were considered not related to study medication. Eleven subjects discontinued due to adverse events, 5 in the metronidazole group (yeast infection – 2 subjects; pyleonephritis – 2 subjects; vaginal itching/discharge) and 6 in the MetroGel group (Bartholins cyst requiring antibiotics; urinary tract infection – 2 subjects; cervicitis; vaginal irritation; and ovarian cyst).

A total of 42% (92/220) of subjects in the metronidazole group and 49% (117/239) of subjects in the MetroGel group experienced an adverse event during the study. Individual adverse events were similar between the two treatment groups. The adverse events that occurred in > 5% of subjects were abdominal pain (4.5% metronidazole group, 7.5% MetroGel group), headache (6.8%, 7.9%, respectively), fungal infection (12.3% and 17.6%), and pruritus (5.5% and 4.2%).

Events occurring in ≥ 1% of subjects treated with metronidazole vaginal gel included: fungal infection (12.3%), headache (6.8%), pruritus (5.5%), abdominal pain (4.5%), nausea (3.2%), dysmenorrhea (2.7%), pharyngitis (1.8%), rash (1.4%), infection (1.4%), diarrhea (1.4%), breast pain (1.4%), and metrorrhagia (1.4%).

The adverse events that were considered definitely or probably related to study medication in ≥1% of subjects in a treatment group were fungal infections (20 [9%] in the metronidazole group and 32 [13%] in the MetroGel group). Symptomatic vaginal candidiasis is a recognized adverse event that occurs in approximately 10% of women during or immediately after antibacterial therapy for BV.

In summary, metronidazole vaginal gel, 0.75% is safe and effective for the treatment of bacterial vaginosis in adult, non-pregnant women.

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/s/

Joette Meyer
5/18/05 02:34:07 PM
MEDICAL OFFICER

Eileen Navarro
5/18/05 04:40:38 PM
MEDICAL OFFICER

45-DAY MEETING
Fileability Checklist
NDA __21-806____
— *CLINICAL* —

Based on your initial overview of the NDA submission:	Yes	No	N/A
1. On its face, is the clinical section of the NDA organized in a manner to allow a substantive review to begin? (See 21 CFR §314.50(d)(5).)	X	☐	☐
2. Is the clinical section of the NDA indexed and paginated in a manner to allow a substantive review to begin? (See 21 CFR §314.50.)	X	☐	☐
3. On its face, is the clinical section of the NDA legible so that a substantive review can begin?	X	☐	☐
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X	☐	☐
5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	X	☐	☐
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X	☐	☐
7. Are all data sets for pivotal efficacy studies complete for all indications requested?	X	☐	☐
8. Do all pivotal efficacy studies appear to be adequate and well controlled within current FDA (see 21 CFR §314.126) and divisional/office policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X	☐	☐
9. Has the applicant submitted case report tabulations (CRT; line listings and patient profiles) in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in a format agreed to previously by the Division? If the CRTs were submitted electronically, are they consistent with CDER's Guidance for Industry – Archiving Submissions for Electronic Format — NDAs?	X	☐	☐
10. Has the applicant submitted a rationale for assuming the applicability of foreign data (disease specific) to the US population?	☐	☐	X

Based on your initial overview of the NDA submission:	Yes	No	N/A
11. Has the applicant submitted all additional required case report forms (CRF) (beyond deaths and dropouts) previously requested by the Division?	☐	☐	X
12. If CRFs were submitted electronically, are they consistent with CDER's Guidance for Industry - Archiving Submissions for Electronic Format — NDAs?	☐	☐	X
13. Has the applicant presented safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X	☐	☐
14. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	☐	☐	X
15. Has the applicant submitted draft labeling consistent with 21 CFR §201.56 and §201.57, current divisional/office policies, and the design of the development package?	X	☐	☐
16. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X	☐	☐

17. From a clinical perspective, is this NDA fileable? If "no", please state why it is not. (Use additional sheet of paper if needed.) ____Yes_____

18. If certain claims are not fileable, please state which claims they are and why they are not fileable. (Use additional sheet of paper if needed.) _____

_____
Clinical Reviewer (sign & date)

_____
Medical Team Leader (sign & date)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joette Meyer
9/10/04 02:22:20 PM
MEDICAL OFFICER

Eileen Navarro
9/10/04 04:06:22 PM
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