

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-806

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA NUMBER: 21-806
SUBMISSION DATE: 5 October 2004
BRAND NAME: N/A
GENERIC NAME: Metronidazole USP
DOSAGE FORM AND STRENGTH(S): Vaginal Gel, 0.75%
INDICATION(S): Treatment of Bacterial Vaginosis
SPONSOR: Teva Pharmaceuticals USA
TYPE OF SUBMISSION: 505(b)(2)
REVIEWER: Gerlie Gieser, Ph.D.
TEAM LEADER: Philip M. Colangelo, Pharm.D., Ph.D.
OCPB DIVISION: DPE3
OND DIVISION: DSPIDP

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I. Executive Summary

To establish bioequivalence between the sponsor's product (Metronidazole USP Gel, 0.75% w/w-Vaginal) and the reference listed drug (RLD; MetroGel-Vaginal®), the sponsor conducted a comparative clinical efficacy and safety trial, and a relative bioavailability (BA) study. Although the sponsor's vaginal gel product was found to be systemically bioequivalent to the RLD, the Office of Generic Drugs (OGD) refused to file the sponsor's application in view of the slightly superior efficacy profile of the applicant's generic formulation compared to the innovator's product. Based on the findings of the relative BA study and the clinical trial, the safety profile of the sponsor's metronidazole gel product was comparable to that of the RLD.

For the treatment of bacterial vaginosis (BV) in nonpregnant adult and adolescent females, MetroGel-Vaginal® is given 1 applicatorful (5 g of 0.75% w/w metronidazole gel) intravaginally once or twice daily

for 5 days. The chemical composition of TEVA's product is the same as that of the RLD, with one exception, i.e, Carbomer 934 in the RLD product was substituted with hypromellose (HPMC;) in the sponsor's metronidazole gel formulation.

In the relative bioavailability study, the plasma C_{max} of metronidazole from the sponsor's vaginal gel was statistically significantly higher than that from the reference vaginal gel. Likewise, the plasma metronidazole AUC_{0-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 C_{max} 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 C_{max} of metronidazole after intravaginal administration is only 2% of the mean plasma C_{max} 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 C_{max} 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.

A. Recommendation:

This submission is acceptable from a clinical pharmacology and biopharmaceutics perspective. The labeling recommendations in Section III-A of the review should be addressed by the sponsor.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Although the C_{max} of the sponsor's metronidazole vaginal gel product was statistically significantly higher (p=0.0231) than that of the reference product (MetroGel-Vaginal®), the 90% confidence intervals of the log-transformed mean metronidazole AUC and C_{max} of sponsor's product were within the 80-125% acceptance criteria for bioequivalence. Figure 1 shows the mean plasma metronidazole concentration time profiles of the test and the reference treatments following a single intravaginal dose of a 5-gram gel (containing approximately 37.5 mg metronidazole) in 38 healthy female volunteers. Table 1A summarizes the findings of the statistical analysis comparing the PK parameters of metronidazole from the test formulation versus the reference formulation.

FIGURE 1
Metronidazole Mean Plasma Concentrations
Following a Single-dose of Metronidazole Gel (=37.5 mg metronidazole)

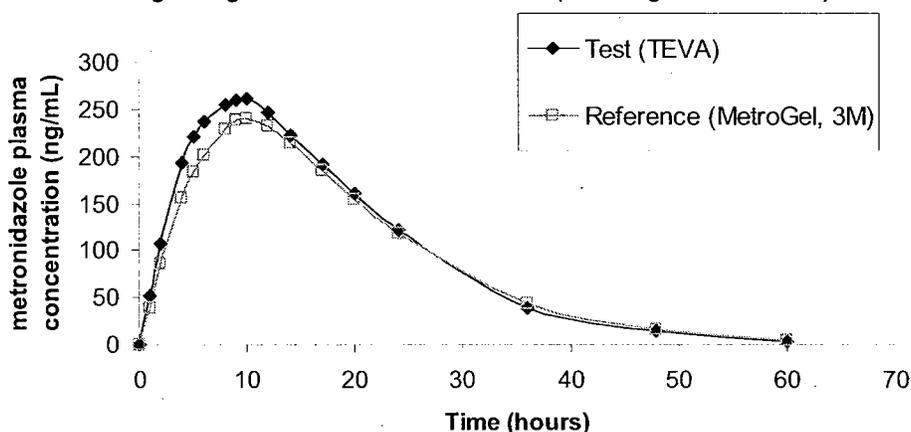


TABLE 1A
Statistical Comparison of Metronidazole Non-Transformed and Log-Transformed Data:
Test versus Reference Gel Products
(Mean \pm SD; N=38)

PHARMACOKINETIC PARAMETER (Unit)	TEST/REFERENCE RATIO (%)	90% C.I.	P value
NON-TRANSFORMED			
AUC _{0-∞} (ng*h/ml)	105	97.6, 113	0.2576
C _{max} (ng/mL)	109	103, 116	0.0265
T _{max} (h)	92	84.2, 100	0.1073
t _{1/2} (h)	95	87.8, 101	0.1885
LOG-TRANSFORMED			
AUC _{0-∞} (ng*h/ml)	106	97.6, 115	0.2451
C _{max} (ng/mL)	110	103, 117	0.0231

The C_{max} of metronidazole following a single intravaginal dose of the sponsor's gel is only 2% of the C_{max} of metronidazole following that seen typically after a single dose of a 500-mg oral tablet (12,785 ng/mL). Adverse systemic effects are expected to be negligible at these lower peak plasma metronidazole concentrations. Thus, a comparison of the AE rates in each treatment group in this crossover relative bioavailability study indicated that the significantly higher metronidazole C_{max} from the test formulation did not translate to a higher AE rate for the test formulation, compared to the reference formulation. Likewise, in the parallel-group clinical trial (total N=334), there was no statistically significant difference between the two treatment groups in the clinical trial with regard to the occurrence of AEs (both p>0.05), as well as with regard to severity or relationship to treatment (both p>0.05).

The systemic absorption of metronidazole from MetroGel-Vaginal® is limited by the drug's permeability across the vaginal epithelium (Cunningham et al., 1994). Thus, it can be speculated that the slightly higher systemic metronidazole concentrations from the sponsor's vaginal product was a manifestation of a

significantly higher local bioavailability at the site of application, although there was no study conducted to specifically look into relative local drug exposures. One possible reason for the slightly higher metronidazole C_{max} from the sponsor's vaginal gel is the difference in dosage formulation (Cunningham et al., 1994). Since hypromellose (used as a substitute for the Carbomer 934 ingredient of the reference formulation) does not possess antimicrobial activity, it is possible that this alternative ingredient helped improve the muco-adhesive properties of the sponsor's formulation which led to a longer retention or contact time with the vaginal mucosa. If so, such improvement in local bioavailability could help explain the slightly superior efficacy of the sponsor's vaginal gel (compared to MetroGel-Vaginal®) in the treatment of female patients diagnosed with bacterial vaginosis (BV).

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 who demonstrated bacteriologic cure, i.e., who had Nugent scores 0 to 3 at the Test-of-Cure Visit (Visit 2) and at the Post-Treatment Visit (Visit 3), following therapy with either the sponsor's metronidazole vaginal gel or the MetroGel-Vaginal® product.

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RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

II. Question Based Review

A. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted a relative bioavailability study, and an efficacy/safety study comparing the sponsor's metronidazole vaginal gel with the reference listed drug product (MetroGel® Vaginal Gel, 3M Pharmaceuticals). The relative bioavailability study was a randomized, crossover study consisting of 38 healthy female adult subjects who received a single applicatorful (5 grams) of the test and reference intravaginal gel consisting of approximately 37.5 mg of metronidazole. In the double-blind, randomized, parallel group clinical trial, 579 female patients with bacterial vaginosis (BV) received either the test or the reference gel formulation (same lot as those tested in the relative BA study) approximately 5 grams once daily at bedtime for 5 days.

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

In the relative bioavailability study, following intravaginal administration of the gel formulations, plasma metronidazole concentrations were measured. In the clinical trial, the proportion of subjects with a therapeutic cure at Visit 3 and Visit 2 were used as primary efficacy and secondary efficacy endpoints, respectively. Therapeutic cure was assessed based on the sum of the clinical score and the Nugent score (for BV vaginal flora).

3. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, refer to Section II-E, Analytical Section.

B. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Age, race, body weight, and body surface area did not appear to significantly influence the systemic bioavailability of metronidazole in female healthy volunteers following a single dose of either the generic or the reference intravaginal gel product. Likewise, when race was taken into consideration, the efficacy findings of the clinical trial were not significantly different. Regardless of the vaginal product used (TEVA generic vaginal gel or MetroGel-Vaginal®), there was a comparable percentage of White and Black female BV patients who demonstrated therapeutic cure (expressed as percentage with Nugent scores = 0 to 3) at the Test-of Cure Visit (Visit 2) and at the Post-Treatment Visit (Visit 3). Refer to Section IV-B, Individual Study Reviews (Study 10136019).

2. What pregnancy and lactation use information is there in the application?

The label of TEVA Generic Metronidazole Vaginal Gel will state that information is only available on the extent of metronidazole exposure to pregnant females and excretion into breast milk following oral (but not following intravaginal) administration of metronidazole. Metronidazole concentrations in the breast milk can reach levels that are comparable to plasma exposures after oral administration. Based on the findings of the bioavailability study (TEVA 10136019), the maximum metronidazole plasma concentration (C_{max}) following an intravaginal dose is about 1/45th the C_{max} following a single dose of the 500 mg oral

metronidazole tablet. For the treatment of bacterial vaginosis in nonpregnant adult and adolescent females, the CDC recommends an oral metronidazole dosage regimen of 500 mg twice daily for 7 days or alternatively, 2 grams as a single dose.

C. Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Smoking did not appear to significantly influence the systemic bioavailability of metronidazole in female healthy volunteers following a single dose of either the generic or the reference intravaginal gel product. Refer to Section IV-B, Individual Study Reviews (Study 10136019).

In the efficacy analysis, the sponsor excluded BV patients who took concomitant medications that were deemed to have the potential to confound the study findings.

D. General Biopharmaceutics

Compare the chemical composition of the test and the reference formulations used in the relative bioavailability and clinical efficacy/safety studies. Does any difference in chemical composition help explain the efficacy/safety findings of the comparative clinical trial?

The sponsor's metronidazole vaginal gel and MetroGel® Vaginal Gel contain the same type and amounts of active and inactive ingredients with one exception. In the sponsor's gel product, the Carbomer 934 () of MetroGel® was substituted with hypromellose (HPMC;). Table 2 below provides a qualitative and quantitative comparison of the two vaginal gel formulations.

TABLE 2
Chemical Composition of the Metronidazole Vaginal Gel Formulations

MetroGel-Vaginal® metronidazole vaginal gel, 0.75% (3M Pharmaceuticals), lot # RKBN00 (expires September 1, 2004)		Metronidazole vaginal gel, 0.75% (TEVA Pharmaceuticals USA) Lot # 1189-064 (manufactured July 16, 2001)	
Ingredient	Percentage (% w/w)	Ingredient	Percentage (% w/w)
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

Assuming the two products were similar in all other attributes (e.g., method of preparation, stability, assay findings), the slightly superior efficacy of the sponsor's vaginal gel product versus the reference product in the treatment of BV patients could probably be attributed to the substitution of Carbomer 934 with HPMC. If so, the greater ability of the gel product to adhere to the vaginal mucosa could lead to longer retention or contact times and thus, greater local bioavailability.

E. Analytical Section

Assay Validation

The plasma samples were assayed for metronidazole using a LC/MS/MS method by _____

Linearity

The assay was linear over the range of _____ and all correlation coefficient "r" values obtained for the _____ calibration curves were _____ or greater. The mean value for the slope was 0.0244.

Precision and Accuracy

The Intra-day precision (CV) and accuracy from three-separate analyses was within the range of _____ for metronidazole, respectively.

The inter-day precision (CV) and accuracy for the calibration curve standard was within the range of _____ and the accuracy was within the range of _____ for metronidazole, respectively. For the QC samples, the inter-day precision and accuracy was within the range of _____ respectively.

The precision values at the ULOQ _____ and the LLOQ _____ were _____ respectively. The accuracy values for the ULOQ and the LLOQ were _____ respectively.

Recovery

The mean recovery of metronidazole from plasma using the QC samples was _____ the mean recovery of the internal standard from plasma was _____

Selectivity and Matrix Effect

There were no interfering peaks in the blank plasma samples at the retention times of metronidazole and the internal standard as seen in the chromatograms.

The accuracy for metronidazole for the high and low concentration QC samples was in the range of _____

Dilution Integrity

The precision (CV) for the diluted plasma sample was 3.9% and 2.8% for 2 and 4 times dilution of metronidazole, respectively. The accuracy for the diluted plasma samples was 99.2% and 102% for 2 and 4 times dilution of metronidazole, respectively.

Partial Volume verification

The precision (CV) for _____ partial volume of metronidazole QC samples was _____, respectively. The accuracy for the _____ partial volume of metronidazole QC samples was _____

STABILITY

Long-term stability of samples under frozen conditions

Metronidazole in human plasma with _____ under frozen storage conditions was stable over the _____ days test duration. The percent change for metronidazole in human plasma over the storage period was -2.7%, +2.6% and -10.2% for the 300, 50, and 5 ng/mL concentrations, respectively. The samples were stored in the freezer prior to analysis for no longer than _____ days upon receipt.

Freeze-Thaw stability

The percent change for all four cycles was between -1.6 and +13.0%, indicating that the plasma samples were stable for at least up to 4 freeze-thaw cycles.

Room Temperature Stability

The percent change from the nominal values was within the range of +0.7% to +2.6%, thus indicating that the plasma samples were stable at room temperature for at least 24 hours.

In-process Stability

The mean percent change for metronidazole from the nominal values was in the range of -1.3 to +7.4%, over at least 77 hours during sample processing at room temperature.

Storage Stability of Extracted Samples in Refrigerator

The percent change for metronidazole from nominal values was in the range of [redacted] for at least [redacted] hours during storage in the refrigerator from the time of reconstitution of the extract.

Stock Solution Stability

The percent change for metronidazole and the internal standard in stock solutions when stored in the refrigerator for [redacted] days was in the range of [redacted] respectively.

Reviewer's Comment:

Quality control samples at low, medium and high concentrations [redacted] were used. The concentration range of the standard samples was [redacted]. The linearity, precision and accuracy of the assay, as well as the stability of metronidazole during storage, processing, and assay were all acceptable. The analytical validation for the assay is considered acceptable because previous studies conducted showed that the Cmax of metronidazole is about [redacted] when the Tmax is at 9 hours after the intravaginal dose. However, for future studies on the applicant's product, the assay should be validated up to at least a test concentration of [redacted] because the peak metronidazole concentrations in this study reached up to [redacted].

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B. INDIVIDUAL STUDY REVIEWS

TEVA Study 10136019

Title: A Study to Evaluate the Relative Bioavailability of Two Metronidazole Vaginal Gel Formulations

Objective:

To evaluate the relative bioavailability of the test formulation of metronidazole vaginal gel with the already marketed reference formulation MetroGel-Vaginal Gel (manufactured by TEVA for 3M Pharmaceuticals) in healthy adult, female subjects

Study Design:

This was a single-dose, randomized, two-period, two-treatment, two-sequence crossover study. The wash-out period was at least 7 days.

Study population:

Thirty eight (38) healthy adult, female subjects were recruited into the study. One of these subjects (Subject #21) withdrew from the study 6 hours after dosing in Period II due to personal reasons. Plasma data in Period I from another subject (Subject #29) was suspiciously low and so was dropped from the analysis.

Majority of the subjects (63%) were Caucasians; 31% were blacks; the remainder of the population was biracial. The mean age was 27 years old (range: 19 to 59 kg). The mean body weight was 65.5 kg (range: 49 to 82 kg). Majority (78%) were of medium build. Fourteen percent (14%) were smokers.

Dosage and Administration:

A single intravaginal application consisting of 5 grams of the gel product was used in the study. Each applicatorful of the gel contains approximately 37.5 mg of metronidazole.

Pharmacokinetic Assessment:

Blood samples were collected at predose (within 60 minutes prior to dosing) and at the following times after dosing: 1, 2, 4, 5, 6, 8, 9, 10, 12, 14, 17, 20, 24, 36, 48, and 60. Plasma samples were stored frozen to at least -17°C until analysis.

Analytical Procedure:

Metronidazole concentrations in the plasma were determined by a validated LC/MS/MS method.

Pharmacokinetic Analysis:

The $AUC_{(0-TLQC)}$ was calculated using the linear trapezoidal rule from the zero time point to the last quantifiable concentration.

The $AUC_{(0-\infty)}$ was calculated by adding C_t/K_{el} to $AUC_{(0-TLQC)}$ where C_t is the last quantifiable concentration and K_{el} is the elimination rate constant.

The C_{max} and T_{max} were obtained by inspection of the plasma concentration-time curve.

The K_{el} was obtained from the slope of the terminal portion of the plasma concentration-time curve, fitted by linear least squares regression.

The half-life ($t_{1/2}$) was calculated by the equation $T_{1/2} = 0.693/ K_{el}$.

Statistical Analysis:

The 90% confidence interval about the ratio of the mean AUC and C_{max} Test value to that for the Reference value and for the power of the ANOVA to detect a 20% difference from the Reference mean

were performed using the LSMEAN values and standard error of estimate values as generated by the SAS software.

Results and Discussion:

Pharmacokinetics-

A linear plot of the mean plasma concentrations as a function of time is given (Figure 1). Tabular summaries of the PK parameters and the statistical analysis to assess the bioequivalence of the two products are given (Table 1 and 1A). For the log transformed data, the 90% confidence intervals about the ratio of the Test mean to Reference mean are within the 80% to 125% limits for all the pharmacokinetic parameters including C_{max} and AUC. However, the difference in C_{max} between the test and the reference products was found to be statistically significant ($p=0.023$).

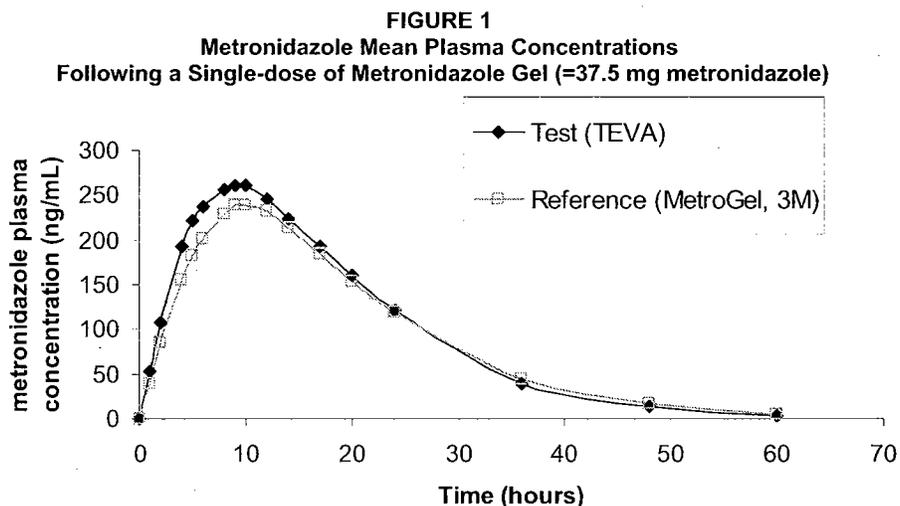


TABLE 1
Pharmacokinetic Parameters of Metronidazole following a single dose of metronidazole vaginal gel
(37.5 mg metronidazole): Test versus Reference gel products
(Mean \pm SD; N=38)

PHARMACOKINETIC PARAMETER, (Unit) [%CV]	TEST (TEVA Generic Metronidazole Vaginal Gel)	REFERENCE (MetroGel® Vaginal Gel, 3M Pharmaceuticals)
AUC _{0-∞} (ng·h/ml)	5989 \pm 1738 [29%]	5693 \pm 1735 [31%]
C _{max} (ng/mL)	281 \pm 72 [26%]	257 \pm 71 [28%]
T _{max} (h)	9.5 \pm 2.8 [19%]	10.3 \pm 3.0 [29%]
t _{1/2} (h)	7.1 \pm 1.4 [19%]	7.5 \pm 1.9 [25%]

TABLE 1A
Statistical Comparison of Metronidazole Non-Transformed and Log-Transformed Data:
Test versus Reference Gel Products
(Mean \pm SD; N=38)

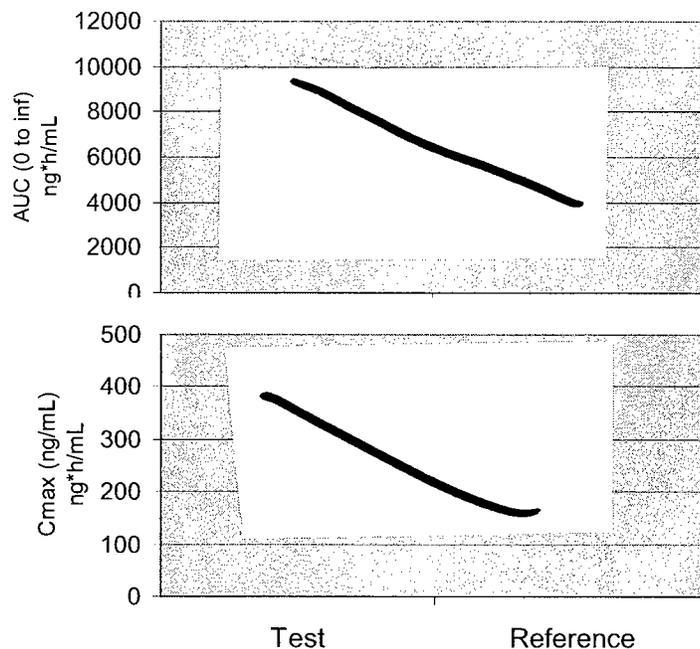
PHARMACOKINETIC PARAMETER (Unit)	TEST/REFERENCE RATIO (%)	90% C.I.	P value
NON-TRANSFORMED			
AUC _{0-∞} (ng*h/ml)	105	97.6, 113	0.2576
C _{max} (ng/mL)	109	103, 116	0.0265
T _{max} (h)	92	84.2, 100	0.1073
t _{1/2} (h)	95	87.8, 101	0.1885
LOG-TRANSFORMED			
AUC _{0-∞} (ng*h/ml)	106	97.6, 115	0.2451
C _{max} (ng/mL)	110	103, 117	0.0231

REVIEWER'S COMMENTS:

1. Individual patient relative bioavailability.

The spaghetti plot below shows the individual subject C_{max} and AUC of metronidazole for each gel product (Figure 2). The mean values are shown as boxed crosses. Majority of the evaluable subjects in this study had relatively higher C_{max} of metronidazole from the applicant's formulation (Product A/Test) compared to that from the reference formulation/Product B. Although this higher C_{max} from the sponsor's formulation is statistically significant, the two products were found to be bioequivalent. The relatively shorter T_{max} of metronidazole from the test product could explain, at least in part, its relatively higher C_{max}, compared to the reference formulation (mean T_{max} = 9.5 hours versus 10.3 hours).

FIGURE 2



2. **Comparison with literature data on MetroGel-Vaginal Formulation.** Based on the findings of Cunningham and co-workers (1994), the PK parameters of metronidazole after a single dose of MetroGel-Vaginal are as follows:

TABLE 3
Metronidazole PK Parameters
After 5 grams of 0.75% Metronidazole Intravaginal Gel

PHARMACOKINETIC PARAMETER (UNIT)	
Cmax (ng/mL)	237 ± 69
Tmax (h)	8.37 ± 2.18
AUC (ng*h/mL)	4977 ± 2671

The PK parameter values for the MetroGel-Vaginal® Formulation obtained in the TEVA relative bioavailability study are comparable to those in the table above.

3. **Influence of co-variates.** The figures below indicate that the systemic bioavailability of Metronidazole Vaginal Gel relative to the reference (MetroGel® Vaginal Gel) was the same regardless of age, race (Caucasian or Black), and smoking status. In addition, the slight (possibly clinically insignificant) effect of BW and BSA on systemic bioavailability of metronidazole following a single intravaginal dose was observed, regardless of the gel product used.

FIGURE 3
Influence of Age on Metronidazole AUC_{0-inf}:
Test (Generic) versus Reference (MetroGel® Vaginal Gel)

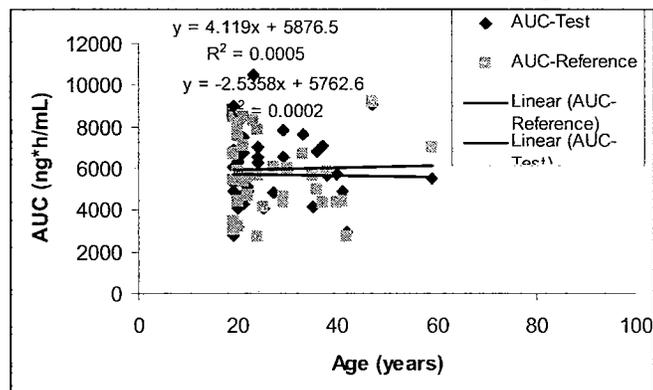


FIGURE 4
Influence of Race on Metronidazole AUC_{0-inf}:
Test (Generic) versus Reference (MetroGel® Vaginal Gel)

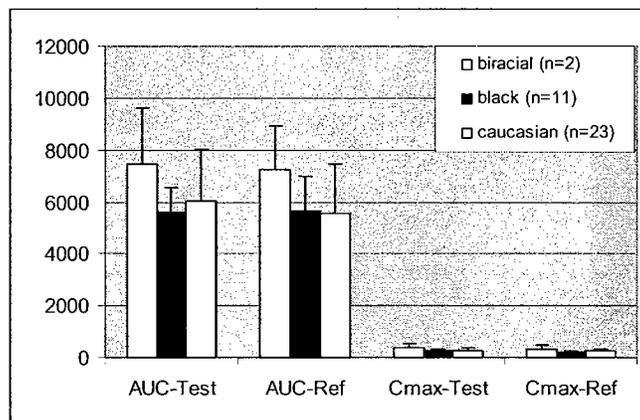


FIGURE 5
Influence of Smoking on Metronidazole AUC_{0-inf}:
Test (Generic) versus Reference (MetroGel® Vaginal Gel)

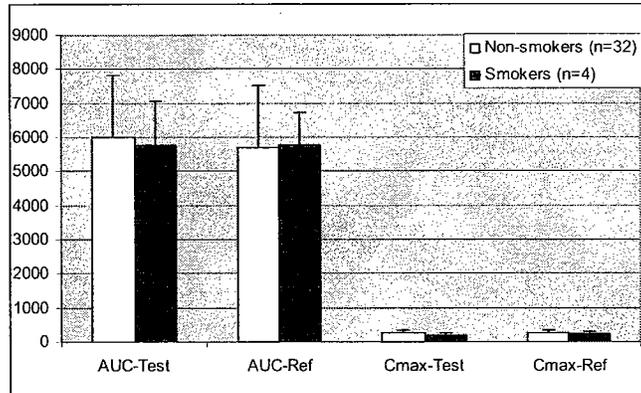


FIGURE 6
Influence of Body Weight on Metronidazole AUC_{0-inf}:
Test (Generic) versus Reference (MetroGel® Vaginal Gel)

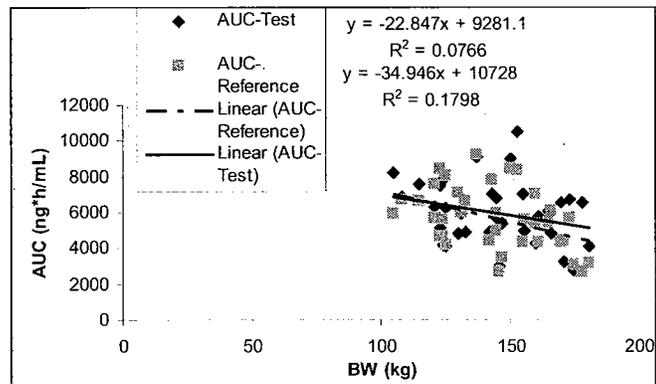
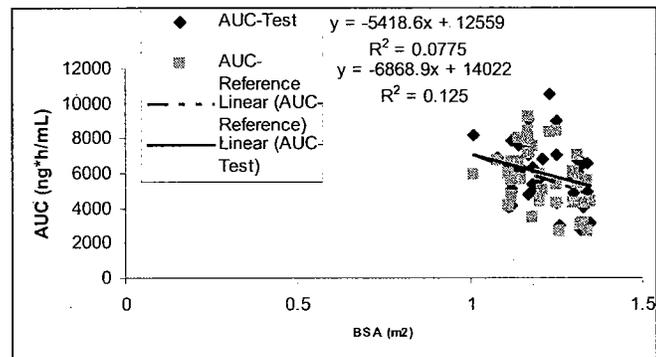


FIGURE 7
Influence of Body Surface Area on Metronidazole AUC_{0-inf}:
Test (Generic) versus Reference (MetroGel® Vaginal Gel)



4. That race was also not a significant co-variate in the efficacy of either the test or reference metronidazole vaginal gel formulations is evident from the similarity in the percentage of Nugent scores equivalent to 0-3 between Whites and Blacks (Table 4 below) in the MITT population. In addition, subset analysis by race did not affect the conclusion that the sponsor's metronidazole vaginal gel was similar, if not slightly better, than the reference treatment (MetroGel®) in reducing the Nugent scores of female patients with bacterial vaginosis.

TABLE 4
Number and Percentage of Female Patients in the MITT Population with Nugent Scores = 0-3

RACE/VISIT NO.	TEVA METRONIDAZOLE GEL	METROGEL®
Visit 2		
Whites	51/65 (78.5 %)	49/71 (69.0%)
Blacks	92/126 (73.0 %)	84/132 (63.6%)
Hispanics	2/3 (66.7 %)	2/2 (100%)
Asians	2/2 (100 %)	0/1 (0%)
Others	1/1 (100%)	1/2 (50%)
Visit 3		
Whites	38/52 (73.1%)	32/52 (61.5 %)
Blacks	76/110 (69.1 %)	67/110 (60.9 %)
Hispanics	3/3 (100%)	2/2 (100%)
Asians	2/2 (100%)	1/1 (100%)
Others	1/1 (100%)	0/0 (0%)

5. On the other hand, the influence of other co-variables (e.g., age, body weight, body surface area) on efficacy of the vaginal gel formulations could not be assessed because of a limited range of these factors in the efficacy population.
6. The relative bioavailability of metronidazole at the site of application was not specifically investigated by the sponsor. The slight superiority of the sponsor's product compared to the innovator's product (MetroGel®) may have been related, at least in part, to the relative muco-adhesive properties (and thus, the relative local bioavailabilities) of the gel formulations.
7. Safety. Table 5 below summarizes the incidence of adverse events in each treatment group of the relative bioavailability. All reported AEs in this single-dose, crossover study were mild in severity.

TABLE 5
Summary of Adverse Event Rates in the Bioequivalence Study
Comparing Metronidazole Vaginal Gel (manufactured by TEVA) to MetroGel Vaginal® (3M Pharmaceuticals)

	Test		Reference	
	Number of Cases	Number of Patients	Number of Cases	Number of Patients
	Metronidazole vaginal gel, 0.75% (TEVA Pharmaceuticals USA) Lot # 1189-064 (manufactured July 16, 2001)		MetroGel-Vaginal® metronidazole vaginal gel, 0.75% (3M Pharmaceuticals), lot # RKBN00 (expires September 1, 2004)	
All-causality AEs	18	15	18	17
AEs with possible, probable or definite relationship to study treatment	12	11	20	15

7. A comparison of these AE rates in each treatment group suggests that the significantly higher metronidazole C_{max} from the Test formulation did not translate to a higher AE rate for the test formulation compared to the reference formulation, in agreement with the clinical trial safety

findings. There was no statistically significant difference between the two treatment groups in the clinical trial with regard to the occurrence of AEs (both $p > 0.05$), as well as with regard to severity or relationship to treatment (both $p > 0.05$).

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Study TCR-03

Title: 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

Study Design:

This was a double-blind, randomized, parallel group, multicenter study of two formulations of metronidazole vaginal gel 0.75% in subjects with bacterial vaginosis. Subjects were randomized (in blocks of 4) in a 1:1 ratio to one of the two treatments:

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

Objective:

To compare the efficacy, safety, and tolerability of TEVA Pharmaceuticals USA's generic formulation of metronidazole vaginal gel, 0.75% to that of 3M Pharmaceuticals' MetroGel-Vaginal metronidazole vaginal gel, 0.75%

Study Population (planned and analyzed):

Female subjects, at least 18 years of age, with a confirmed clinical diagnosis of bacterial vaginosis and free from vulvovaginitis of non-bacterial origin.

Enrolled: 579

Analyzed:

Intent-To-Treat (ITT) – 459

Modified ITT – 421

Per-Protocol – 314

A summary of the demographic and other baseline characteristics by treatment group is given in Table 6. In each treatment group, most (~65%) of the subjects were blacks; about 33% were whites. The ITT treatment groups were comparable for all demographic characteristics (all $p > 0.05$), as were the mITT (all $p > 0.05$) and PP treatment groups (all $p > 0.05$). It was noted that a greater proportion of subjects in the reference group had a history of *Trichomonas vaginalis* infection (19% in the reference group vs. 11% in the test group; $p = 0.006$).

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TABLE 6

Table 11.2.1.A: Baseline Characteristics for Intent-To-Treat Subjects

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%)	133 (54%)	
	Hispanic	3 (1%)	3 (1%)	
	Asian	2 (1%)	1 (0%)	
	Other	1 (0%)	2 (1%)	
Age (years)	Mean ± Std	32.09 ± 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	58 (26%)	53 (22%)	0.774 ¹
	Neisseria Gonorrhoeae	18 (8%)	21 (9%)	0.589 ¹
	Herpes Simplex	19 (9%)	15 (6%)	0.314 ¹
	Active Genital Warts	17 (8%)	12 (5%)	0.157 ¹
Systolic BP (mmHg)	Mean ± Std	116.41 ± 11.16	114.53 ± 11.90	0.411 ²
	Min - Max	92.0 - 160.0	84.0 - 158.0	
Diastolic BP (mmHg)	Mean ± Std	75.07 ± 7.86	73.99 ± 8.34	0.472 ²
	Min - Max	56.0 - 96.5	60.0 - 100.0	
Temperature (°F)	Mean ± Std	98.21 ± 0.61	98.21 ± 0.59	0.524 ²
	Min - Max	96.2 - 99.5	96.3 - 99.4	
Heart Rate (bpm)	Mean ± Std	74.62 ± 9.08	74.68 ± 8.50	0.763 ²
	Min - Max	50.0 - 106.0	52.0 - 96.0	

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.

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Dosing and Administration:

Each subject inserted intravaginally one applicatorful of metronidazole vaginal gel (approximately 5 grams of the gel containing approximately 37.5 mg of metronidazole) once daily at bedtime for 5 days.

Efficacy Assessment:

Primary Endpoint-

- proportion of subjects with a therapeutic cure at Visit 3.

Secondary Endpoint-

- proportion of subjects with a therapeutic cure at Visit 2.

Safety and Tolerability Assessment:

- The incidence of all adverse events reported during the study was summarized by treatment group.
- The proportion of subjects completing treatment was compared between the test and reference treatment groups for all mITT subjects.

Results:

Regardless of efficacy endpoint, the applicant's product was determined to be superior to the reference (MetroGel®) product (Table 7).

TABLE 7
Primary and Secondary Efficacy Assessments

Efficacy Endpoint	Subjects	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%	90% Confidence Interval [†]
Primary Efficacy: Therapeutic Cure Rate At Visit 3	Per-Protocol	(N=155)	(N=159)	{ 5.0%, 25.65% }
		86 (55%)	63 (40%)	
	Modified Intent-to-Treat [‡]	(N=206)	(N=215)	{ 4.0%, 20.91% }
		111 (54%)	89 (41%)	
Secondary Efficacy: Therapeutic Cure Rate At Visit 2	Per-Protocol	(N=155)	(N=159)	{ 5.67%, 25.46% }
		100 (65%)	78 (49%)	
	Modified Intent-to-Treat [‡]	(N=206)	(N=215)	{ 4.19%, 20.79% }
		134 (65%)	113 (53%)	

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.

[†] Confidence intervals from Wald's method with Yates' continuity correction.

[‡] A last-observation-carried-forward (LOCF) approach was used for missing efficacy results for the MITT subjects.

The adverse event rate was not statistically significantly different between the applicant's product and the reference (MetroGel®) product (Table 8 and 9).

TABLE 8
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	52 (41.8%)	117 (49.0%)	0.125 [†]
Adverse event(s) probably related or definitely related to study medication	25 (11.4%)	41 (17.2%)	0.077 [†]

[†] P-values for treatment comparisons from Pearson's chi square test for ITT subjects pooled from all study centers.

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TABLE 9
Treatment-Emergent Adverse Events by Severity and Relationship

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	UNK	0 (0%)	1 (1%)	0.105 [†]
	Mild	53 (24%)	80 (33%)	
	Moderate	32 (15%)	30 (12%)	
	Severe	7 (3%)	6 (2%)	
Relationship of Events to Study Medication	Not Related	41 (19%)	57 (23%)	0.052 [†]
	Possibly Related	26 (12%)	19 (8%)	
	Probably Related	25 (11%)	38 (16%)	
	Definitely Related	0 (0%)	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.

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Sponsor's Conclusions:

Efficacy-

TEVA Pharmaceuticals USA's metronidazole vaginal gel, 0.75% was determined to be not clinically equivalent (slightly superior) to MetroGel-Vaginal® metronidazole vaginal gel, 0.75% in all primary and secondary PP and mITT analyses at all post-Baseline visits.

Safety-

- The two treatment groups were comparable. There was no significant statistical difference between the two treatment groups with regard to the occurrence of AEs (both $p > 0.05$). 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 reference 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.
- The study did not demonstrate any safety concerns for adults with bacterial vaginosis.

REVIEWER'S COMMENTS:1. *Demographic and Other Baseline Characteristics*

The two treatment groups in this parallel study were comparable in terms of race and age distribution, as well as in terms of baseline vital signs (systolic and diastolic BP, body temperature and heart rate). Except for *Trichomonas vaginalis* which was noted to be of slightly higher incidence in the reference (MetroGel®) group than in the test group (19% versus 11%; MITT population), all other rates pertaining to history of urogenital disorders were similar between the test and the reference groups.

2. *Concomitant Medications: Relative Use of Hormonal Agents*

In the efficacy analysis, the sponsor excluded patients who took concomitant medications that were deemed to have the potential to confound the study findings.

Because metronidazole is metabolized to a significant extent, the influence of the concomitant use of oral contraceptives (OCs) and hormone replacement therapy (HRT) on the study findings was evaluated. There was a comparable number (72/180 versus 80/182) of female patients in each treatment group that were on OCs or HRT during the conduct of this clinical trial. Thus, the slightly (10%; statistically significantly) higher systemic C_{max} of metronidazole from the applicant's intravaginal gel formulation could not be attributed to a potentially significant drug interaction between these hormonal agents and the systemically available metronidazole.

3. *Relative Bioavailability: Relevance to Relative Safety and Efficacy*

The test formulation passed the criteria for bioequivalence to the reference formulation (in terms of C_{max} and AUC). The clinical lot of the applicant's formulation tested in the relative bioavailability study was the same lot tested in the therapeutic trial.

Though the C_{max} of systemically available metronidazole from the applicant's formulation was statistically significantly higher than that from the reference formulation (MetroGel®), the resulting blood levels from both test and reference formulations were lower than that reported after 500 mg single oral dose of metronidazole. Thus, any difference in systemic levels between the two formulations did not result in a significant difference in rates of systemic adverse events.

In consideration of the relatively low systemic levels of metronidazole achieved from intravaginal administration, the efficacy of metronidazole in the treatment of bacterial vaginosis could be attributed primarily to the drug's local bioavailability. Because the local absorption of the drug was not quantified in this study, it is unknown whether a higher local bioavailability of metronidazole from the applicant's formulation contributed to its superior efficacy over the reference formulation.

4. *Chemical Composition of the Formulations*

The table below summarizes the chemical composition of the test and reference formulations used in the relative bioavailability study, as well as in the clinical efficacy/safety trial (TCR-03). Study TCR-03 was conducted from Jan 11, 2002 to March 17, 2003.

As can be seen from the table above, the only difference of the test formulation from the reference formulation is Hypromellose (HPMC,) instead of Carbomer 934 (). Like carbomers, hypromellose is an adjuvant that confers mucoadhesive properties to the gel formulation. It appears from the findings of the therapeutic trial conducted by the sponsor, that hypromellose may have offered an advantage over Carbomer 934 in enhancing the local and sustained release of metronidazole to the intravaginal mucosa. This finding appears to be in conjunction with the literature evidence suggesting that between HPMC and Carbopol-934, the former shows better bioadhesion both *in vitro* and *in vivo* at pH 5 to 6 (Chari et al., 1999). If so, the longer retention or contact time with the vaginal mucosa could probably explain the slightly higher metronidazole systemic exposure (C_{max}, AUC) achieved from the sponsor's vaginal gel in the relative bioavailability study.

TABLE 10
Comparison of the Chemical Composition of the Metronidazole Vaginal Gel Formulations

MetroGel-Vaginal® metronidazole vaginal gel, 0.75% (3M Pharmaceuticals), lot # RKBN00 (expires September 1, 2004)		Metronidazole vaginal gel, 0.75% (TEVA Pharmaceuticals USA) Lot # 1189-064 (manufactured July 16, 2001)	
Ingredient	Percentage (% w/w)	Ingredient	Percentage (% w/w)
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

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C. Cover Sheet and OCPB Filing/Review Form**Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form**General Information About the Submission

	Information		Information
NDA Number	21-806 (N-000)	Brand Name	Metronidazole Vaginal Gel, 0.75%
OCPB Division (I, II, III)	DPEIII	Generic Name	Metronidazole
Medical Division	HFD-590 (DSPIDP)	Drug Class	Nitroimidazole Antibacterial/Antiprotozoal
OCPB Reviewer	Gerlie Gieser	Indication(s)	Treatment of Bacterial Vaginosis
OCPB Team Leader	Philip M. Colangelo	Dosage Form	Intravaginal Gel
		Dosing Regimen	1 applicatorful (5 grams gel containing about 37.5 mg metronidazole) once daily at bedtime for 5 days
Date of Submission	05 October 2004	Route of Administration	intravaginal
Estimated Due Date of OCPB Review		Sponsor	TEVA Pharmaceuticals
PDUFA Due Date		Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X	1	1	versus MetroGel-Vaginal®
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X (single-dose, crossover)	1	1	versus MetroGel-Vaginal®
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	2	2	2	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable). For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Comments have been sent to firm (or attachment included), FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD),

CDR

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Gerlie Gieser
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Phil Colangelo
5/17/05 04:31:58 PM
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