# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number:** 020868

**Trade Name:** FLAGYL ER 750 MG. TABLET

**Generic Name:** METRONIDAZOLE EXTENDED RELEASE TABLET

**Sponsor:** G. D. SEARLE AND COMPANY

**Approval Date:** 11/26/97

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: 020868

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| Approval Letter | X | | | |
| Tenative Approval Letter | | | | |
| Approvable Letter | | | | |
| Final Printed Labeling | | | | |
| Medical Review(s) | X | | | |
| Chemistry Review(s) | | | | |
| EA/FONSI | | | | |
| Pharmacology Review(s) | | | | |
| Statistical Review(s) | X | | | |
| Microbiology Review(s) | | | | |
| Clinical Pharmacology Biopharmaceutics Review(s) | X | | | |
| Bioequivalence Review(s) | | | | |
| Administrative Document(s) | X | | | |
| Correspondence | | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number:** 020868

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

**NDA 20-868**

Lynne E. Weissberger, Ph.D.
Associate Director
Regulatory Affairs
G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

NOV 26 1997

Dear Dr. Weissberger:

Please refer to your new drug application (NDA) dated May 29, 1997, received May 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flagyl ER® (metronidazole extended release tablets) 750 mg.

We acknowledge receipt of your amendments dated June 2, and 16, August 4 and 28, October 10, and 27, and November 3, 6, and 26, 1997. The user fee goal date is May 29, 1998.

This new drug application provides for the indication of bacterial vaginosis (BV).

We have completed the review of this application, including the draft labeling submitted May 29, 1997, and November 26, 1997, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated November 26, 1997 (enclosed). Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to this labeling may render the product misbranded and an unapproved new drug.

Please submit twenty-five copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated **"FINAL PRINTED LABELING"** for approved **NDA 20-868.** Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Special Pathogens and Immunologic

Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

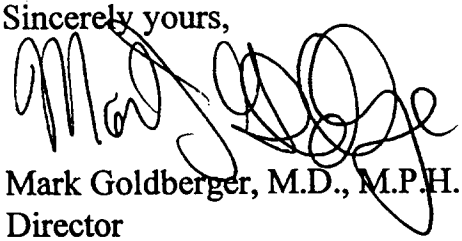
Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Pauline Fogarty
Regulatory Health Project Manager
(301) 827-2125

Sincerely yours,



Mark Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ENCLOSURE

cc: Original NDA 20-868 11/26/97
HFD-590/Div. Files
HFD-590/Goldberger
HFD-590/Albrecht 11/26/97
HFD-590/Leissa 11/26/97
HFD-590/Winfield 11/26/97
HFD-590/Schmuff
HFD-590/Seggel
HFD-590/Utrup
HFD-590/Lard
HFD-590/Kumi 11/26/97
HFD-590/Ajayi
HFD-590/Chakravarty
HFD-590/Shen
HFD-590/McMaster 11/26/97
HFD-590/Hastings
HFD-590/Fogarty
HFD-104/LeSane
HFD-830/E. Sheinin
DISTRICT OFFICE
HFD-2/M.Lumpkin
HFD- 101 /L. Carter
HFD-002/ORM (with labeling)
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735 (with labeling)
HFD-021/J.Treacy (with labeling)
HFI-20/Press Office (with labeling)
D . Anderson(Div . Sec)
drafted:Nov 25, 1997
final: 11/26/97
APPROVAL

APPEARS THIS WAY
ON ORIGINAL

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020868

## MEDICAL REVIEW(S)

# Medical Team Leader's Memorandum
# NDA 20-868

Date: 26 November, 1997

Generic drug name: metronidazole

Trade drug name: Flagyl ER, 750 mg tablet

Applicant: G.D. Searle & Co.

Proposed labeling: Bacterial vaginosis (BV) at a dose of 750 mg po qd for 7 days.

In support of the Flagyl ER new drug application, Searle submitted data from two single-blind, randomized, controlled, multicenter trials: N13-95-02-015 and N13-95-02-017. 2% CLEOCIN cream intravaginally qd for 7 days was the comparator in both trials. Both studies were similar with the following exception: study N13-95-02-015 was a dose-ranging clinical trial with a third arm where patients only received 5 days of Flagyl ER treatment as well.

As discussed by Dr. Winfield, when the reviewer's evaluability criteria were used, the following cure rates were observed using either clinical criteria OR Gram-stain criteria:

| | **SUCCESS RATES FOR EVALUABLE PATIENTS AT 1 MONTH (According to reviewing MO)** | | | | | |
|---|---|---|---|---|---|---|
| | **Clinical success rates** | | | **Gram Stain (Nugent criteria) success rates** | | |
| | Flagyl ER | Cleocin | Corrected 95% CI | Flagyl ER | Cleocin | Corrected 95% CI |
| N13-95-02-015 | 77/126 (61%) | 80/135 (59%) | -11%, 15% | 53/103 (51%) | 62/113 (55%) | -18%, 11% |
| N13-95-02-017 | 74/119 (62%) | 50/117 (43%) | 6%, 33% | 51/99 (52%) | 34/93 (37%) | 0.03%, 30% |

Based on the data derived from these studies, Flagyl ER was equivalent to 2% Cleocin cream in the dose-ranging study (015) but superior in study 017.

Side effects were more commonly seen in the Flagyl ER arm vs. the Cleocin arm. Of special note, when both studies were combined, 9% of Flagyl ER recipients complained of a metallic taste while <1% of Cleocin recipients reported the same concern.

In Searle's original proposed labeling, there were additional clinical/microbiology issues that had to be resolved:

1. Searle proposed a large Clinical Studies section claiming that a "statistically-significant higher clinical cure rate was observed with 7-day oral metronidazole compared to 2% clindamycin vaginal cream....(and)...Flagyl ER restored normal vaginal pH better and significantly faster than clindamycin." Since this effect was only seen in one of the studies, we told Searle we would that they not make generalized labeling claims like this, but we would allow them to include a clinical cure rate table showing the individual efficacies for both studies. The applicant agreed. Furthermore, we told them that they could use either FDA or Searle cure

rates in this section. We warned them that if they would want to detail Flagyl ER with journal articles that had different efficacy rates than those in the clinical studies section, that this could cause problems with DDMAC. Searle accepted this risk and responded that they would prefer to use FDA's cure rates.

2. Searle proposed including various bacterial pathogens associated with BV in the "first list" of the microbiology subsection. We told them that since BV is a poorly understood, polymicrobial infection, where resetting the microbial balance seems to be the important therapeutic measure with antimicrobial therapy, we would prefer not including these data in this first part of the Microbiology subsection. Rather, they could include these bacterial isolates in the "second list" – where "their clinical significance is unknown." The applicant agreed.

3. As stated above, a metallic taste was reported in 9% of Flagyl ER recipients. We concluded this information was underrepresented in the proposed label and that the 9% rate should be specifically noted in the Adverse Reactions section. The applicant agreed.

Conclusion: I agree with Dr. Winfield's (the reviewing Medical Officer) recommendation that Flagyl ER should be approved for the treatment of bacterial vaginosis at a dose of 750 mg po qd for 7 days.

Searle demonstrated superiority to 2% Cleocin cream in only one of the two studies. Although this is reflected in the Clinical Studies section, I do not believe Searle, on balance, should be allowed to make superiority claims without mentioning the results of both studies in all promotional material.

APPEARS THIS WAY
ON ORIGINAL

Brad Leissa, M.D.
Medical Team Leader/HFD-590

cc: Orig. NDA
HFD-590
HFD-590/MO/Winfield
HFD-590/MTL/Leissa
HFD-725/Biostats/Shen
HFD-590/CSO/Fogarty
HFD-590/DepDivDir/Albrecht

Concurrence Only
HFD-590/DivDir/Goldberger

APPEARS THIS WAY
ON ORIGINAL

DATE SUBMITTED BY SPONSOR : MAY 29, 1997
DATE RECEIVED BY CDER: MAY 30, 1997
DATE RECEIVED BY REVIEWER: JUNE 20. 1997
DATE REVIEW STARTED: JULY 15, 1997
DATE REVIEW COMPLETED: NOVEMBER 05,1997

# MEDICAL OFFICER'S REVIEW OF NDA 20-868

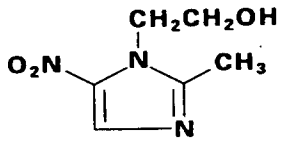
APPLICANT: G.D.Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

GENERIC NAME: Metronidazole MR Tablet

TRADE NAME: Flagyl MR

CHEMICAL NAME: 2-methyl-5-nitroimidazole-1-ethanol

CHEMICAL STRUCTURE:




MOLECULAR FORMULAR: $C_6 H_9 N_3 O_3$

MOLECULAR WEIGHT: 171.16

PHARMACOLOGIC CATEGORY : Anti-bacterial and Anti-protozoal

DOSAGE FORM: Tablet

ROUTE OF ADMINISTRATION: Oral

PROPOSED INDICATION AND USAGE: Flagyl MR is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis or anaerobic vaginosis.)

PROPOSED DOSAGE AND ROUTE OF ADMINISTRATION: One tablet orally (approximately 750 milligrams of metronidazole) daily for 7 days.

RELATED DRUGS:
NDAs 12-623, 20-334

MATERIAL REVIEWED: 12 Volumes

BACKGROUND: Bacterial Vaginosis (BV) continues to be one of the most common vaginal conditions in the reproductive age female seen in the physician's office today. It represents approximately 40% of all vaginitis surpassing both vaginal candidiasis and vaginal trichomoniasis. It causes significant patient discomfort and has been implicated in several gynecologic diseases and disorders, including recurrent urinary tract infections, adnexal tenderness, postpartum endometritis, increased risk of infection after gynecologic surgery, laparoscopically-proven pelvic inflammatory disease and preterm labor.

Bacterial vaginosis (BV) has been recognized as a distinct clinical entity since 1955, when Gardner and Dukes identified *Haemophilus vaginalis* (now *Gardnerella vaginalis*) as the etiologic agent (1). Historically the variety of terms that have been used to describe BV (nonspecific vaginitis, anaerobic vaginitis, *Haemophilus vaginalis* vaginitis, *Corynebacterium* vaginitis, *Gardnerella vaginalis*) reflect the poor understanding of the pathophysiology and microbiology of this condition. Through the years , investigators have learned that BV is not a simple infection: it is not caused by a single pathogen, and there is no inflammatory response as seen in trichomonal or yeast vaginitis (2). The etiology of bacterial vaginosis (BV) is thought to be the result of a replacement of the normal, lactobacillus-dominant vaginal flora with several other organisms including *Gardnerella vaginalis, Mobiluncus mulieris, Mobiluncus curtissi, Mycoplasma hominis* and anaerobes (*Peptostreptococcus spp,* and *Bacteroides spp.*)

The clinical criteria used to diagnose BV were standardized by Amsel et al. in 1983. He defined BV as the presence of three or more of the following signs: a white, homogeneous discharge which smoothly coats the vaginal walls; the presence of bacetria-coated vaginal epithelial cells ("clue cells") on a wet mount or gram-stained preparation of vaginal fluid; a vaginal pH greater than 4.5; and a characteristic amine odor when vaginal secretions are alkalinized (3). Amsel found that the presence of two or more signs on a swab of vaginal fluid diagnosed BV with 100% sensitivity, 98% specificity, 91% positive predictive value (PPV) and 100% negative predictive value.

Since these criteria were first proposed, the validity of individual signs has been studied extensively by investigators. Eschenbach et al (4), found that the presence of clue cells was more specific for BV when they represented $\geq$ 20% of epithelial cells. He also found that vaginal pH of 4.7 or greater was the most sensitive sign in patients with at least 20% clue cells. However, pH was the least specific sign. Thomason (5) also found that clue cells were the most sensitive and specific sign of BV, but cautions against using clue cells as the sole diagnostic criterion. Several studies have found that homogeneous discharge was not helpful in diagnosing BV (5,6). Some women with BV may have slight or no vaginal discharge, and it may be difficult to evaluate discharge in women who have douched or had recent intercourse. (7). The "whiff" test for volatile amines has been described as a powerful predictor of BV by some, (5,8) but Eschenbach (4) reported a PPV of only 76% for the test compared with a Gram stain diagnosis of BV. Since

clinical signs are very difficult to standardize between clinicians, Gram stain has been used to augment the clinical findings. Eschenbach (4) found that the presence of clue cells correlated most highly with Gram stain criteria for BV.

Two systems have been developed for interpreting Gram stains of vaginal discharge for BV. The older method, developed by Spiegel et al. (9), compares the number of large Gram-positive bacilli (termed lactobacillus morphotypes) with the numbers of small Gram-variable coccobacilli (*Gardnerella vaginalis* morphotypes) and morphotypes typical of Gram-negative anaerobes and Gram-positive cocci. Bacterial vaginosis is considered present by the Spiegel criteria if lactobacillus morphotypes are fewer than five per oil immersion field and if there are five or more *G. vaginalis* morphotypes together with five or more other morphotypes (gram- positive cocci, small gram-negative rods, curved gram-variable rods or fusiforms) per oil immersion field. If five or more lactobacilli and fewer than five other morphotypes are present per oil immersion field, the Gram stain is considered to be normal.

The second method of Gram stain interpretation uses a scoring system and was developed by Nugent et al.(10). It is more specific for the diagnosis of BV than the Spiegel criteria by virtue of its emphasis on morphotypes which are most reliably associated with BV (lactobacillus, *G. vaginalis* and *Bacteroides* spp. and *Mobiluncus* spp.). The scoring system provides a 0 to 10 point scale for the evaluation of the vaginal flora and is based on a weighted sum of the following bacterial morphotypes found on microscopic examination under oil immersion (x1000):

a. Lactobacillus (large gram-positive rods);
b. *G.Vaginalis/Bacteroides* Spp. (small gram-variable rods/small gram-negative rods);
c. *Mobiluncus* Spp. (curved gram-variable rods).

Scoring system (0 to 10) for Gram-stained vaginal smears*

| Score** | Lactobacillus morphotypes | Gardnerella and Bacteroides 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. Total score = lactobacilli + *G vaginalis* and *Bacteroides* spp. + curved rods.

** 0, No morphotypes present; 1, <1 morphotype present; 2, 1 to 4 morphotypes present; 3, 5 to 30 morphotypes present; 4, 30 or more morphotypes present.

The criterion for bacterial vaginosis according to Nugent's criteria is a score of 7 or higher; a score of 4 to 6 is considered intermediate, and a score of 0 to 3 is considered normal.

The diagnosis of BV is best made by the examination of vaginal fluid for the presence of "clue cells", an amine odor after the addition of KOH and a vaginal pH > 4.5. A Gram stain as detailed above should be used to complement or confirm the clinical evaluation of the patient with abnormal vaginal discharge.

**Rationale for Flagyl ® MR**

The current recommended treatment for bacterial vaginosis by the Centers for Disease Control is metronidazole 500 mg po twice daily for 7 days although this regimen has not received FDA approval. The recommended alternative treatments, which are FDA approved regimens, include: Metrogel Vaginal (metronidazole 0.75%), one applicator full (5 grams) intravaginally, once or twice daily for 5 days; or Cleocin Vaginal Cream (clindamycin cream 2%), one full applicator (5 grams) intravaginally at bedtime for 7 days. The applicant desires to obtain approval for a once daily dosing regimen for 7 days of a modified-release oral tablet containing 750 mg of metronidazole.

The applicant states that a once-daily dosing with Flagyl MR® (metronidazole 750 mg) is expected to improve compliance when compared to a more frequent dosing regimen and improved compliance will result in more patients receiving adequate therapy, a lower rate of treatment failure, and a lower rate of BV recurrence.

## CLINICAL STUDIES

In an attempt to obtain approval for the use of Flagyl MR® in the treatment of BV, the Applicant conducted two controlled clinical studies in the United States under Protocols N13-95-02-015 (015) and N13-95-02-017 (017), respectively, which compared the safety and efficacy of Flagyl MR® (metronidazole 750 mg tablets) to Cleocin® (2% clindamycin phosphate vaginal cream) in the treatment of bacterial vaginosis. The results of these studies as determined by the Applicant and the Reviewing Medical Officer is the subject of this review.

The Chemistry, Microbiology and Clinical Pharmacology for Flagyl MR® may be found in the Chemistry Review dated 11/24/97, the Microbiology Review dated 11/24/97, and the Biopharmacology Review dated 11/24/97, respectively.

## MATERIAL AND METHODS

### Study Design

Two Phase III studies were conducted to evaluate the safety and efficacy of Flagyl MR®, a 750 mg metronidazole modified-release tablet, compared to 2% clindamycin vaginal

cream (Cleocin®) for treatment of BV. The design of these studies is summarized in Table 1.

**Table 1. Summary of Phase III Controlled Trials**

| STUDY<br><br>P: PROTOCOL NUMBER* | STUDY DESIGN | NUMBER OF SUBJECTS<br>MEAN AGE<br>AGE RANGE<br>RACE | DOSAGE FORM<br>ROUTE OF ADMINISTRATION | DURATION OF TREATMENT |
|---|---|---|---|---|
| P: N13-95-02-015 | Single-blind, randomized, controlled, multicenter, dose finding study | 445 Subjects<br>Mean Age: 32 yrs<br>Age Range:<br>223 Caucasian<br>173 Black<br>49 Oriental/Other | = Flagyl MR 750 mg orally once daily<br>= Flagyl MR 750 mg orally once daily<br>= Cleocin 2% Cream vaginally at bedtime | 5 days<br>7 days<br>7days |
| P; N13-95-02-017 | Single-blind, randomized, controlled, multicenter | 264 Subjects<br>Mean Age: 33 yrs<br>Age Range:<br>183 Caucasian<br>70 Black<br>11 Oriental/Other | = Flagyl MR 750 mg orally once daily<br>= Cleocin 2% Cream vaginally at bedtime | 7 days<br>7 days |

*Study protocol numbers will be denoted -015 and-017 throughout document.

Study N13-95-02-015 was a multi-center, single-blind, randomized, controlled dose duration study. This study will be referred to as Study -015 in this document. A total of 445 women with a clinical diagnosis of BV were enrolled into one of three treatment groups:

Treatment A: One Flagyl MR® tablet containing 750 mg of metronidazole administered once daily for five consecutive days followed by a matching placebo tablet administered once daily for two days.

Treatment B: One Flagyl MR® 750-mg tablet administered once daily for seven consecutive days.

Treatment C: One applicator full of Cleocin® (clindamycin phosphate 2% vaginal cream, (Upjohn) inserted into the vagina once daily, preferably at bedtime, for seven consecutive days.

Study N13-95-02-017 was a multi-center, single-blind, randomized, controlled study in which 264 women were enrolled.. This study will be referred to as Study -017 in this document. Women with a clinical diagnosis of BV were enrolled in one of the two active treatment groups:

Treatment A: One Flagyl MR® tablet containing 750 mg of metronidazole administered once daily for seven consecutive days.

Treatment B: One applicator full of Cleocin® (Clindamycin phosphate 2% vaginal cream, Upjohn) inserted into the vagina once daily, preferably at bedtime, for seven consecutive days.

Aside from the number of treatment groups, the two studies were identical in population and design. Female patients 15 years of age or older with a clinical diagnosis of BV including i) vaginal discharge, ii) positive amine odor on alkalinization of vaginal fluid when mixed with 10% potassium hydroxide solution, iii) presence of one clue cell per field in 20 high power fields (x400) on direct wet mount examination, and iv) pH of vaginal fluid >4.5 were eligible to enroll in the studies. Patients with evidence of uterine infection, gonorrhea, chlamydia, syphilis, active genital herpes, or yeast infection were excluded from the studies. Concurrent use of antimicrobial agents (vaginal, or systemic) was disallowed during the entire duration of the study. All patients were requested to abstain from sexual intercourse during the course of treatment, and to refrain from douching and applying intravaginal products during the entire study period. All patients gave written informed consent before participating in the studies.

At study enrollment a medical and gynecologic history was obtained, a physical and pelvic examination was performed, and vaginal samples were obtained. Patients received allocated treatment and were asked to return for visit 2 (4-7 day post treatment; study days 11-14), and visit 3 (28-32 days post treatment; study days 35-39). At visit 2 and visit 3 the physical and pelvic exams were repeated and vaginal samples were obtained. A complete biochemistry, hematology and urine analysis was completed at study entry, visit 2 and visit 3 for all patients. Concurrent illnesses/adverse events and concomitant medications were recorded. In addition, at each visit the patients were asked to complete a standardized list of self reported complaints.

At each visit, vaginal samples for the following tests were obtained sequentially in the following manner:

- pH determination: Vaginal discharge samples were obtained from the lateral vaginal walls, avoiding contact with cervical mucus. The pH of the vaginal discharge was measured using ColopHast pH paper (pH 4.0 to 7.0).
- "Whiff" test and wet mount microscopy: Lateral vaginal walls were swabbed with a cotton tip applicator, and a liberal amount of discharge was placed on each of two slides. Two drops of 10% potassium hydroxide (KOH) solution were mixed with the discharge on the first slide for detection of a " fishy" amine odor. Two drops of 0.9% saline were mixed with the discharge on the second slide. A cover slip was placed on both slides, and each slide was examined under a light microscope. The saline slide was used for detection of clue cells, trichomonads, WBC, epithelial cells, and parabasal cells. The KOH slide was examined for the presence of typical hyphae and blastosphere of yeast cells.

- Culture for *Gardnerella vaginalis*: Vaginal sample were obtained using a sterile rayon tipped applicator and immediately inserted into a labeled Port-a-cul transport tube. Culture of *Gardnerella vaginalis* was performed by a central laboratory . Growth of Gardnerella vaginalis was identified by characteristic colonies, morphological characteristics and gram stain.

- Culture for yeast/candida: Vaginal samples were obtained using a separate rayon -tipped applicator and immediately inserted into a transport tube with Amies medium with charcoal. Culture of yeast was performed by a central laboratory

- Gram stain: Lateral vaginal walls were swabbed with a cotton-tipped applicator and rolled across a slide to make a smear. Then the slide was air-dryed. Blinded gram stain reading was performed in a central laboratory . Gram stain results were scored using both Spiegel and Nugent criteria (9,10).

**Study Populations**

Efficacy analyses (by Applicant and Medical Officer) were based on the following two patient populations:

1) Clinically Evaluable (CE) patients - defined in each study as patients who met all of the following criteria:

   - At entry, the patient had a clinical diagnosis of bacterial vaginosis: vaginal discharge with a positive amine odor on alkalinization of vaginal fluid, presence of clue cells, and pH of vaginal fluid > 4.5.

2) Gram Stain Evaluable (GSE) patients - defined in each study as patients who met all criteria above and at entry had gram stain confirmation of BV on examination of vaginal secretion.

**Note: The applicant used Spiegel's criteria for confirmation of BV while the Reviewing Medical Officer used the Nugent's criteria for confirmation of BV.**

The primary end-point for efficacy as determined by the Applicant was based on the clinical assessment at 4-7 days and 28-32 days post treatment. In addition an overall outcome measure was generated based on the least favorable of the two assessments, as defined in the Table 2. The following definitions of cure, improvement and failure apply to the Applicant's data analyses.

"Cure" was defined as a return to normal of all 3 diagnostic criteria: pH of vaginal discharge <4.5, absence of a "fishy" amine odor when mixed with 10% KOH solution, and an absence of clue cells.

"Improvement" was defined as a return to normal for 2 of 3 of these diagnostic criteria.

"Failure" was defined as a return to normal of 1 or none of these diagnostic criteria, or discontinuation of medication by the patient due to treatment failure.

For the Gram stain evaluable patients a cure was defined as a return of the Gram stain to normal according to Spiegel's criteria and the absence of clue cells and odor.

Table 2
Clinical Assessments at Visit 1, Visit 2 and Overall (By Applicant)

| VISIT AT 4-7 DAYS | VISIT AT 28-32 DAYS | OVERALL OUTCOME |
|---|---|---|
| Cure | Cure<br>Improvement<br>Failure | Cure<br>Improvement<br>Failure |
| Improvement | Cure<br>Improvement<br>Failure | Improvement<br>Improvement<br>Failure |
| Failure | Cure<br>Improvement<br>Failure | Failure<br>Failure<br>Failure |

In the Medical Officer's analyses, the primary end-point for efficacy was based upon the clinical assessment at 28-32 days post-treatment. Assessment at this visit was defined as cure or failure. For the clinically evaluable population, cure was defined as: the absence of clue cells and "fishy" amine odor with a pH $\leq$4.7. For the GSE population a cure was defined as normal Gram stain score ( 0-3) according to Nugent's criteria and the absence of clue cells and odor and a pH.of $\leq$ 4.7.

Safety analyses by the Applicant and Medical Officer included all randomized patients who received at least one dose of study medication and included all adverse events reported by the patient or the investigator. All safety data were provided by the Applicant.

**Reviewer's Comment: Based on the results of the dose ranging study (-015) that included patients who received Flagyl MR® for 5 days, Flagyl MR® for 7 days and Cleocin® vaginal cream for 7 days, the Applicant decided to seek approval of Flagyl MR® for 7 days. A second study (-017) was conducted to support the findings of Study 015. Although the Applicant reported efficacy and safety results for patients who received Flagyl MR® for 5 days, this review will include only the results of**

**Flagyl MR® when used for 7 days compared to Cleocin® vaginal cream for 7 days in the Applicant's and Medical Officer's data analyses, respectively.**

**Results** (Study 015)

Objective : The objective of this study was to evaluate the efficacy and safety of the metronidazole 750 mg MR tablet compared to the Cleocin® (clindamycin phosphate vaginal cream,) in the treatment of bacterial vaginosis.

**Demographics**

A total of 294 patients was enrolled and randomized, 139 in the Flagyl® MR 750 mg group and 155 in the Cleocin® group. There were no statistically significant differences between treatment groups with respect to demographics and baseline characteristics (age, race, height and weight). For all randomized patients, the mean age range was 31.5 years in the Flagyl® group and 31.9 years ) for the Cleocin® group. In the Flagyl® group 53 % were Caucasian and 37% Black compared to 51% Caucasian and 39% Black in the Cleocin® group. See Table 3.

STUDY 15
TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 3

DEMOGRAPHIC AND BASELINE CHARACTERISTICS
ALL RANDOMIZED PATIENTS

| | FLAGYL MR 750MG x 7 DAYS | CLEOCIN |
|---|---|---|
| AGE (years) | | |
| N | 139 | 155 |
| MEAN | 31.5 | 31.9 |
| STD. DEV. | 9.33 | 9.12 |
| MEDIAN | 31.0 | 31.0 |
| RANGE | | |
| <20 | 10 | 6 |
| 20-29 | 53 | 60 |
| 30-39 | 48 | 60 |
| 40-49 | 24 | 23 |
| >=50 | 4 | 6 |
| RACE/ETHNIC ORIGIN | | |
| CAUCASIAN | 73( 53%) | 80( 51%) |
| BLACK | 52( 37%) | 60( 39%) |
| ORIENTAL | 0( 0%) | 0( 0%) |
| OTHER | 14( 10%) | 15( 10%) |
| TOTAL | 139(100%) | 155(100%) |
| HEIGHT (CM) | | |
| N | 139 | 154 |
| MEAN | 163.22 | 164.11 |
| STD. DEV. | 6.78 | 6.60 |
| MEDIAN | 162.60 | 165.05 |
| RANGE | | |
| WEIGHT (KG) | | |
| N | 138 | 152 |
| MEAN | 70.99 | 71.30 |
| STD DEV | 18.65 | 21.12 |
| MEDIAN | 65.00 | 66.70 |
| RANGE | | |

Clinically-evaluable patients were those who met all of the criteria as described in the (Study Population) section. In the Applicant's analyses, the clinically-evaluable population consisted of 256 patients: 90% (125/139) of the Flagyl MR® group and 85% (131/155) in the Cleocin® group (Tables 4 and 5). Gram stain evaluable patients were those who had a diagnosis of BV on entry confirmed by Gram stain (Spiegel's criteria) in addition to meeting all of the criteria as described in the (Study Population) section. In the Applicant's analyses there was a total of 144 patients: 52% (72/139) of the Flagyl MR® group and 46% (72/155) in the Cleocin® group (Tables 4 and 5).

TABLE 4
STUDY 15
EVALUABLE PATIENTS BY APPLICANT ( FLAGYL MR 750 MG)

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | % | EVALUABLE GRAM STAIN # | % |
|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 4 | 3 | (75) | 2 | (50) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 6 | 5 | (84) | 2 | (34) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 8 | 6 | (75) | 4 | (50) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 10 | 9 | (90) | 5 | (50) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 16 | 15 | (94) | 8 | (50) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 12 | 11 | (92) | 8 | (67) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 3 | (100) | 2 | (67) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 6 | 6 | (100) | 4 | (67) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 1 | 1 | (100) | 1 | (100) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 2 | 2 | (100) | 1 | (50) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 2 | 2 | (100) | 2 | (100) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 7 | (100) | 5 | (72) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 14 | 12 | (86) | 5 | (36) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 8 | 6 | ((75) | 5 | (63) |
| JAN H. STAFL, MD EUGENE, OREGON | 4 | 4 | (100) | 3 | (75) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 2 | 2 | (100) | 1 | (25) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 4 | (100) | 2 | (100) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 12 | 11 | (92) | 7 | (59) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 6 | 5 | (83) | 2 | (34) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 8 | 7 | (88) | 2 | (25) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 2 | 2 | (100) | 0 | (0) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 2 | 2 | (100) | 1 | (50) |
| TOTAL | 139 | 125 | (90) | 72 | (52) |

TABLE 5
STUDY 15
EVALUABLE PATIENTS BY APPLICANT
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | % | EVALUABLE GRAM STAIN # | % |
|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 6 | 5 | (83) | 2 | (33) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 6 | 3 | (50) | 1 | (17) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 8 | 5 | (63) | 4 | (50) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 11 | 10 | (91) | 4 | (36) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 16 | 13 | (81) | 4 | (25) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 12 | 11 | (92) | 4 | (33) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 3 | (100) | 2 | (67) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 7 | 7 | (100) | 3 | (43) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 3 | 3 | (100) | 2 | (67) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 3 | 3 | (100) | 2 | (62) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 3 | 3 | (100) | 2 | (67) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 7 | (100) | 6 | (86) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 15 | 12 | (80) | 10 | (67) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 8 | 6 | (75) | 5 | (63) |
| JAN H. STAFL, MD EUGENE, OREGON | 5 | 5 | (100) | 3 | (60) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 1 | 0 | (0) | 0 | (0) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 4 | (100) | 1 | (25) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 14 | 12 | (86) | 9 | (64) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 6 | 4 | (67) | 2 | (33) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 12 | 10 | (83) | 4 | (33) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 1 | 1 | (100) | 1 | (100) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 4 | 4 | (100) | 1 | (25) |
| TOTAL | 155 | 131 | (85) | 72 | (46) |

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ON ORIGINAL

In the Medical Officer's analyses, the clinically-evaluable population consisted of 91% (126/139) of the Flagyl MR® group and 87% (135/155) in the Cleocin® group (Tables 6 and 7). In the Medical Officer's analyses a total of 216 was Gram stain (Nugent's criteria) evaluable patients: 75% (103/139) in the Flagyl group and 73% (113/155) in the Cleocin group ( Tables 6 and 7).

TABLE 6

STUDY 15
EVALUABLE PATIENTS BY MEDICAL OFFICER
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | % | EVALUABLE GRAM STAIN # | % |
|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 4 | 4 | (100) | 3 | (75) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 6 | 5 | (84) | 2 | (34) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 8 | 6 | (75) | 6 | (75) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 10 | 9 | (90) | 9 | (90) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 16 | 15 | (94) | 11 | (69) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 12 | 12 | (100) | 12 | (100) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 3 | (100) | 3 | (100) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 6 | 6 | (100) | 6 | (100) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 1 | 1 | (100) | 1 | (100) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 2 | 2 | (100) | 1 | (50) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 2 | 2 | (100) | 2 | (100) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 7 | (100) | 7 | (100) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 14 | 11 | (79) | 7 | (50) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 8 | 6 | ((75) | 6 | (75) |
| JAN H. STAFL, MD EUGENE, OREGON | 4 | 4 | (100) | 4 | (100) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 2 | 2 | (100) | 2 | (100) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 4 | (100) | 2 | (50) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 12 | 11 | (92) | 8 | (67) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 6 | 5 | (83) | 5 | (83) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 8 | 7 | (88) | 3 | (38) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 2 | 2 | (100) | 2 | (100) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 2 | 2 | (100) | 1 | (50) |
| TOTAL | 139 | 126 | (91) | 103 | (75) |

TABLE 7

STUDY 15
EVALUABLE PATIENTS BY MEDICAL OFFICER
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | % | EVALUABLE GRAM STAIN # | % |
|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 6 | 5 | (84) | 4 | (67) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 6 | 5 | (84) | 4 | (67) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 8 | 6 | (75) | 6 | (75) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 11 | 10 | (91) | 7 | (64) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 16 | 11 | (69) | 7 | (44) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 12 | 11 | (92) | 9 | (75) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 3 | (100) | 3 | (100) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 7 | 7 | (100) | 4 | (58) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 3 | 3 | (100) | 3 | (100) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 3 | 3 | (100) | 3 | (100) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 3 | 3 | (100) | 3 | (100) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 7 | (100) | 7 | (100) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 15 | 12 | (80) | 12 | (80) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 8 | 7 | (88) | 7 | (88) |
| JAN H. STAFL, MD EUGENE, OREGON | 5 | 4 | ( 80) | 4 | (80) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 1 | 0 | (0) | 0 | (0) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 4 | (100) | 4 | (100) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 14 | 12 | (86) | 11 | (79) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 6 | 5 | (84) | 5 | (84) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 12 | 12 | (100) | 7 | (59) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 1 | 1 | (100) | 1 | (100) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 4 | 4 | (100) | 2 | (50) |
| TOTAL | 155 | 135 | (87) | 113 | (73) |

The number of non-evaluable patients and the reasons for non-evaluability is listed below for each treatment group as assessed by the Applicant.

Study 15

Non-evaluable Patients by Applicant

Flagyl MR 750 mg

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Spiegel's criteria at study entry | 53 |
| Lost to follow-up | 8 |
| Used other anti-microbials during study | 3 |
| Clinical criteria for bv not met | 1 |
| Use study medication for less than 5 days | 2 |
| Total | 67 |

Cleocin Vaginal Cream

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Spiegel's criteria at study entry | 59 |
| Lost to follow-up | 16 |
| Used other anti-microbials during study | 1 |
| Used study medication for less than 5 days | 4 |
| Received no medication | 2 |
| IUD present | 1 |
| Total | 83 |

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ON ORIGINAL

The number of non-evaluable patients and the reasons for non-evaluability is listed below for each treatment group as assessed by the Medical Officer.

Study 15

Non-evaluable Patients by Medical Officer

Flagyl MR 750 mg

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Nugent's criteria at study entry | 23 |
| Lost to follow-up | 13 |
| Total | 36 |

Cleocin Vaginal Cream

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Nugent's criteria at study entry | 22 |
| Lost to follow-up | 17 |
| Clinical criteria for BV not met | 1 |
| Received no medication | 2 |
| Total | 42 |

In the Applicants analyses, the primary efficacy end-point was clinical outcome at visits 2 and 3. Criteria for determination of outcome of clinically evaluable patients were pH of vaginal discharge $\leq 4.5$, absence of "fishy" amine odor when mixed with 10% KOH solution, and absence of clue cells. In the Gram stain evaluable group, in addition to the above criteria , the Gram stain would have to return to normal according to Spiegel's criteria as defined on page 3. Post-treatment assessments were defined as cure, improvement or failure at each post-treatment visit and at the overall assessment. Results for all evaluable patients are found in Tables 9 and 10. Clinical cure was reported 57% (71/125) of the Flagyl MR® clinically-evaluable group and 49% (64/131) of the Cleocin® clinically evaluable group. In the Gram stain evaluable group, 53% (38/72) of the Flagyl® patients and 46% (33/72) of the Cleocin® patients reported cures.

In the Medical Officer's analyses, the primary efficacy end-point was clinical outcome at visit 3. Criteria for determination of outcome of clinically evaluable patients were pH $\geq 4.7$, absence of "fishy" odor when mixed with 10% KOH solution, and absence of clue cells. In the Gram stain evaluable group, in addition to the above, the Gram stain would

have to have a score of (0-3) according to Nugent's criteria. Post treatment assessments were considered as cure or failure. Results of all evaluable patients are found in Tables 11 and 12. Clinical cure was reported in 61% (77/126) of the Flagyl MR® clinically evaluable patients and 59% (80/135) of the Cleocin® clinically-evaluable patients. In the Gram stain evaluable patients, 51% (53/103) in the Flagyl group and 55% (62/113) of the Cleocin patients were assessed as cures. A summary of the cures for all evaluable patients is shown in Table 8 below.

TABLE 8

STUDY 15

PATIENTS CURED

(ACCORDING TO MEDICAL OFFICER'S ANALYSES)

| | CLINICALLY EVALUABLE PATIENTS CURED | | | GRAM STAIN EVALUABLE PATIENTS CURED | | |
|---|---|---|---|---|---|---|
| | FLAGYL | CLEOCIN | 95%CI | FLAGYL | CLEOCIN | 95% CI |
| APPLICANT | 57% (71/125) | 49% (64/131) | -5.03, 20.92 | 53% (38/72) | 46% (33/72 | -10.74, 24.63 |
| MEDICAL OFFICER | 61% (77/126) | 60% (80/135) | -10.80, 14.50 | 51% (53/103) | 55% 62/113) | -17.66 10.83 |

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ON ORIGINAL

TABLE 9

STUDY 15
NUMBER OF PATIENTS ASSESSED AS CURED BY APPLICANT
AT END OF STUDY
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE # | (%) |
|---|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 3 | 1 | (34) | 2 | 1 | (50) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 5 | 2 | (40) | 2 | 1 | ((50) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 6 | 4 | (67) | 4 | 2 | (50) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 9 | 2 | (23) | 5 | 0 | (0) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 15 | 12 | (80) | 8 | 6 | (75) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 11 | 7 | (64) | 8 | 6 | (75) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 0 | (0) | 2 | 0 | (0) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 6 | 5 | (84) | 4 | 4 | (100) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 1 | 0 | (0) | 1 | 0 | (0) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 2 | 0 | (0) | 1 | 0 | (0) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 2 | 0 | (0) | 2 | 0 | (0) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 4 | (58) | 5 | 3 | (60) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 12 | 3 | (25) | 5 | 0 | (0) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 6 | 3 | (50) | 5 | 2 | (40) |
| JAN H. STAFL, MD EUGENE, OREGON | 4 | 4 | (100) | 3 | 3 | (100) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 2 | 1 | (50) | 2 | 1 | (50) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 2 | (50) | 1 | 0 | (0) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 11 | 9 | (82) | 7 | 5 | (72) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 5 | 3 | (60) | 2 | 2 | (100) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 7 | 5 | (72) | 2 | 2 | (100) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 2 | 1 | (50) | 0 | 0 | (0) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 2 | 0 | (0) | 1 | 0 | (0) |
| TOTAL | 125 | 71 | (57) | 72 | 38 | (53) |

TABLE 10

STUDY 15
NUMBER OP PATIENTS ASSESSED AS CURED BY APPLICANT
AT END OF STUDY
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE # | (%) |
|---|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 5 | 3 | (60) | 2 | 1 | (50) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 3 | 0 | (0) | 1 | 0 | (0) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 5 | 4 | (80) | 4 | 3 | (75) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 10 | 3 | (30) | 4 | 1 | (25) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 13 | 9 | (69) | 4 | 3 | (75) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 11 | 7 | (64) | 4 | 2 | (50) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 1 | (33) | 2 | 1 | (50) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 7 | 7 | (100) | 3 | 3 | (100) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 3 | 0 | (0) | 2 | 0 | (0) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 3 | 1 | (33) | 2 | 1 | (50) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 3 | 1 | (33) | 2 | 0 | (0) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 3 | (43) | 6 | 2 | (33) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 12 | 5 | (42) | 10 | 4 | (40) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 6 | 3 | (50) | 5 | 2 | (40) |
| JAN H. STAFL, MD EUGENE, OREGON | 5 | 2 | (40) | 3 | 1 | (33) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 0 | 0 | (0) | 0 | 0 | (0) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 0 | (0) | 1 | 0 | (0) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 12 | 7 | (58) | 9 | 6 | (33) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 4 | 1 | (25) | 2 | 0 | (0) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 10 | 6 | (60) | 4 | 2 | (50) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 1 | 1 | (100) | 1 | 1 | (100) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 4 | 0 | (0) | 1 | 0 | (0) |
| TOTAL | 131 | 64 | (49) | 72 | 33 | (46) |

TABLE 11

STUDY 15
NUMBER OP PATIENTS ASSESSED AS CURED BY MEDICAL OFFICER
AT END OF STUDY
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE # | (%) |
|---|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 4 | 1 | (20) | 3 | 3 | (100) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 5 | 2 | (40) | 2 | 1 | (50) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 6 | 4 | (67) | 6 | 3 | (50) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 9 | 6 | (67) | 9 | 4 | (44) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 15 | 13 | (87) | 11 | 5 | (45) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 12 | 8 | (67) | 12 | 5 | (42) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 0 | (0) | 3 | 1 | (33) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 6 | 5 | (83) | 6 | 3 | (50) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 1 | 0 | (0) | 1 | 0 | (0) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 2 | 1 | (50) | 1 | 1 | (100) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 2 | 0 | (0) | 2 | 0 | (0) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 4 | (57) | 7 | 3 | (43_ |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 11 | 3 | (27) | 7 | 3 | (43) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 6 | 3 | (50) | 6 | 2 | (50) |
| JAN H. STAFL, MD EUGENE, OREGON | 4 | 4 | (100) | 4 | 2 | (50) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 2 | 1 | (50) | 2 | 2 | (100) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 3 | (75) | 2 | 1 | (50) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 11 | 9 | (82) | 8 | 5 | (62) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 5 | 4 | (80) | 5 | 3 | (60) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 7 | 5 | (71) | 3 | 3 | (100) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 2 | 1 | (50) | 2 | 2 | (100) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 2 | 0 | (0) | 1 | 1 | (100) |
| TOTAL | 126 | 77 | (61) | 103 | 53 | (51) |

TABLE 12

STUDY 15
NUMBER OP PATIENTS ASSESSED AS CURED BY MEDICAL OFFICER
AT END OF STUDY
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE. # | (%) |
|---|---|---|---|---|---|---|
| SOPHIA H. ANTHONY, MD VERONA, NEW JERSEY | 5 | 3 | (60) | 4 | 2 | (50) |
| DAVID BAKER, MD STONY BROOK, NEW YORK | 5 | 1 | (20) | 4 | 2 | (50) |
| LYNN BORGATTA, MD, MPH WHITE PLAINS, NEW YARK | 6 | 4 | (67) | 6 | 3 | (50) |
| JAY M. COOPER, MD PHOENIX, ARIZONA | 10 | 4 | (40) | 7 | 4 | (58) |
| JOHN M ESTESS, MD HOLLANDALE, MISSISSIPPI | 11 | 9 | (82) | 7 | 3 | (43) |
| ROBERT B. JONES, MD, PHD INDIANAPOLIS, INDIANA | 11 | 9 | (82) | 9 | 3 | (34) |
| LISA A. MARR, MD PORTLAND, OREGON | 3 | 2 | (67) | 3 | 3 | (100) |
| JAMES MAXWELL, MD COLORADO SPGS, COLORADO | 7 | 7 | (100) | 4 | 3 | (75) |
| JAMES MCGREGOR, MD, CM DENVER, COLORADO | 3 | 0 | (0) | 3 | 2 | (67) |
| ROBERT MESSER, MD LUBBOCK, TEXAS | 3 | 1 | (33) | 3 | 1 | (33) |
| GILLES R. G. MONIF, MD OMAHA, NEBRASKA | 3 | 2 | (67) | 3 | 1 | (33) |
| HOWARD A. REISMAN, MD ROSWELL, GEORGIA | 7 | 5 | (72) | 7 | 4 | (58) |
| JEFFERY B. ROSEN, MD CORAL GABLES, FLORIDA | 12 | 9 | (75) | 12 | 9 | (75) |
| JANE R. SCHWEBKE, MD BIRMINGHAM, ALABAMA | 7 | 5 | (72) | 7 | 5 | (72) |
| JAN H. STAFL, MD EUGENE, OREGON | 4 | 2 | (50) | 4 | 2 | (50) |
| GARY E. STEIN, PHARM.D EAST LANSING, MICHAGAN | 0 | 0 | (0) | 0 | 0 | (0) |
| BARBARA A. TYLER, MD BRYAN, TEXAS | 4 | 0 | (0) | 4 | 1 | (25) |
| NEIL M. KASSMAN, MD STATESVILLE, N. CAROLINA | 12 | 9 | (75) | 11 | 6 | (55) |
| HAROLD C WIESENFELD, MD PITTSBURGH, PENNSYLVANIA | 5 | 1 | (20) | 5 | 3 | (60) |
| ROMONA I. SLUPIK, MD CHICAGO, ILLINOIS | 12 | 6 | (50) | 7 | 3 | (43) |
| THOMAS S. WALTER, MD DUNEDIN, FLORIDA | 1 | 1 | (100) | 1 | 1 | (100) |
| STEPHEN E. DANIELS, DO HOUSTON, TEXAS | 4 | 0 | (0) | 2 | 1 | (50) |
| TOTAL | 135 | 80 | (60) | 113 | 62 | (55) |

**SAFETY** (Study 15)

Compliance was measured by a count of tablets or applicators returned at visit 2. There was no statistically significant difference between groups with respect to medication compliance. In the Flagyl MR® 7-day group, 94% (131/139) of patients took all seven tablets of study medication; 1 patient took 6 tablets and 1 patient took 2 tablets; compliance data were missing for 6 patients (4%). In the Cleocin® group, 90% (138/154) of patients used all seven applicators of study medication; 2 patients used 6 applicators, 2 used 5 applicators, 1 patient used 3 applicators, 2 patients used 2 applicators, and 2 patients used no applicators; compliance data were missing for 7 patients (5%).

**Adverse Events**

Safety was assessed for all patients who received at least one dose of study medication. A total of 290 patients received at least one dose of study medication: 138 patients in the Flagyl MR® group and 152 in the Cleocin® group.

Overall Incidence of Adverse Events

Incidence of adverse events are presented by severity within body system for all patients who received at least one dose of study medication in Table 13. At least one adverse event was reported by 66% ( 91/138) of patients in the Flagyl MR® group and 65% (99/152) of patients in the Cleocin® group. Of the 91 patients reporting adverse events in the Flagyl MR® group, the greatest severity reported was mild for 37% (34/91), moderate for 52 % (47/91), and severe for 11% (10/91) Of the 99 patients in the Cleocin® group reporting adverse events, the greatest severity reported was mild for 38% (38/99), moderate for 48% (48/99), and severe for 13% (13/99).

TABLE 13
INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM
PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION (ALL CAUSALITY)

| | FLAGYL MR 750 MG X 7 DAYS (N = 138) | | | | CLEOCIN N = (152) | | | |
|---|---|---|---|---|---|---|---|---|
| SUMMARY (NUMBER OF PATIENTS | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | 34 | 47 | 10 | 91 (66%) | 38 | 48 | 13 | 99 ( 65%) |
| PATIENTS WITH NO ADVERSE EVENTS | | | | 47 ( 34%) | | | | 53 ( 35%) |
| PATIENTS WITH NO ADVERSE EVENT INFORMATION | | | | 0 ( 0%) | | | | 0 ( 0%) |
| ALL PATIENTS WITH AT LEAST ONE DOSE | | | | 138 (100%) | | | | 152 (100%) |

Adverse events are presented by decreasing order of incidence (following incidence in the Flagyl MR® group first) for all patients with at least one dose of study medication in Table 14. The adverse events reported by the most patients were headaches (17%) of the Flagyl MR® group and 17% of the Cleocin® group), vaginitis (14%) of the Flagyl MR® group and 11% of the Cleocin® group), nausea ( 9%) of the Flagyl MR® group and 3% of the Cleocin® group), taste perversion (7%) of the Flagyl MR® group and 1% in the Cleocin® group, rhinitis (7%) in the Flagyl MR® group and (3%) in the Cleocin® group. influenza-like symptoms (6%) in the Flagyl MR® group and 6% in the Cleocin® group, infection bacterial and moniliasis 5% in each treatment group, pruritis genital 4% in the Flagyl MR® group and 5% in the Cleocin® group, upper respiratory infection 3% in the Flagyl MR® group and 5% in the Cleocin® group, urinary tract infection 3% in the Flagyl MR® group and 5% in the Cleocin® group and abdominal pain 2% in the Flagyl MR® group and 5% in the Cleocin® group. All other adverse events were reported by less than 5% of the patients in each treatment group.

TABLE 14
INCIDENCE OF ADVERSE EVENTS BY SEVERITY
PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION (ALL CAUSALITY)

| | FLAGYL MR 750 MG X 7 DAYS (N = 138) | | | | CLEOCIN N = (152) | | | |
|---|---|---|---|---|---|---|---|---|
| ADVERSE EVENT NUMBER OF PATIENTS IN EACH CATEGORY | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| HEADACHE | 14 | 9 | 1 | 24 (17%) | 12 | 11 | 3 | 26 (17%) |
| VAGINITIS | 10 | 10 | 0 | 20 (14%) | 9 | 8 | 0 | 17 (11%) |
| NAUSEA | 11 | 2 | 0 | 13 ( 9%) | 2 | 3 | 0 | 5 ( 3%) |
| TASTE PERVERSION | 5 | 3 | 1 | 9 (7%) | 1 | 0 | 0 | 1 (1%) |
| RHINITIS | 6 | 3 | 0 | 9( 7%) | 3 | 1 | 0 | 4 (3%) |
| INFECTION BACTERIAL | 5 | 1 | 1 | 7 (5 %) | 5 | 3 | 0 | 8 ( 5%) |
| INFLUENZA-LIKE SYNDROME | 3 | 5 | 0 | 8 (6%) | 6 | 3 | 0 | 9 (6%) |
| MONIALIASIS | 4 | 3 | 0 | 7 (5%) | 1 | 4 | 2 | 7 ( 5%) |
| PRURITUS GENITAL | 1 | 3 | 1 | 5 (4%) | 3 | 4 | 0 | 7 (5%) |
| UPPER RESPIRATORY INFECTION | 3 | 0 | 1 | 4 (3%) | 3 | 4 | 0 | 7 (5%) |
| URINARY TRACTR INFECTION | 0 | 4 | 0 | 4 (3%) | 3 | 4 | 1 | 8 (5%) |
| ABDOMINAL PAIN | 2 | 1 | 0 | 3 (2%) | 5 | 2 | 0 | 7 (5%) |

Of the 91 patients in the Flagyl MR® group who reported adverse events, attribution to study medication, as assessed by the investigator, was reported as none for 41% (37/91) , uncertain for 24% (22/91), and probable for 35% (32/91), Table 15. Of the 99 patients in the Cleocin® group who reported adverse events, attribution to study medication, as assessed by the investigator, was reported as none for 58% (57/99), uncertain for 25% (25/99), and probable for 17% (17/99). Headache, vaginitis, nausea and taste perversion were the most frequently reported adverse events in the Flagyl MR® group. Headache and vaginitis were the most frequently reported adverse events in the Cleocin® group. (Table 15).

TABLE 15
INCIDENCE OF ADVERSE EVENTS BY ATTRIBUTION, WITHIN BODY SYSTEM
PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION

| | FLAGYL MR 750 MG X 7 DAYS (N = 138) | CLEOCIN (N = 133) |
|---|---|---|
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | | |
| NONE | 37 (27%) | 57 (43%) |
| UNCERTAIN | 22 (16%) | 25 (19%) |
| PROBABLY | 32 (23%) | 17 (13%) |
| TOTAL | 91 (66%) | 99 (65%) |

Adverse Events Causing Withdrawal

Three adverse events in two patients in the Flagyl® group resulted in the withdrawal from the study. No patients randomized to the Cleocin® group were withdrawn from the study due to adverse events.

Patient US0017-121, a 20-year-old black female randomized to the Flagyl MR® group, was discontinued from the study due to moderate psychosis. The event was considered serious and is discussed in the serious adverse event section, which follows.

Patient US0024-341, a 30-year-old Caucasian female randomized to the Flagyl MR® group, was withdrawn from the study for moderate pruritus and urticaria which began 2 days after initiation of study medication. The events resolved in one day and were assessed by the investigator as probably related to study medication.

Serious Adverse Events

There were two serious adverse events reported in the Flagyl MR group during the study.

Patient US0016-522 was a 38-year-old Hispanic female who was randomized to the Flagyl MR® group. She began therapy on 02/12/96 and completed on 02/18/96. The patient returned for visit 2 on 02/23/96 and was scheduled for visit 3 on 03/18/96. The patient's medical history was significant only for tubal ligation in 1990. On 02/27/96 the patient went to the emergency room after taking an overdose of what was believed to be ibuprofen (Advil); the exact medication was not known. The patient was discharged from the hospital on the same day under the care of her psychiatrist. No additional information is available. The investigator considered the event to be unrelated to study medication

Patient US0017-121 was a 20-year-old black female randomized to the Flagyl MR® group and began study medication on 10/02/95. The patient was seen on 10/10/95; she was accompanied by her male companion, for whom she requested a check-up and HIV testing. The staff complied with her request, but she was very interruptive. She also complained that her tongue felt unusual, and examination showed it to be coated. Although a return visit was scheduled for 10/21/95, the patient returned the following day and was very inquisitive about her study medication. A compliance count revealed that the patient did not take her day 7 medication. The patient refused to give the staff the box or envelope containing the blister packs. She returned the following day angry, inappropriate, and agitated, refusing the blood draw and the request for a urine specimen. She refused to return the medication card, and told the staff to "remove the death threat" against her. The patient was admitted to the psychiatric unit on 10/16/95 for acute psychotic onset. The patient had no known history of psychiatric illness. The psychiatrist who was treating her believed the patient's psychotic behavior was unlikely related to study medication because the patient had received "other " unspecified medications at the time. The investigator considered the event unrelated to study medication.

**Yeast**

Table 16 shows that the number of positive cultures were similar among the two treatment groups at baseline. This number increased over time to 32% (45/139) for the Flagyl MR® group , and 30% (46/154) for the Cleocin® group by visit 3.

TABLE 16
SUMMARY OF YEAST CULTURE DATA
ALL RANDOMIZED PATIENTS

| | FLAGYL MR 750 MG 7 DAYS (N = 139 | CLEOCIN (N = 154) | P-VALUE |
|---|---|---|---|
| YEAST CULTURE | | | |
| VISIT 1 | | | |
| YES | 29 (21%) | 28 (18%) | 0.643 |
| NO | 110 (79%) | 125 ( 81%) | |
| MISSING | 0 | 1 | |
| TOTAL | 139 (100%) | 154 (100%) | |
| VISIT 2 | | | |
| YES | 41 ( 29%) | 36 ( 23%) | 0.460 |
| NO | 91 (65%) | 105 (68%) | |
| MISSING | 7 ( 5%) | 13 ( 8%) | |
| TOTAL | 139(100%) | 154(100%) | |
| VISIT 3 | | | |
| YES | 45 ( 32%) | 46 (30%) | 0.500 |
| NO | 84 (60%) | 90 ( 58%) | |
| MISSING | 10( 7%) | 18 ( 12%) | |
| TOTAL | 139 (100%) | 154 (100%) | |

**Pregnancies**

There were no pregnancies reported during the study.

**Deaths**

There were no deaths reported during this study

**Summary of Study 15**

Efficacy

The purpose of this single-blind, randomized, controlled comparative, multicenter study was to evaluate the efficacy and safety of Flagyl MR® (metronidazole modified release) 750 mg tablet compared to Cleocin® (2% clindamycin phosphate vaginal cream) in the treatment of bacterial vaginosis (BV). Eligible female patients with bacterial vaginosis were randomized and received one metronidazole 750 mg MR oral tablet once daily for 7 days; or one applicator full of Cleocin® 2% (clindamycin phosphate vaginal cream) inserted into the vagina once daily for 7 consecutive days. Patients were evaluated for a clinical response at 4-7 days and 28-32 days after completion of treatment.

Two hundred ninety-four (294) patients were enrolled into this study at 22 sites. One hundred thirty-nine (139) were randomized to the Flagyl MR® 7-day group (138 received at least one dose), and 155 to the Cleocin®group (152 patients received at least one dose). The treatment groups were similar at baseline with respect to demographics.

Of the enrolled patients 87% (256/294) were considered clinically evaluable for BV by the Applicant and 89% (261/294) were considered clinically evaluable by the Medical Officer. BV was confirmed according to Spiegel's criteria in 49% (144/294) of the enrolled patients by the Applicant and in 73% (216/294 ) according to Nugent's criteria by the Medical Officer.

Results of clinical cure by the Applicant suggest a larger percentage of Flagyl MR® than Cleocin® patients were cured overall. For all randomized patients, a clinical cure was reported in 57% of the Flagyl MR® group and 49% in the Cleocin® group. In patients who had Gram stain confirmation of BV by the Applicant, a cure rate of 53% was observed in the Flagyl MR® treatment group and 46% in the Cleocin® treatment group. The 95% confidence intervals for the difference in the cure rates between treatment groups indicate that treatment with Flagyl MR® was statistically equivalent to treatment with Cleocin®.

Results for the clinical cures assessed by the Medical Officer reveal similar findings. Sixty-one percent (61%) of the clinically evaluable patients were assessed as cures in the Flagyl MR® group compared to 60% of the Cleocin® treatment group. In the Gram stain evaluable population 52% of the Flagyl® treatment group and 55% of the Cleocin® treatment group were considered as cures.

Safety

At least one adverse event was reported by 66% (91/138) of the Flagyl® treatment group and 65% (99/152) of the Cleocin® treatment group. The adverse events reported by most patients (all causality) were headache (17% in each treatment group), vaginitis (14% of the Flagyl® treatment group and 11% of the Cleocin® treatment group), and nausea (9% of the Flagyl® treatment group and 3% of the Cleocin® treatment group). All other adverse events were reported by less than 10% of patients in each treatment group.

Conclusion

The results of this study indicate that Flagyl MR® 750 mg tablets when taken once daily for 7 days in the treatment of bacterial vaginosis(BV) appears to be equivalent in efficacy and safety to the use of Cleocin® vaginal cream intravaginally once daily for 7 days.

**Results** (Study 017)

Objective : The objective of this study was to evaluate the efficacy and safety of the metronidazole 750 mg MR® tablet compared to the Cleocin® (clindamycin phosphate vaginal cream) in the treatment of bacterial vaginosis.

**Demographics**

A total of 264 patients was enrolled and randomized, 131 in the Flagyl® MR 750 mg group and 133 in the Cleocin® group. There were no statistically-significant differences between treatment groups with respect to demographics and baseline characteristics (age, race, height and weight). For all randomized patients, the mean age range was 33.0 years in the Flagyl® group and 32.8 years for the Cleocin® group. In the Flagyl® group 69 % were Caucasian and 28% Black compared to 69% Caucasian and 25% Black in the Cleocin® group. See Table 17.

STUDY 17
TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 17
DEMOGRAPHIC AND BASELINE CHARACTERISTICS
ALL RANDOMIZED PATIENTS

| | FLAGYL MR 750MG x 7 DAYS | CLEOCIN |
|---|---|---|
| AGE (years) | | |
| N | 131 | 133 |
| MEAN | 33.0 | 32.8 |
| STD. DEV. | 10.65 | 10.24 |
| MEDIAN | 31.0 | 31.0 |
| RANGE | | |
| <20 | 6 | 6 |
| 20-29 | 51 | 55 |
| 30-39 | 48 | 37 |
| 40-49 | 23 | 26 |
| >=50 | 10 | 9 |
| RACE/ETHNIC ORIGIN | | |
| CAUCASIAN | 91( 69%) | 92( 69%) |
| BLACK | 37( 28%) | 33( 25%) |
| ORIENTAL | 1( 1%) | 1( 1%) |
| OTHER | 2( 2%) | 7( 5%) |
| TOTAL | 131(100%) | 133(100%) |
| HEIGHT (CM) | | |
| N | 127 | 127 |
| MEAN | 164.44 | 162.99 |
| STD. DEV. | 7.50 | 7.12 |
| MEDIAN | 165.00 | 162.60 |
| RANGE | | |
| WEIGHT (KG) | | |
| N | 129 | 132 |
| MEAN | 70.68 | 69.37 |
| STD DEV | 18.14 | 18.67 |
| MEDIAN | 67.10 | 63.55 |
| RANGE | | |

Clinically-evaluable patients were those who met all of the criteria as described in (Study Population) section. In the Applicant's analyses, the clinically-evaluable population consisted of 226 patients: 87% (114/131) of the Flagyl MR® group and 84% (112/133) in the Cleocin ® group. (Tables 18 and 19). Gram stain evaluable patients were those who had a diagnosis of BV on entry confirmed by Gram stain (Spiegel's criteria) in addition to meeting all of the criteria as described in the (Study Population) section. In the Applicant's analyses there was a total of 139 patients: 53% (70/131) of the Flagyl MR® group and 52% (69/133) in the Cleocin® group (Tables 18 and 19).

TABLE 18

STUDY 17
EVALUABLE PATIENTS BY APPLICANT
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | % | EVALUABLE GRAM STAIN # | % |
|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 6 | 5 | (83) | 3 | (50) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 14 | 14 | (100) | 4 | (60) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 13 | 13 | (100) | 12 | (92) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 2 | 2 | (100) | 1 | (50) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 6 | 5 | (83) | 4 | (67) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 6 | (100) | 3 | (50) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 6 | 5 | (83) | 1 | (17) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 4 | 2 | (50) | 2 | (50) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 17 | 15 | (88) | 9 | (53) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 14 | 11 | (79) | 9 | (64) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 14 | 13 | (93) | 11 | (79) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 10 | 8 | (80) | 4 | (40) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 6 | 3 | (50) | 2 | (33) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 4 | (100) | 2 | (50) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 3 | 3 | (100) | 1 | (33) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 6 | 5 | (83) | 2 | (33) |
| TOTAL | 131 | 114 | (87) | 70 | (53) |

TABLE 19

STUDY 17
EVALUABLE PATIENTS BY APPLICANT
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | (%) | EVALUABLE GRAM STAIN # | (%) |
|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 5 | 5 | (100) | 2 | (40) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 15 | 13 | (87) | 5 | (33) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 12 | 9 | (75) | 7 | (58) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 3 | 2 | (67) | 2 | (67) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 7 | 6 | (86) | 3 | (43) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 6 | (100) | 2 | (33) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 7 | 5 | (71) | 1 | (14) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 3 | 3 | (38) | 2 | (67) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 18 | 16 | (89) | 10 | (56) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 13 | 10 | (77) | 7 | (54) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 15 | 14 | (93) | 13 | (87) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 11 | 8 | (73) | 7 | (64) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 6 | 5 | (83) | 4 | (67) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 3 | (75) | 2 | (50) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 3 | 3 | (100) | 0 | (0) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 5 | 4 | (80) | 2 | (40) |
| TOTAL | 133 | 112 | (84) | 69 | (52) |

In the Medical Officer's analyses, the clinically-evaluable population consisted of 91% (119/131) of the Flagyl MR® group and 88% (117/133) in the Cleocin® group . (Tables 20 and 21). In the Medical Officer's analyses a total of 119 was Gram stain (Nugent's criteria) evaluable patients: 76% (99/131) in the Flagyl® treatment group and 70% (93/133) in the Cleocin® treatment group (Tables 20 and 21).

TABLE 20

STUDY 17
EVALUABLE PATIENTS BY MEDICAL OFFICER
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | % | EVALUABLE GRAM STAIN # | % |
|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 6 | 6 | (100) | 6 | (100) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 14 | 12 | (86) | 6 | (43) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 13 | 13 | (100) | 13 | (100) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 2 | 2 | (100) | 2 | (100) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 6 | 6 | (100) | 6 | (100) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 6 | (100) | 4 | (67) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 6 | 4 | (67) | 2 | (33) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 4 | 4 | (100) | 4 | (100) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 17 | 15 | (88 | 13 | (76) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 14 | 13 | (93) | 13 | (93) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 14 | 14 | (100) | 14 | (100) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 10 | 10 | (100) | 7 | (70) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 6 | 3 | (50) | 3 | (50) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 4 | (100) | 3 | (75) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 3 | 2 | (67) | 1 | (33) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 6 | 5 | (83) | 2 | (33) |
| TOTAL | 131 | 119 | (91) | 99 | (76) |

TABLE 21

STUDY 17
EVALUABLE PATIENTS BY APPLICANT
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER ENROLLED | EVALUABLE CLINICAL # | (%) | EVALUABLE GRAM STAIN # | (%) |
|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 5 | 4 | (80) | 4 | (80) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 15 | 15 | (100) | 9 | (60) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 12 | 9 | (75) | 7 | (78) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 3 | 3 | (100) | 3 | (100) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 7 | 7 | (100) | 5 | (71) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 5 | (83) | 2 | (17) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 7 | 4 | (57) | 3 | (43) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 3 | 3 | (100) | 3 | (100) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 18 | 16 | (89) | 12 | (67) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 13 | 12 | (92) | 12 | (92) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 15 | 14 | (93) | 13 | (87) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 11 | 9 | (82) | 8 | (73) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 6 | 5 | (83) | 5 | (83) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 4 | (100) | 3 | (75) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 3 | 2 | (67) | 1 | (33) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 5 | 5 | (100) | 3 | (60) |
| TOTAL | 133 | 117 | (88) | 93 | (70) |

The number of non-evaluable patients and the reasons for non-evaluability is listed below for each treatment group as assessed by the Applicant.

Study 17

Non-evaluable Patients by Applicant

Flagyl MR 750 mg

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Spiegel's criteria at study entry | 44 |
| Lost to follow-up | 9 |
| Used other anti-microbials during study | 3 |
| Clinical criteria for bv not met | 5 |
| Total | 61 |

Cleocin Vaginal Cream

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Spiegel's criteria at study entry | 43 |
| Lost to follow-up | 13 |
| Used other anti-microbials during study | 3 |
| Used study medication for less than 5 days | 2 |
| Clinical criteria for BV not met at entry | 3 |
| Total | 64 |

The number of non-evaluable patients and the reasons for non-evaluability is listed below for each treatment group as assessed by the Medical Officer.

Study 17

Non-evaluable Patients by Medical Officer

Flagyl MR 750 mg

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Nugent's criteria at study entry | 20 |
| Lost to follow-up | 12 |
| Total | 32 |

Cleocin Vaginal Cream

Reasons for non-evaluability

| | |
|---|---|
| Did not meet Nugent's criteria at study entry | 24 |
| Lost to follow-up | 16 |
| Total | 40 |

In the Applicants analyses, the primary efficacy end-point was clinical outcome at visits 2 and 3. Criteria for determination of outcome of clinically evaluable patients were pH of vaginal discharge $\leq 4.5$, absence of "fishy" amine odor when mixed with 10% KOH solution, and absence of clue cells. In the Gram stain evaluable group, in addition to the above criteria , the Gram stain would have to return to normal according to Spiegel's criteria as defined on page 3. Post-treatment assessments were defined as cure, improvement or failure at each post-treatment visit and as an overall assessment. Results for all evaluable patients are found in Tables 23 and 24. Clinical cure was reported 54% (61/114) of the Flagyl MR clinically-evaluable group and 37% (41/112) of the Cleocin clinically evaluable group. In the Gram stain evaluable group, 50% (35/70) of the Flagyl patients and 36% (29/69) of the Cleocin patients reported cures.

In the Medical Officer's analyses, the primary efficacy end-point was clinical outcome at visit 3. Criteria for determination of outcome of clinically evaluable patients were pH $\geq 4.7$, absence of "fishy" odor when mixed with 10% KOH solution, and absence of clue cells. In the Gram stain evaluable group, in addition to the above, the Gram stain would have to have a score of (0-3) according to Nugent's criteria. Post treatment assessments were considered as cure or failure. Results of all evaluable patients are found in Tables 25 and 26. Clinical cure was reported in 62% (74/119) of the Flagyl MR® clinically evaluable patients and 43% (50/117) of the Cleocin® clinically-evaluable patients. In the

Gram stain evaluable patients, 52% (51/99) in the Flagyl® group and 37% (34/93) of the Cleocin® patients were assessed as cures. A summary of the cures for all evaluable patients is shown in Table 22 below.

TABLE 22

STUDY 17

PATIENTS CURED

| | CLINICALLY EVALUABLE PATIENTS CURED | | | GRAM STAIN EVALUABLE PATIENTS CURED | | |
|---|---|---|---|---|---|---|
| | FLAGYL | CLEOCIN | 95%CI | FLAGYL | CLEOCIN | 95% CI |
| APPLICANT | 54% (61/114) | 37% (41/112) | 3.23, 30.57 | 50% (35/70) | 36% (25/69) | -3.98, 31.51 |
| MEDICAL OFFICER | 62% (74/119) | 43% (50/117) | 6.10, 32.80 | 52% (51/99) | 37% (34/93) | 0.03 , 29.88 |

APPEARS THIS WAY
ON ORIGINAL

TABLE 23

STUDY 17
NUMBER OP PATIENTS ASSESSED AS CURED BY APPLICANT
AT END OF STUDY
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE # | (%) |
|---|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 5 | 2 | (40) | 3 | 0 | (0) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 14 | 7 | (50) | 4 | 2 | (50) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 13 | 7 | (54) | 12 | 6 | (50) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 2 | 2 | (100) | 1 | 1 | (100) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 5 | 2 | (40) | 4 | 1 | (25) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 5 | (83) | 3 | 2 | (67) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 5 | 1 | (20) | 1 | 0 | (0) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 2 | 1 | (50) | 2 | 1 | (50) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 15 | 10 | (67) | 9 | 6 | (67) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 11 | 5 | (45) | 9 | 5 | (56) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 13 | 8 | (62) | 11 | 7 | (64) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 8 | 3 | (38) | 4 | 1 | (25) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 3 | 1 | (33) | 2 | 0 | (0) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 3 | (75) | 2 | 2 | (100) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 3 | 1 | (33) | 1 | 0 | (0) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 5 | 3 | (60) | 2 | 1 | (50) |
| TOTAL | 114 | 61 | (54) | 70 | 35 | (50) |

APPEARS THIS WAY
ON ORIGINAL

TABLE 24

STUDY 17
NUMBER OP PATIENTS ASSESSED AS CURED BY APPLICANT
AT END OF STUDY
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE # | (%) |
|---|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 5 | 2 | (40) | 2 | 1 | (50) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 13 | 3 | (23) | 5 | 0 | (0) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 9 | 4 | (44) | 7 | 3 | (43) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 2 | 1 | (50) | 2 | 1 | (50) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 6 | 2 | (33) | 3 | 1 | (33) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 3 | (50) | 2 | 1 | (50) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 5 | 1 | (20) | 1 | 0 | (0) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 3 | 2 | (67) | 2 | 1 | (50) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 16 | 4 | (25) | 10 | 1 | (10) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 10 | 2 | (20) | 7 | 2 | (29) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 14 | 10 | (71) | 13 | 9 | (69) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 8 | 1 | (13) | 7 | 1 | (14) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 5 | 3 | (60) | 4 | 2 | (50) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 3 | 1 | (33) | 2 | 1 | (50) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 3 | 0 | (0) | 0 | 0 | (0) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 4 | 2 | (50) | 2 | 1 | (50) |
| TOTAL | 112 | 41 | (37) | 69 | 25 | (36) |

APPEARS THIS WAY
ON ORIGINAL

TABLE 25

STUDY 17
NUMBER OP PATIENTS ASSESSED AS CURED BY MEDICAL OFFICER
AT END OF STUDY
FLAGYL MR 750 MG

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN EVALUABLE # | (%) |
|---|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 6 | 2 | (33) | 6 | 2 | (33) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 12 | 8 | (67) | 6 | 3 | (50) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 13 | 7 | (54) | 13 | 9 | (69) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 2 | 2 | (100) | 2 | 1 | (50) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 6 | 3 | (50) | 6 | 1 | (17) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 6 | 5 | (83) | 4 | 2 | (50) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 4 | 1 | (25) | 2 | 0 | (0) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 4 | 3 | (75) | 4 | 1 | (25) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 15 | 11 | (73) | 13 | 7 | (54) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 13 | 7 | (54) | 13 | 10 | (77) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 14 | 11 | (79) | 14 | 7 | (50) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 10 | 4 | (40) | 7 | 3 | (43) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 3 | 2 | (67) | 3 | 1 | (33) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 3 | (75) | 3 | 2 | (67) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 2 | 1 | (50) | 1 | 1 | (100) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 5 | 3 | (60) | 2 | 1 | (50) |
| TOTAL | 119 | 74 | (62) | 99 | 51 | (52) |

APPEARS THIS WAY
ON ORIGINAL

TABLE 26

STUDY 17
NUMBER OP PATIENTS ASSESSED AS CURED BY MEDICAL OFFICER
AT END OF STUDY
CLEOCIN VAGINAL CREAM

| INVESTIGATOR LOCATION | NUMBER CLINICALLY EVALUABLE | CURES CLINICALLY EVALUABLE # | (%) | NUMBER GRAM STAIN EVALUABLE | CURES GRAM STAIN. EVALUABLE # | ( %) |
|---|---|---|---|---|---|---|
| J. CHRISTOPHER CAREY, MD OKLAHOMA CITY, OKLAHOMA | 4 | 2 | (50) | 4 | 2 | (50) |
| MARGARET DREHOBL, MD SAN DIEGO, CALIFORNIA | 15 | 5 | (33) | 9 | 1 | (11) |
| ROBERT FRIEDMAN, MD HOUSTON , TEXAS | 9 | 5 | (56) | 7 | 2 | (29) |
| STANLEY GALL, MD LOUISVILLE, KENTUCKY | 3 | 2 | (67) | 3 | 2 | (67) |
| DAN C. HENRY, MD SALT LAKE CITY, UTAH | 7 | 2 | (29) | 5 | 1 | (20) |
| JOHN SCHOENBERGER, MD REDWOOD , CALIFORNIA | 5 | 4 | (80) | 2 | 1 | (50) |
| ROBIN KROLL, MD SEATTLE, WASHINGTON | 4 | 1 | (25) | 3 | 1 | (33) |
| LARRY LEGRAND, MD DUBUQUE, IOWA | 3 | 3 | (100) | 3 | 2 | (67) |
| CHERYL MILLER, PHARM.D. SAINT LOUIS, MISSOURI | 16 | 4 | (25) | 12 | 2 | (17) |
| MARCIA MONTGOMERY, MD NASHVILLE , TENNESSEE | 12 | 3 | (25) | 12 | 6 | (50) |
| ROBERT L . PARKER JR., MD WINSTON-SALEM, N. CAROLINA | 14 | 10 | (71) | 13 | 7 | (54) |
| DEBRA K SEPULVEDA, MD. MPH PORTLAND, MAINE | 9 | 0 | (0) | 8 | 2 | (25) |
| NEIL SILVERMAN, MD PHILADELPHIA, PENNSYLVANIA | 5 | 5 | (100) | 5 | 2 | (40) |
| JOHN V. HEYDEN, MD RENTON, WASHINGTON | 4 | 1 | (25) | 3 | 1 | (33) |
| EDWARD ZBELLA, MD CLEARWATER, FLORIDA | 2 | 0 | (0) | 1 | 1 | (100) |
| ELIZABETH T. CAMPBELL, MD CHAMPAIGN, ILLINOIS | 5 | 3 | (60) | 3 | 1 | (33) |
| TOTAL | 117 | 50 | (43) | 93 | 34 | (37) |

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ON ORIGINAL

SAFETY (017)

Compliance was measured by a count of tablets or applicators returned at visit 2. There was no statistically-significant difference between groups with respect to medication compliance. In the Flagyl MR® group, 91% (119/131) of patients took all seven tablets of study medication; 2% (2/131) took five tablets and 1% (1/131) took 6 tablets Compliance data were missing for 7% (9/131) of the Flagyl MR® group. In the Cleocin® group, 89% (119/133) of patients used all seven applicators of study medication; 2% (2/133) used no applicators, 1% (1/133) used four applicators and 1% (1/133) used six applicators. Compliance was missing in 5% (7/133) of the Cleocin® group.

**Adverse Events**

Safety was assessed for all patients who received one dose of study medication. A total of 262 patients received at least one dose of study medication: 129 patients in the Flagyl MR® group and 133 in the Cleocin® group.

Overall Incidence of Adverse Events

Incidence of adverse events are presented by severity within body system for all patients who received at least one dose of study medication in Table 27. At least one adverse event was reported by 83% (107/129) of patients in the Flagyl MR® group and 79% (105/133) of patients in the Cleocin® group. Of the patients reporting adverse events in the Flagyl MR® group, the greatest severity reported was mild for 38% (41/107), moderate for 48% (51/107), and severe for 14% (15/107). Of the patients in the Cleocin® group reporting adverse events, the greatest severity reported was mild for 40% (42/105), moderate for 48% (50/105), and severe for 12% (13/105).

TABLE 27
INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM
PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION ( ALL CAUSALITY)

| | FLAGYL MR 750 MG X 7 DAYS (N = 129) | | | | CLEOCIN N = 133) | | | |
|---|---|---|---|---|---|---|---|---|
| SUMMARY (NUMBER OF PATIENTS | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | 41 | 51 | 15 | 107 (83%) | 42 | 50 | 13 | 105 ( 79%) |
| PATIENTS WITH NO ADVERSE EVENTS | | | | 22 ( 17%) | | | | 28 ( 21%) |
| PATIENTS WITH NO ADVERSE EVENT INFORMATION | | | | 0 ( 0%) | | | | 0 ( 0%) |
| ALL PATIENTS WITH AT LEAST ONE DOSE | | | | 129 (100%) | | | | 133 (100%) |

Adverse events are presented by decreasing order of incidence (following incidence in the Flagyl MR® group first) for all patients with at least one dose of study medication in Table 28. The adverse events reported by the most patients were headaches (19%) of the Flagyl MR® group and 14% of the Cleocin® group), vaginitis (15%) of the Flagyl MR® group and 12% of the Cleocin® group), nausea (12% of the Flagyl MR® group and 2% of the Cleocin® group), taste perversion (11%) of the Flagyl MR® group and 0% of the Cleocin® group, genital pruritus (7% of the Flagyl MR® group and 14% of the Cleocin® group). All other adverse events were reported by less than 10% of the patients in each treatment group.

TABLE 28
STUDY 17
INCIDENCE OF ADVERSE EVENTS BY SEVERITY
PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION (ALL CAUSALITY)

| | FLAGYL MR 750 MG X 7 DAYS (N = 129) | | | | CLEOCIN N = 133) | | | |
|---|---|---|---|---|---|---|---|---|
| ADVERSE EVENT NUMBER OF PATIENTS IN EACH CATEGORY | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| HEADACHE | 18 | 3 | 3 | 24 (19%) | 10 | 6 | 1 | 17 (13%) |
| VAGINITIS | 11 | 8 | 0 | 19 (15%) | 8 | 6 | 1 | 15 (15%) |
| NAUSEA | 10 | 5 | 0 | 15 (12%) | 1 | 2 | 0 | 3 ( 2%) |
| TASTE PERVERSION | 10 | 3 | 1 | 14 (11%) | 0 | 0 | 0 | 0 ( 0%) |
| INFECTION BACTERIAL | 3 | 9 | 0 | 12 ( 9%) | 6 | 3 | 0 | 9 ( 7%) |
| INFLUENZA-LIKE SYNDROME | 4 | 3 | 2 | 9 ( 7%) | 7 | 4 | 0 | 11 (8%) |
| PRURITUS GENITAL | 5 | 3 | 1 | 9 (7%) | 3 | 8 | 3 | 18 (14%) |

Of the 107 patients in the Flagyl MR® group who reported adverse events, attribution to study medication, as assessed by the investigator, was reported as none for 40% (43/107), uncertain for 37% (40/107), and probable for 22%. Of the 205 patients in the Cleocin® group who reported adverse events, attribution to study medication, as assessed by the investigator, was reported as none for 50% (53/105), uncertain for 40% (42/105), and probable for 10% (10/105). Headache vaginitis , nausea and taste perversion were the most frequently reported adverse events in the Flagyl MR® group. Headache, vaginitis and pruritus genital were the most frequently reported adverse events in the Cleocin® group (Table 29).

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ON ORIGINAL

TABLE 29
INCIDENCE OF ADVERSE EVENTS BY ATTRIBUTION, WITHIN BODY SYSTEM
PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION

| | FLAGYL MR 750 MG X 7 DAYS (N = 129) | CLEOCIN N = 133) |
|---|---|---|
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | | |
| NONE | 43 (37%) | 53 (40%) |
| UNCERTAIN | 40 (31%) | 42 (32%) |
| PROBABLY | 24 (19%) | 10 ( 8%) |
| TOTAL | 107 (83%) | 105 (79%) |

Adverse Events Causing Withdrawal

Four adverse events in three patients in the Cleocin® group resulted in the withdrawal from the study. No patients randomized to the Flagyl® group were withdrawn from the study due to adverse events.

Patient US008-020, a 41-year-old randomized to the Cleocin® group, was withdrawn from the study due to a moderate vaginal rash which began on day 3. The rash resolved in 7 days; the investigator was uncertain of the relationship to study medication.

Patient US 0007-102, a 34-year-old randomized to the Cleocin® group, was withdrawn from the study due to severe vaginal irritation which began on day 0 and severe urinary frequency which began on day 1. The vaginal irritation resolved in 7 days and was assessed by the investigator as probably related to the study medication. The urinary frequency resolved in 8 days; the investigator was uncertain of the relationship to study medication.

Patient US0016-255, a 32-year-old randomized to the Cleocin® group, was withdrawn from the study due to moderate pelvic pain which began on day 9. The event was continuing at the time of last contact and the investigator was uncertain of the relationship to study medication.

**Pregnancies**

There were three pregnancies reported during the study. Patient US007-101 was a 40-year-old treated with Flagyl MR® 750 mg daily from 11/30/95 to 12/06/95. She completed the study on 01/08/96. During the pre-operative blood work for a scheduled reconstructive surgery the patient had a positive serum pregnancy test on 01/25/96. She

was diagnosed with an intrauterine death which was not considered to be drug-related. Results from a dilation and curettage performed on 02/02/96 indicated that the patient had been eight weeks pregnant (date of conception was 12/08/95).

Patient US0010-133 was a 35-year-old treated with Flagyl® 750 mg daily from 09/22/95. A pregnancy test on 10/27/95 was positive, and the date of conception was estimated to be 10/01/95. The patient decided to carry the pregnancy to term and delivered a healthy male child on 06/27/96 after an uneventful pregnancy. The baby is reported to be in good health.

Patient US0005-173 was a 32-year-old treated with Flagyl® 750 mg daily from 01/29/96 to 02/04/96. At the time of study entry, the patient's last menstrual period was on 01/11/96 and her urine pregnancy test was negative. The patient was seen for visit 2 on 02/09/96; a pregnancy test was done and was negative. The patient returned for visit 3 (end of study visit) on 02/26/96 with complaints of fatigue and that she had missed her menstrual period. A urine pregnancy test was done and as positive. The patient informed the site that she had protected sexual intercourse (used condoms) on the weekends of 02/10-11/96 and 02/16-17/96. An ultrasound performed on 03/30/96 estimated a due date of 10/13/96, suggesting a conception date of 01/20/96 which was prior to the start of the study participation. An emergency cesarean section was performed at 35 weeks on 09/15/96 for fetal distress due to umbilical cord torsion. The male baby was placed on a ventilator due to lung immaturity, but otherwise was doing well. The baby was discharged from the hospital on 09/20/96 and was reported as progressing well.

**Yeast**

Table 30 shows that the number of positive cultures were slightly higher for the Cleocin® group at baseline, increased slightly for the Flagyl® group while barely increasing for the Cleocin® group at visit 2 and increased slightly for the Cleocin® group while barely increasing for the Flagyl MR® group at visit 3. By visit 3 the number of positive cultures for yeast was similar for the two treatment groups.

TABLE 30
SUMMARY OF YEAST CULTURE DATA
ALL RANDOMIZED PATIENTS

| | FLAGYL MR 750 MG 7 DAYS (N = 131) | CLEOCIN (N = 133) | P-VALUE |
|---|---|---|---|
| YEAST CULTURE | | | |
| VISIT 1 | | | |
| YES | 22 (17%) | 27 ( 20%) | 0.374 |
| NO | 109 ( 83%) | 105 ( 79%) | |
| MISSING | 0 | 1 | |
| TOTAL | 131 (100%) | 133 (100%) | |
| VISIT 2 | | | |
| YES | 31 ( 24%) | 28 ( 21%) | 0.726 |
| NO | 91 (69%) | 94 (71%) | |
| MISSING | 9 ( 7%) | 11 ( *%) | |
| TOTAL | 131(100%) | 133(100%) | |
| VISIT 3 | | | |
| YES | 33 ( 25%) | 34 (26%) | 0.884 |
| NO | 87 ( 66%) | 87 ( 65%) | |
| MISSING | 11( 8%) | 12 ( 9%) | |
| TOTAL | 131 (100%) | 133 (100%) | |

Serious Adverse Events
There were no serious adverse events reported during this study.

Deaths
There were no deaths reported during this study

**Summary of Study 017**

Efficacy

The purpose of this single-blind, randomized, controlled comparative, multicenter study was to evaluate the efficacy and safety of Flagyl MR® (metronidazole modified release)) 750 mg tablet compared to Cleocin® (2% clindamycin phosphate vaginal cream) in the treatment of bacterial vaginosis (BV). Eligible female patients with bacterial vaginosis were randomized and received one metronidazole 750 mg MR oral tablet once daily for 7 days; or one applicator full of Cleocin® 2% (clindamycin phosphate vaginal cream) inserted into the vagina once daily for 7 consecutive days. Patients were evaluated for a clinical response at 4-7 days and 28-32 days after completion of treatment.

Two hundred sixty-four (264) patients were enrolled into this study at 16 sites. One hundred thirty-one (131) were randomized to the Flagyl MR® 7-day group (129 received

at least one dose), and 133 were randomized to the Cleocin® group (all patients received at least one dose of study medication). The treatment groups were similar at baseline with respect to demographics.

Of the enrolled patients 86% (226/264) were considered clinically evaluable for BV by the Applicant and 89% (236/264) were considered clinically evaluable by the Medical Officer. BV was confirmed according to Spiegel's criteria in 53% (139/264) of the enrolled patients by the Applicant and in 72% (192/264 ) according to Nugent's criteria by the Medical Officer.

Results of clinical cure by the Applicant indicate a larger percentage of Flagyl MR® than Cleocin® patients were cured overall. For all randomized patients, a clinical cure was reported in 54% of the Flagyl MR® group and 37% in the Cleocin® group. In patients who had Gram stain confirmation of BV by the Applicant, a cure rate of 50% was observed in the Flagyl MR® treatment group and 36% in the Cleocin® treatment group. The 95% confidence intervals for the difference in the cure rates between treatment groups indicate that treatment with Flagyl MR® was statistically superior to treatment with Cleocin®.

Results for the clinical cures assessed by the Medical Officer reveal similar findings. Sixty-two percent (62%) of the clinically evaluable patients were assessed as cures in the Flagyl® group compared to 43% of the Cleocin® treatment group. In the Gram stain evaluable population 52% of the Flagyl® treatment group and 37% of the Cleocin® treatment group were considered as cures.

Safety

At least one adverse event was reported by 83% (107/129) of the Flagyl® treatment group and 79% (105/133) of the Cleocin® treatment group. Three patients in the Cleocin® group were discontinued due to adverse events (moderate pelvic pain, moderate vaginal rash, and severe vaginal irritation and urinary frequency).

The adverse events reported by most patients were headache (19% of the Flagyl MR® group and 14% of the Cleocin® group), vaginitis (15% of the Flagyl MR® group and 12% of the Cleocin® group), nausea ( 12% of the Flagyl MR® group and 2% of the Cleocin® group), taste perversion (11% of the Flagyl MR® group and 0% of the Cleocin® group), and genital pruritus 7% of the Flagyl MR® group and 14% of the Cleocin® group). All other adverse events were reported by less than 10% of patients in each treatment group.

Conclusion: The results of this study indicate that Flagyl MR® 750 mg tablets when taken once daily for 7 days in the treatment of bacterial vaginosis(BV) appears to be superior in efficacy and safety to the use of Cleocin® vaginal cream when used intravaginally once daily for 7 days.

NDA SUMMARY

Efficacy

The Applicant submitted this NDA for the purpose of obtaining approval for the use of Flagyl MR® 750 mg tablets once daily for 7 days in treating patients with bacterial vaginosis (BV). The Applicant states that a once-daily dosing with Flagyl MR® is expected to improve compliance when compared to a more frequent dosing regimen and improved compliance will result in more patients receiving adequate therapy, a lower rate of treatment failure, and a lower rate of BV recurrence. To obtain approval for this indication, the Applicant submitted the results of two studies that compared the efficacy and safety of the once daily dose regimen to a once daily dose regimen of Cleocin® (2% clindamycin vaginal cream) for 7 days.

The primary efficacy of the treatment regimens was based on the success rate at the final visit (28 - 32 days post therapy). There were two evaluable groups defined for efficacy. The clinical evaluable group was defined as patients who at entry had a clinical diagnosis of bacterial vaginosis based on: a vaginal discharge with a positive amine odor on alkalinization with KOH, presence of 20% clue cells and a pH of vaginal fluid $\geq$4.5. The Gram stain evaluable group were those patients who on entry had Gram stain confirmation (either by Spiegel's or Nugent's criteria) in addition to the criteria stated above. Since the protocols were essentially identical and the study populations were essentially the same, data from the two studies is considered capable of being pooled for efficacy and safety.

In the Applicant's pooled data, for the clinically evaluable population a total of 55% (132/239) were determined as cured in the Flagyl MR® group and 43% (105/243) in the Cleocin® group. For the Gram stain evaluable population 51% (73/142) in the Flagyl MR® group and 41% (58/141) in the Cleocin® group were assessed as cures.

In the Medical Officer's analyses, for the clinically evaluable population 62% (151/245) of the Flagyl® treatment group and 52% (130/252) of the Cleocin treatment group were assessed as cures. In the Gram stain evaluable population 52% (104/202) of the Flagyl MR® group and 47% (96/206) of the Cleocin® group were considered cures.

The 95% confidence interval for the between difference of the two groups as assessed by the Applicant and the Medical Officer indicate that Flagyl MR® is statistically equivalent to Cleocin® 2% vaginal cream in treating bacterial vaginosis (Table 31).

TABLE 31

PATIENTS CURED POOLED DATA

| | CLINICALLY EVALUABLE PATIENTS CURED | | | GRAM STAIN EVALUABLE PATIENTS CURED | | |
|---|---|---|---|---|---|---|
| | FLAGYL | CLEOCIN | 95%CI | FLAGYL | CLEOCIN | 95% CI |
| APPLICANT | 55% (132/239) | 43% (105/243) | 2.74, 21.30 | 51% (73/142) | 41% (58/141 | -1.99, 22.54 |
| MEDICAL OFFICER | 62% (151/245 | 52% (130/252) | 0.97, 19.12 | 52% (104/202) | 47% (96/206) | -5.30 15.06 |

## SAFETY

Table 32 lists the incidence of adverse events by severity and by body system. Table 33 lists these adverse events by decreasing incidence. Overall 74% of the 7 day Flagyl MR® group had at least one adverse event compared with 72% of the Cleocin® group. The majority of adverse events were rated in severity as mild or moderate.

The most frequently reported adverse events were headache, yeast vaginitis, nausea, and taste perversion. The incidence of headache was similar in both treatment groups with 18% of patients in the 7 day Flagyl MR® group reporting headaches compared to 15% in the Cleocin® group. Only one occurrence of headache was found to be probably related to therapy in the 7 day Flagyl MR® group (Table 7). Vaginitis occurred in 15% of patients in the 7 day Flagyl MR® group and 12 % of patients in the Cleocin® group. Vaginitis was rated as probably caused by study medication in 26% of cases (12 of 39 for the 7 day Flagyl MR group and 7 of 33 in the Cleocin® group)..

Table 34 provides the incidence of adverse events by attribution. The most frequently reported adverse considered attributable to Flagyl MR® therapy were nausea and taste perversion. In the 7-day Flagyl MR® group the incidence of nausea was 10% and for taste perversion was 9%. No patients withdrew from the study because of nausea, and one patient withdrew from the study because of taste perversion.

Two other adverse events, the incidence of which was not equally distributed across the two treatment groups, were genital pruritus and perineal pain. Genital pruritus was noticed in 9% of patients in the Cleocin® group, compared to 5% in the 7day Flagyl MR® treatment group. Perineal pain was present in 6% of Cleocin® treated patients compared to 2% of the Flagyl MR®treated patients.

Tables 35 provide the pair-wise comparison of the incidence of adverse events across treatment groups listed by body system and by adverse event. In general the incidence of adverse reactions were equally distributed among the two treatment groups.

Only two serious adverse events occurred: One instance each of drug overdose and psychosis in the 7 day Flagyl MR group. Detailed information regarding these was presented in the individual study report.

The incidence of adverse events causing withdrawal are shown in Table 36. Five patients had adverse events that caused withdrawal from the study. Two patients in the 7 day Flagyl MR treated group had a diagnosis of psychosis, or pruritus/hives, Three patients in the Cleocin treatment group reported severe genital pruritus, moderate vaginal rash or moderate pelvic pain.

Vulvovaginal candidiasis or yeast vaginitis is a recognized risk of treatment with systemic or topical antibacterial agents. The incidence of vaginitis reported as an adverse event was reported in 39 patients (15%) in the 7 day Flagyl MR® group and 33 patients (12%) in the Cleocin® group. Table 37 reports the rate of superinfection during treatment of BV. Yeast superinfection was assessed by the presence of branching pseudo-hyphae on microscopic examination of vaginal discharge and by culture identification of yeast species (total yeast species and *Candida albicans* species are shown separately). The rate of superinfection assessed by the presence of branching pseudo-hyphae on wet mount examination was 22% and 19% for the 7 day Flagyl MR® and the Cleocin® groups, respectively. Similarly, the rate of superinfection assessed by a positive yeast culture was 36% and 35% for the 7 day Flagyl MR® and the Cleocin® groups, respectively. When focusing on the subset of yeast positive cultures with isolation of *Candida albicans* species only, the rate of superinfection was 29% and 31% for the 7 day Flagyl MR® and Cleocin® groups respectively.

From a safety point of view, the two treatment groups were found to be statistically comparable.

Consultation with the Division of Biometrics confirms the findings of the Medical Officer and the complete statistical review of this NDA may be found in the review done by Liji Shen, Ph.D. dated November, 24, 1997.

(Labeling Review To be Completed)

**Conclusion**

From the data provided by the Applicant and the analyses performed by the Applicant and the Medical officer, Flagyl MR® (metronidazole 750 mg oral tablet) administered once daily for 7 days appears to be statistically comparable to Cleocin® 2% vaginal cream (2% clindamycin phosphate vaginal cream) given qhs for 7 days in the treatment of bacterial vaginosis. The number of patients reporting adverse events judged to be related to therapy was also statistically comparable in both treatment groups.

**Recommendation:** From a clinical perspective, I recommend approval of this NDA which will provide for the treatment of bacterial vaginosis with a once daily dosing of Flagyl MR® for 7 days.

Joseph K. Winfield, M. D.
Reviewing Medical Officer

cc: NDA 20-868
HFD-340
HFD-590
HFD-590-Dep/Dir/RAlbrecht
HFD-590/MO/JKWinfield
HFD-590 MO/DDavis
HFD-590/Micro
HFD-590/Chem
HFD-590/Pharm
HFD-725/Stat/Shen
HFD-590-/TmLdr/BLeissa BL 11/26/97

**Concurrence Only:**
HFD-590/Div/Dir/MGoldberger

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TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| | FLAGYL MR 750MG x 7 DAYS (N=267) | | | | CLEOCIN (N=285) | | | |
|---|---|---|---|---|---|---|---|---|
| SUMMARY (NUMBER OF PATIENTS) (a) | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | 75 | 98 | 25 | 198( 74%) | 80 | 98 | 26 | 204( 72%) |
| PATIENTS WITH NO ADVERSE EVENTS | | | | 69( 26%) | | | | 81( 28%) |
| PATIENTS WITH NO ADVERSE EVENTS INFORMATION | | | | 0( 0%) | | | | 0( 0%) |
| ALL PATIENTS WITH AT LEAST ONE DOSE | | | | 267(100%) | | | | 285(100%) |
| ALL RANDOMIZED PATIENTS | | | | 270 | | | | 287 |

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32



INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES



| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | | | | CLEOCIN (N=285) | | | |
|---|---|---|---|---|---|---|---|---|
| | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| APPLICATION SITE DISORDERS | | | | | | | | |
| DERMATITIS CONTACT | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| OTITIS EXTERNA | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| AUTONOMIC NERVOUS SYSTEM DISORDERS | | | | | | | | |
| MOUTH DRY | 4 | 0 | 1 | 5( 2%) | 1 | 1 | 0 | 2( 1%) |
| SALIVA INCREASED | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 5 | 0 | 1 | 6( 2%) | 1 | 1 | 0 | 2( 1%) |



Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
(b) Adverse events are sorted by descending total incidence of this treatment column within body system.
For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

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|---|---|---|---|---|---|---|---|---|
| BODY AS A WHOLE - GENERAL DISORDERS | | | | | | | | |
| INFLUENZA-LIKE SYMPTOMS | 7 | 8 | 2 | 17( 6%) | 13 | 7 | 0 | 20( 7%) |
| BACK PAIN | 2 | 1 | 1 | 4( 1%) | 2 | 3 | 0 | 5( 2%) |
| PAIN | 3 | 1 | 0 | 4( 1%) | 3 | 3 | 0 | 6( 2%) |
| FATIGUE | 1 | 1 | 0 | 2( 1%) | 1 | 1 | 1 | 3( 1%) |
| INJURY-ACCIDENTAL | 2 | 0 | 0 | 2( 1%) | 0 | 1 | 1 | 2( 1%) |
| ALLERGY | 1 | 0 | 0 | 1( 0%) | 2 | 0 | 0 | 2( 1%) |
| ASTHENIA | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| CHEST PAIN | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| CRYING ABNORMAL | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| CYST, NOS | 1 | 0 | 0 | 1( 0%) | 0 | 1 | 0 | 1( 0%) |
| EDEMA | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| FEVER | 0 | 1 | 0 | 1( 0%) | 1 | 1 | 1 | 3( 1%) |
| HOT FLUSHES | 0 | 1 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| OVERDOSE | 0 | 0 | 1 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| PREVIOUSLY SCHEDULED SURGERY | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| FACE EDEMA | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| GRANULOMATOUS LESION | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| LABORATORY TEST ABNORMAL | 0 | 0 | 0 | 0( 0%) | 3 | 2 | 1 | 6( 2%) |
| MALAISE | 0 | 0 | 0 | 0( 0%) | 0 | 3 | 0 | 3( 1%) |
| RIGORS | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 1 | 1( 0%) |
| OVERALL INCIDENCE | 16 | 17 | 4 | 37( 14%) | 26 | 19 | 4 | 49( 17%) |

Notes:
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For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS | | | | | | | | |
| HEADACHE | 32 | 12 | 4 | 48( 18%) | 22 | 17 | 4 | 43( 15%) |
| DIZZINESS | 7 | 3 | 1 | 11( 4%) | 2 | 1 | 0 | 3( 1%) |
| MIGRAINE | 0 | 1 | 2 | 3( 1%) | 0 | 1 | 1 | 2( 1%) |
| HYPOKINESIA | 2 | 0 | 0 | 2( 1%) | 0 | 0 | 0 | 0( 0%) |
| HYPERESTHESIA | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| TWITCHING | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| HYPOESTHESIA | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| PARESTHESIA | 0 | 0 | 0 | 0( 0%) | 1 | 1 | 0 | 2( 1%) |
| VERTIGO | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 1 | 1( 0%) |
| OVERALL INCIDENCE | 37 | 15 | 7 | 59( 22%) | 23 | 20 | 6 | 49( 17%) |



Notes:
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|---|---|---|---|---|---|---|---|---|
| GASTRO-INTESTINAL SYSTEM DISORDERS | | | | | | | | |
| NAUSEA | 21 | 7 | 0 | 28( 10%) | 3 | 5 | 0 | 8( 3%) |
| DIARRHEA | 7 | 3 | 1 | 11( 4%) | 3 | 0 | 0 | 3( 1%) |
| ABDOMINAL PAIN | 6 | 4 | 0 | 10( 4%) | 9 | 3 | 1 | 13( 5%) |
| VOMITING | 3 | 3 | 0 | 6( 2%) | 1 | 3 | 0 | 4( 1%) |
| DYSPEPSIA | 3 | 1 | 1 | 5( 2%) | 2 | 1 | 0 | 3( 1%) |
| FLATULENCE | 1 | 4 | 0 | 5( 2%) | 1 | 0 | 0 | 1( 0%) |
| CONSTIPATION | 2 | 0 | 1 | 3( 1%) | 3 | 1 | 0 | 4( 1%) |
| TONGUE DISCOLORATION | 2 | 1 | 0 | 3( 1%) | 0 | 0 | 0 | 0( 0%) |
| GASTROENTERITIS | 0 | 1 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| GLOSSITIS | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| RECTAL DISORDER | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| STOMATITIS | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| STOMATITIS ULCERATIVE | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| TONGUE DISORDER | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| GINGIVITIS | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| HEMORRHOIDS | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| TOOTH DISORDER | 0 | 0 | 0 | 0( 0%) | 1 | 2 | 0 | 3( 1%) |
| OVERALL INCIDENCE | 34 | 20 | 3 | 57( 21%) | 18 | 12 | 1 | 31( 11%) |

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Notes:,
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
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|---|---|---|---|---|---|---|---|---|
| HEARING AND VESTIBULAR DISORDERS | | | | | | | | |
| TINNITUS | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| EARACHE | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| HEART RATE AND RHYTHM DISORDERS | | | | | | | | |
| PALPITATION | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| TACHYCARDIA | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |



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|---|---|---|---|---|---|---|---|---|
| | MILD | MOD | SEV | TOTAL | MILD | MOD | SEV | TOTAL |
| LIVER AND BILIARY SYSTEM DISORDERS | | | | | | | | |
| SGPT INCREASED | 1 | 3 | 0 | 4( 1%) | 2 | 2 | 0 | 4( 1%) |
| SGOT INCREASED | 1 | 2 | 0 | 3( 1%) | 1 | 1 | 0 | 2( 1%) |
| BILIRUBINEMIA | 1 | 0 | 0 | 1( 0%) | 0 | 1 | 0 | 1( 0%) |
| HEPATIC FUNCTION ABNORMAL | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| AG RATIO ABNORMAL | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 1 | 4 | 0 | 5( 2%) | 2 | 2 | 0 | 4( 1%) |
| METABOLIC AND NUTRITIONAL DISORDERS | | | | | | | | |
| HYPERGLYCEMIA | 1 | 1 | 1 | 3( 1%) | 1 | 2 | 0 | 3( 1%) |
| PHOSPHATASE ALKALINE INCREASED | 1 | 1 | 0 | 2( 1%) | 0 | 1 | 0 | 1( 0%) |
| GLYCOSURIA | 0 | 0 | 1 | 1( 0%) | 0 | 2 | 0 | 2( 1%) |
| WEIGHT INCREASE | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| HYPERURICEMIA | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| HYPOCALCEMIA | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| LDH INCREASED | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| WEIGHT DECREASE | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 3 | 2 | 1 | 6( 2%) | 1 | 4 | 0 | 5( 2%) |

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(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
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|---|---|---|---|---|---|---|---|---|
| MUSCULO-SKELETAL SYSTEM DISORDERS | | | | | | | | |
| MYALGIA | 0 | 2 | 0 | 2( 1%) | 2 | 1 | 0 | 3( 1%) |
| ARTHRALGIA | 1 | 0 | 0 | 1( 0%) | 1 | 2 | 0 | 3( 1%) |
| ARTHRITIS | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| TENDINITIS | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 1 | 3 | 0 | 4( 1%) | 3 | 4 | 0 | 7( 2%) |
| PLATELET, BLEEDING & CLOTTING DISORDERS | | | | | | | | |
| EPISTAXIS | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| PLATELETS ABNORMAL | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| THROMBOCYTHEMIA | 1 | 0 | 0 | 1( 0%) | 1 | 1 | 0 | 2( 1%) |
| PURPURA | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 3 | 0 | 0 | 3( 1%) | 2 | 1 | 0 | 3( 1%) |



Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
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|---|---|---|---|---|---|---|---|---|
| PSYCHIATRIC DISORDERS | | | | | | | | |
| NERVOUSNESS | 2 | 3 | 0 | 5( 2%) | 2 | 0 | 0 | 2( 1%) |
| DEPRESSION | 2 | 2 | 0 | 4( 1%) | 1 | 0 | 0 | 1( 0%) |
| EMOTIONAL LABILITY | 1 | 3 | 0 | 4( 1%) | 1 | 0 | 0 | 1( 0%) |
| INSOMNIA | 1 | 2 | 1 | 4( 1%) | 1 | 3 | 0 | 4( 1%) |
| ANXIETY | 1 | 2 | 0 | 3( 1%) | 0 | 2 | 0 | 2( 1%) |
| THINKING ABNORMAL | 1 | 1 | 0 | 2( 1%) | 0 | 0 | 0 | 0( 0%) |
| AGITATION | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| ANOREXIA | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| DEPRESSION AGGRAVATED | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| DYSPAREUNIA | 0 | 1 | 0 | 1( 0%) | 1 | 1 | 0 | 2( 1%) |
| LIBIDO DECREASED | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| PARANOID REACTION | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| PSYCHOSIS | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| SOMNOLENCE | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 3 | 15 | 1 | 19( 7%) | 7 | 6 | 0 | 13( 5%) |
| RED BLOOD CELL DISORDERS | | | | | | | | |
| ANEMIA | 2 | 0 | 0 | 2( 1%) | 3 | 0 | 0 | 3( 1%) |
| OVERALL INCIDENCE | 2 | 0 | 0 | 2( 1%) | 3 | 0 | 0 | 3( 1%) |

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(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
(b) Adverse events are sorted by descending total incidence of this treatment column within body system.
For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| REPRODUCTIVE DISORDERS, FEMALE | | | | | | | | |
| VAGINITIS | 21 | 18 | 0 | 39( 15%) | 17 | 14 | 1 | 32( 11%) |
| DYSMENORRHEA | 8 | 1 | 0 | 9( 3%) | 3 | 4 | 0 | 7( 2%) |
| INTERMENSTRUAL BLEEDING | 4 | 2 | 0 | 6( 2%) | 3 | 1 | 0 | 4( 1%) |
| PERINEAL PAIN FEMALE | 0 | 5 | 1 | 6( 2%) | 7 | 6 | 3 | 16( 6%) |
| MENSTRUAL DISORDER | 1 | 2 | 1 | 4( 1%) | 2 | 1 | 1 | 4( 1%) |
| PREGNANCY UNINTENDED | 0 | 0 | 3 | 3( 1%) | 0 | 0 | 1 | 1( 0%) |
| BREAST PAIN FEMALE | 1 | 1 | 0 | 2( 1%) | 0 | 0 | 0 | 0( 0%) |
| LEUKORRHEA | 1 | 0 | 1 | 2( 1%) | 1 | 3 | 4 | 8( 3%) |
| MENORRHAGIA | 0 | 2 | 0 | 2( 1%) | 1 | 1 | 0 | 2( 1%) |
| UTERINE CRAMPING | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| UTERINE HEMORRHAGE | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| VAGINAL BURNING | 0 | 0 | 1 | 1( 0%) | 4 | 2 | 1 | 7( 2%) |
| VAGINAL DRYNESS | 1 | 0 | 0 | 1( 0%) | 1 | 2 | 0 | 3( 1%) |
| VAGINAL NEOPLASM BENIGN | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| VULVA DISORDER | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 1 | 1( 0%) |
| WITHDRAWAL BLEEDING | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| AMENORRHEA | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| BREAST FIBROADENOSIS | 0 | 0 | 0 | 0( 0%) | 2 | 1 | 0 | 3( 1%) |
| BREAST MALFORMATION | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| CERVICAL DYSPLASIA | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| CERVICAL SMEAR TEST POSITIVE | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| CERVICITIS | 0 | 0 | 0 | 0( 0%) | 5 | 1 | 0 | 6( 2%) |
| ENDOMETRIOSIS | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVARIAN DISORDER | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| VAGINAL HEMORRHAGE | 0 | 0 | 0 | 0( 0%) | 2 | 1 | 0 | 3( 1%) |
| OVERALL INCIDENCE | 35 | 29 | 4 | 68( 25%) | 39 | 33 | 10 | 82( 29%) |

APPEARS THIS WAY
ON ORIGINAL

Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
(b) Adverse events are sorted by descending total incidence of this treatment column within body system.
For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| RESISTANCE MECHANISM DISORDERS | | | | | | | | |
| INFECTION BACTERIAL | 8 | 10 | 1 | 19( 7%) | 11 | 6 | 0 | 17( 6%) |
| MONILIASIS | 6 | 3 | 0 | 9( 3%) | 1 | 5 | 2 | 8( 3%) |
| HERPES SIMPLEX | 3 | 1 | 0 | 4( 1%) | 0 | 2 | 1 | 3( 1%) |
| INFECTION VIRAL | 1 | 1 | 0 | 2( 1%) | 1 | 3 | 0 | 4( 1%) |
| OTITIS MEDIA | 1 | 1 | 0 | 2( 1%) | 0 | 0 | 0 | 0( 0%) |
| INFECTION FUNGAL | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| INFECTION | 0 | 0 | 0 | 0( 0%) | 4 | 2 | 0 | 6( 2%) |
| OVERALL INCIDENCE | 20 | 16 | 1 | 37( 14%) | 17 | 18 | 3 | 38( 13%) |



Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
(b) Adverse events are sorted by descending total incidence of this treatment column within body system.
For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| RESPIRATORY SYSTEM DISORDERS | | | | | | | | |
| RHINITIS | 8 | 4 | 0 | 12( 4%) | 9 | 1 | 0 | 10( 4%) |
| UPPER RESP TRACT INFECTION | 5 | 4 | 2 | 11( 4%) | 4 | 6 | 0 | 10( 4%) |
| PHARYNGITIS | 5 | 2 | 1 | 8( 3%) | 3 | 1 | 0 | 4( 1%) |
| SINUSITIS | 1 | 6 | 0 | 7( 3%) | 2 | 3 | 1 | 6( 2%) |
| COUGHING | 2 | 1 | 1 | 4( 1%) | 1 | 2 | 0 | 3( 1%) |
| BRONCHOSPASM | 1 | 2 | 0 | 3( 1%) | 0 | 0 | 0 | 0( 0%) |
| LARYNGITIS | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| RESPIRATORY DISORDER | 1 | 0 | 0 | 1( 0%) | 0 | 1 | 0 | 1( 0%) |
| BRONCHITIS | 0 | 0 | 0 | 0( 0%) | 0 | 2 | 0 | 2( 1%) |
| OVERALL INCIDENCE | 19 | 17 | 3 | 39( 15%) | 17 | 14 | 1 | 32( 11%) |



Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
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For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| SKIN AND APPENDAGES DISORDERS | | | | | | | | |
| PRURITUS GENITAL | 6 | 6 | 2 | 14( 5%) | 10 | 12 | 3 | 25( 9%) |
| RASH ERYTHEMATOUS | 3 | 1 | 0 | 4( 1%) | 5 | 0 | 1 | 6( 2%) |
| URTICARIA | 2 | 2 | 0 | 4( 1%) | 1 | 0 | 0 | 1( 0%) |
| PRURITUS | 1 | 2 | 0 | 3( 1%) | 2 | 1 | 0 | 3( 1%) |
| SKIN DISORDER | 1 | 1 | 0 | 2( 1%) | 1 | 0 | 0 | 1( 0%) |
| DERMATITIS FUNGAL | 1 | 0 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| RASH | 1 | 0 | 0 | 1( 0%) | 4 | 2 | 0 | 6( 2%) |
| SWEATING INCREASED | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| NAIL DISORDER | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| PRURITUS ANI | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| RASH MACULO-PAPULAR | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 1 | 1( 0%) |
| SKIN ODOR ABNORMAL | 0 | 0 | 0 | 0( 0%) | 1 | 1 | 2 | 4( 1%) |
| OVERALL INCIDENCE | 15 | 9 | 2 | 26( 10%) | 24 | 17 | 7 | 48( 17%) |
| SPECIAL SENSES OTHER, DISORDERS | | | | | | | | |
| TASTE PERVERSION | 15 | 6 | 2 | 23( 9%) | 1 | 0 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 15 | 6 | 2 | 23( 9%) | 1 | 0 | 0 | 1( 0%) |

APPEARS THIS WAY
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Notes:
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(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
(b) Adverse events are sorted by descending total incidence of this treatment column within body system.
For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| URINARY SYSTEM DISORDERS | | | | | | | | |
| URINE ABNORMAL | 7 | 0 | 0 | 7( 3%) | 4 | 0 | 0 | 4( 1%) |
| URINARY TRACT INFECTION | 0 | 6 | 0 | 6( 2%) | 5 | 9 | 2 | 16( 6%) |
| URINARY URGENCY | 1 | 2 | 0 | 3( 1%) | 0 | 1 | 0 | 1( 0%) |
| DYSURIA | 2 | 0 | 0 | 2( 1%) | 4 | 1 | 0 | 5( 2%) |
| PYURIA | 2 | 0 | 0 | 2( 1%) | 0 | 1 | 0 | 1( 0%) |
| MICTURITION FREQUENCY | 0 | 1 | 0 | 1( 0%) | 0 | 1 | 1 | 2( 1%) |
| ALBUMINURIA | 0 | 0 | 0 | 0( 0%) | 1 | 0 | 0 | 1( 0%) |
| CYSTITIS | 0 | 0 | 0 | 0( 0%) | 1 | 1 | 0 | 2( 1%) |
| POLYURIA | 0 | 0 | 0 | 0( 0%) | 2 | 1 | 0 | 3( 1%) |
| URETHRAL DISORDER | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 11 | 8 | 0 | 19( 7%) | 16 | 15 | 3 | 34( 12%) |
| VASCULAR (EXTRACARDIAC) DISORDERS | | | | | | | | |
| FLUSHING | 1 | 1 | 0 | 2( 1%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 1 | 1 | 0 | 2( 1%) | 0 | 0 | 0 | 0( 0%) |



Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
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For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 32

INCIDENCE OF ADVERSE EVENTS BY SEVERITY, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM<br>ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b)<br>750MG x 7 DAYS<br>(N=267)<br>MILD | MOD | SEV | TOTAL | CLEOCIN<br>(N=285)<br>MILD | MOD | SEV | TOTAL |
|---|---|---|---|---|---|---|---|---|
| VISION DISORDERS | | | | | | | | |
| VISION ABNORMAL | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| IRITIS | 0 | 0 | 0 | 0( 0%) | 0 | 1 | 0 | 1( 0%) |
| OVERALL INCIDENCE | 1 | 0 | 0 | 1( 0%) | 1 | 1 | 0 | 2( 1%) |
| WHITE CELL AND RES DISORDERS | | | | | | | | |
| LEUKOCYTOSIS | 1 | 0 | 0 | 1( 0%) | 1 | 0 | 0 | 1( 0%) |
| LYMPHADENOPATHY | 0 | 1 | 0 | 1( 0%) | 0 | 0 | 0 | 0( 0%) |
| LEUKOPENIA | 0 | 0 | 0 | 0( 0%) | 0 | 0 | 0 | 0( 0%) |
| OVERALL INCIDENCE | 1 | 1 | 0 | 2( 1%) | 1 | 0 | 0 | 1( 0%) |



Notes:
MOD = Moderate, SEV = Severe
(a) If an adverse event is reported more than once during a treatment period, the greatest known severity is presented. If a patient had more than one adverse event within a body system, only the greatest known severity is counted in the overall incidence.
(b) Adverse events are sorted by descending total incidence of this treatment column within body system.
For study 17, patients 166, 293, and 297 each had an adverse event in which the severity could not be determined. Therefore, these events are not included in the table.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 33

INCIDENCE OF ADVERSE EVENTS

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| HEADACHE | 48( 18%) | 44( 15%) |
| VAGINITIS | 39( 15%) | 33( 12%) |
| NAUSEA | 28( 10%) | 8( 3%) |
| TASTE PERVERSION | 23( 9%) | 1( 0%) |
| INFECTION BACTERIAL | 19( 7%) | 17( 6%) |
| INFLUENZA-LIKE SYMPTOMS | 17( 6%) | 20( 7%) |
| PRURITUS GENITAL | 14( 5%) | 25( 9%) |
| RHINITIS | 12( 4%) | 10( 4%) |
| DIARRHEA | 11( 4%) | 3( 1%) |
| DIZZINESS | 11( 4%) | 3( 1%) |
| UPPER RESP TRACT INFECTION | 11( 4%) | 10( 4%) |
| ABDOMINAL PAIN | 10( 4%) | 13( 5%) |
| DYSMENORRHEA | 9( 3%) | 7( 2%) |
| MONILIASIS | 9( 3%) | 8( 3%) |
| PHARYNGITIS | 8( 3%) | 4( 1%) |
| SINUSITIS | 7( 3%) | 6( 2%) |
| URINE ABNORMAL | 7( 3%) | 4( 1%) |
| INTERMENSTRUAL BLEEDING | 6( 2%) | 4( 1%) |
| PERINEAL PAIN FEMALE | 6( 2%) | 16( 6%) |
| URINARY TRACT INFECTION | 6( 2%) | 16( 6%) |
| VOMITING | 6( 2%) | 4( 1%) |
| DYSPEPSIA | 5( 2%) | 3( 1%) |
| FLATULENCE | 5( 2%) | 1( 0%) |
| MOUTH DRY | 5( 2%) | 2( 1%) |
| NERVOUSNESS | 5( 2%) | 2( 1%) |
| BACK PAIN | 4( 1%) | 5( 2%) |
| COUGHING | 4( 1%) | 3( 1%) |
| DEPRESSION | 4( 1%) | 1( 0%) |
| EMOTIONAL LABILITY | 4( 1%) | 1( 0%) |
| HERPES SIMPLEX | 4( 1%) | 3( 1%) |
| INSOMNIA | 4( 1%) | 4( 1%) |
| MENSTRUAL DISORDER | 4( 1%) | 4( 1%) |
| PAIN | 4( 1%) | 6( 2%) |
| RASH ERYTHEMATOUS | 4( 1%) | 6( 2%) |
| SGPT INCREASED | 4( 1%) | 4( 1%) |

Notes:
(a) If a patient had adverse events of more than one category, that patient is counted under each category.
(b) Adverse events are sorted by descending incidence of this treatment column.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 33

INCIDENCE OF ADVERSE EVENTS

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| URTICARIA | 4( 1%) | 1( 0%) |
| ANXIETY | 3( 1%) | 2( 1%) |
| BRONCHOSPASM | 3( 1%) | 0( 0%) |
| CONSTIPATION | 3( 1%) | 4( 1%) |
| HYPERGLYCEMIA | 3( 1%) | 3( 1%) |
| MIGRAINE | 3( 1%) | 3( 1%) |
| PREGNANCY UNINTENDED | 3( 1%) | 1( 0%) |
| PRURITUS | 3( 1%) | 3( 1%) |
| SGOT INCREASED | 3( 1%) | 2( 1%) |
| TONGUE DISCOLORATION | 3( 1%) | 0( 0%) |
| URINARY URGENCY | 3( 1%) | 1( 0%) |
| ANEMIA | 2( 1%) | 3( 1%) |
| BREAST PAIN FEMALE | 2( 1%) | 0( 0%) |
| DYSURIA | 2( 1%) | 5( 2%) |
| FATIGUE | 2( 1%) | 3( 1%) |
| FLUSHING | 2( 1%) | 0( 0%) |
| HYPOKINESIA | 2( 1%) | 0( 0%) |
| INFECTION VIRAL | 2( 1%) | 4( 1%) |
| INJURY-ACCIDENTAL | 2( 1%) | 2( 1%) |
| LEUKORRHEA | 2( 1%) | 8( 3%) |
| MENORRHAGIA | 2( 1%) | 2( 1%) |
| MYALGIA | 2( 1%) | 3( 1%) |
| OTITIS MEDIA | 2( 1%) | 0( 0%) |
| PHOSPHATASE ALKALINE INCREASED | 2( 1%) | 1( 0%) |
| PYURIA | 2( 1%) | 1( 0%) |
| SKIN DISORDER | 2( 1%) | 1( 0%) |
| THINKING ABNORMAL | 2( 1%) | 0( 0%) |
| AGITATION | 1( 0%) | 0( 0%) |
| ALLERGY | 1( 0%) | 2( 1%) |
| ANOREXIA | 1( 0%) | 0( 0%) |
| ARTHRALGIA | 1( 0%) | 3( 1%) |
| ARTHRITIS | 1( 0%) | 0( 0%) |
| ASTHENIA | 1( 0%) | 0( 0%) |
| BILIRUBINEMIA | 1( 0%) | 1( 0%) |
| BRONCHITIS | 1( 0%) | 2( 1%) |

APPEARS THIS WAY ON ORIGINAL

Notes:
(a) If a patient had adverse events of more than one category, that patient is counted under each category.
(b) Adverse events are sorted by descending incidence of this treatment column.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 33

INCIDENCE OF ADVERSE EVENTS

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| CHEST PAIN | 1( 0%) | 0( 0%) |
| CRYING ABNORMAL | 1( 0%) | 0( 0%) |
| CYST, NOS | 1( 0%) | 1( 0%) |
| DEPRESSION AGGRAVATED | 1( 0%) | 0( 0%) |
| DERMATITIS FUNGAL | 1( 0%) | 0( 0%) |
| DYSPAREUNIA | 1( 0%) | 2( 1%) |
| EDEMA | 1( 0%) | 1( 0%) |
| EPISTAXIS | 1( 0%) | 0( 0%) |
| FEVER | 1( 0%) | 3( 1%) |
| GASTROENTERITIS | 1( 0%) | 1( 0%) |
| GLOSSITIS | 1( 0%) | 0( 0%) |
| GLYCOSURIA | 1( 0%) | 2( 1%) |
| HEPATIC FUNCTION ABNORMAL | 1( 0%) | 0( 0%) |
| HOT FLUSHES | 1( 0%) | 1( 0%) |
| HYPERESTHESIA | 1( 0%) | 0( 0%) |
| INFECTION FUNGAL | 1( 0%) | 0( 0%) |
| LARYNGITIS | 1( 0%) | 1( 0%) |
| LEUKOCYTOSIS | 1( 0%) | 1( 0%) |
| LIBIDO DECREASED | 1( 0%) | 1( 0%) |
| LYMPHADENOPATHY | 1( 0%) | 0( 0%) |
| MICTURITION FREQUENCY | 1( 0%) | 2( 1%) |
| OVERDOSE | 1( 0%) | 0( 0%) |
| PALPITATION | 1( 0%) | 0( 0%) |
| PARANOID REACTION | 1( 0%) | 0( 0%) |
| PLATELETS ABNORMAL | 1( 0%) | 0( 0%) |
| PREVIOUSLY SCHEDULED SURGERY | 1( 0%) | 0( 0%) |
| PSYCHOSIS | 1( 0%) | 0( 0%) |
| RASH | 1( 0%) | 6( 2%) |
| RECTAL DISORDER | 1( 0%) | 0( 0%) |
| RESPIRATORY DISORDER | 1( 0%) | 1( 0%) |
| SALIVA INCREASED | 1( 0%) | 0( 0%) |
| SOMNOLENCE | 1( 0%) | 0( 0%) |
| STOMATITIS | 1( 0%) | 0( 0%) |
| STOMATITIS ULCERATIVE | 1( 0%) | 0( 0%) |
| SWEATING INCREASED | 1( 0%) | 1( 0%) |

Notes:
(a) If a patient had adverse events of more than one category, that patient is counted under each category.
(b) Adverse events are sorted by descending incidence of this treatment column.

APPEARS THIS WAY ON ORIGINAL

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 33

INCIDENCE OF ADVERSE EVENTS

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| THROMBOCYTHEMIA | 1( 0%) | 2( 1%) |
| TINNITUS | 1( 0%) | 0( 0%) |
| TONGUE DISORDER | 1( 0%) | 0( 0%) |
| TWITCHING | 1( 0%) | 0( 0%) |
| UTERINE CRAMPING | 1( 0%) | 0( 0%) |
| UTERINE HEMORRHAGE | 1( 0%) | 0( 0%) |
| VAGINAL BURNING | 1( 0%) | 7( 2%) |
| VAGINAL DRYNESS | 1( 0%) | 3( 1%) |
| VAGINAL NEOPLASM BENIGN | 1( 0%) | 1( 0%) |
| VISION ABNORMAL | 1( 0%) | 1( 0%) |
| VULVA DISORDER | 1( 0%) | 1( 0%) |
| WEIGHT INCREASE | 1( 0%) | 0( 0%) |
| WITHDRAWAL BLEEDING | 1( 0%) | 0( 0%) |
| AG RATIO ABNORMAL | 0( 0%) | 1( 0%) |
| ALBUMINURIA | 0( 0%) | 1( 0%) |
| AMENORRHEA | 0( 0%) | 1( 0%) |
| BREAST FIBROADENOSIS | 0( 0%) | 3( 1%) |
| BREAST MALFORMATION | 0( 0%) | 1( 0%) |
| CERVICAL DYSPLASIA | 0( 0%) | 1( 0%) |
| CERVICAL SMEAR TEST POSITIVE | 0( 0%) | 1( 0%) |
| CERVICITIS | 0( 0%) | 6( 2%) |
| CYSTITIS | 0( 0%) | 2( 1%) |
| DERMATITIS CONTACT | 0( 0%) | 1( 0%) |
| EARACHE | 0( 0%) | 1( 0%) |
| ENDOMETRIOSIS | 0( 0%) | 0( 0%) |
| FACE EDEMA | 0( 0%) | 0( 0%) |
| GINGIVITIS | 0( 0%) | 1( 0%) |
| GRANULOMATOUS LESION | 0( 0%) | 1( 0%) |
| HEMORRHOIDS | 0( 0%) | 1( 0%) |
| HYPERURICEMIA | 0( 0%) | 1( 0%) |
| HYPOCALCEMIA | 0( 0%) | 1( 0%) |
| HYPOESTHESIA | 0( 0%) | 0( 0%) |
| INFECTION | 0( 0%) | 6( 2%) |
| IRITIS | 0( 0%) | 1( 0%) |
| LABORATORY TEST ABNORMAL | 0( 0%) | 6( 2%) |

APPEARS THIS WAY
ON ORIGINAL

Notes:
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TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 33

INCIDENCE OF ADVERSE EVENTS

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| LDH INCREASED | 0( 0%) | 1( 0%) |
| LEUKOPENIA | 0( 0%) | 0( 0%) |
| MALAISE | 0( 0%) | 3( 1%) |
| NAIL DISORDER | 0( 0%) | 1( 0%) |
| OTITIS EXTERNA | 0( 0%) | 0( 0%) |
| OVARIAN DISORDER | 0( 0%) | 1( 0%) |
| PARESTHESIA | 0( 0%) | 2( 1%) |
| POLYURIA | 0( 0%) | 3( 1%) |
| PRURITUS ANI | 0( 0%) | 0( 0%) |
| PURPURA | 0( 0%) | 1( 0%) |
| RASH MACULO-PAPULAR | 0( 0%) | 1( 0%) |
| RIGORS | 0( 0%) | 1( 0%) |
| SKIN ODOR ABNORMAL | 0( 0%) | 4( 1%) |
| TACHYCARDIA | 0( 0%) | 0( 0%) |
| TENDINITIS | 0( 0%) | 1( 0%) |
| TOOTH DISORDER | 0( 0%) | 3( 1%) |
| URETHRAL DISORDER | 0( 0%) | 1( 0%) |
| VAGINAL HEMORRHAGE | 0( 0%) | 3( 1%) |
| VERTIGO | 0( 0%) | 1( 0%) |
| WEIGHT DECREASE | 0( 0%) | 0( 0%) |



Notes:
(a) If a patient had adverse events of more than one category, that patient is counted under each category.
(b) Adverse events are sorted by descending incidence of this treatment column.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 33

INCIDENCE OF ADVERSE EVENTS

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| SUMMARY (NUMBER OF PATIENTS) (a) | FLAGYL MR (b) 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | 198( 74%) | 204( 72%) |
| PATIENTS WITH NO ADVERSE EVENTS | 69( 26%) | 81( 28%) |
| PATIENTS WITH NO ADVERSE EVENTS INFORMATION | 0( 0%) | 0( 0%) |
| ALL PATIENTS WITH AT LEAST ONE DOSE | 267(100%) | 285(100%) |
| ALL RANDOMIZED PATIENTS | 270 | 287 |

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 34

INCIDENCE OF ADVERSE EVENTS BY ATTRIBUTION, WITHIN BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| | FLAGYL MR 750MG x 7 DAYS (N=267 ) | | | | CLEOCIN (N=285 ) | | | |
|---|---|---|---|---|---|---|---|---|
| SUMMARY (NUMBER OF PATIENTS) (a) | NONE | UNCERT | PROB | TOTAL | NONE | UNCERT | PROB | TOTAL |
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT | 80 | 62 | 56 | 198( 74%) | 110 | 67 | 27 | 204( 72%) |
| PATIENTS WITH NO ADVERSE EVENTS | | | | 69( 26%) | | | | 81( 28%) |
| PATIENTS WITH NO ADVERSE EVENTS INFORMATION | | | | 0( 0%) | | | | 0( 0%) |
| ALL PATIENTS WITH AT LEAST ONE DOSE | | | | 267(100%) | | | | 285(100%) |
| ALL RANDOMIZED PATIENTS | | | | 270 | | | | 287 |



Notes:
UNCERT = Uncertain, PROB = Probable
(a) If an adverse event is reported more than once during a treatment period, the greatest known attribution is presented.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 35

COMPARISON OF INCIDENCES OF ADVERSE EVENTS BY BODY SYSTEM

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| BODY SYSTEM (WHO CODED TERM) | FLAGYL MR 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) | P-VALUE (a) |
|---|---|---|---|
| APPLICATION SITE DISORDERS | 0( 0%) | 1( 0%) | 1.000 |
| AUTONOMIC NERVOUS SYSTEM DISORDERS | 6( 2%) | 2( 1%) | 0.164 |
| BODY AS A WHOLE - GENERAL DISORDERS | 37( 14%) | 49( 17%) | 0.293 |
| CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS | 59( 22%) | 51( 18%) | 0.241 |
| GASTRO-INTESTINAL SYSTEM DISORDERS | 57( 21%) | 31( 11%) | 0.001 |
| HEARING AND VESTIBULAR DISORDERS | 1( 0%) | 1( 0%) | 1.000 |
| HEART RATE AND RHYTHM DISORDERS | 1( 0%) | 0( 0%) | 0.484 |
| LIVER AND BILIARY SYSTEM DISORDERS | 5( 2%) | 4( 1%) | 0.745 |
| METABOLIC AND NUTRITIONAL DISORDERS | 6( 2%) | 5( 2%) | 0.766 |
| MUSCULO-SKELETAL SYSTEM DISORDERS | 4( 1%) | 7( 2%) | 0.547 |
| PLATELET, BLEEDING & CLOTTING DISORDERS | 3( 1%) | 3( 1%) | 1.000 |
| PSYCHIATRIC DISORDERS | 19( 7%) | 13( 5%) | 0.208 |
| RED BLOOD CELL DISORDERS | 2( 1%) | 3( 1%) | 1.000 |
| REPRODUCTIVE DISORDERS, FEMALE | 68( 25%) | 83( 29%) | 0.341 |
| RESISTANCE MECHANISM DISORDERS | 37( 14%) | 38( 13%) | 0.901 |
| RESPIRATORY SYSTEM DISORDERS | 39( 15%) | 32( 11%) | 0.254 |
| SKIN AND APPENDAGES DISORDERS | 26( 10%) | 48( 17%) | 0.017 |
| SPECIAL SENSES OTHER, DISORDERS | 23( 9%) | 1( 0%) | 0.000 |
| URINARY SYSTEM DISORDERS | 19( 7%) | 34( 12%) | 0.061 |
| VASCULAR (EXTRACARDIAC) DISORDERS | 2( 1%) | 0( 0%) | 0.234 |
| VISION DISORDERS | 1( 0%) | 2( 1%) | 1.000 |
| WHITE CELL AND RES DISORDERS | 2( 1%) | 1( 0%) | 0.612 |

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 35

COMPARISON OF INCIDENCES OF ADVERSE EVENTS (a)

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) | FLAGYL MR 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) | P-VALUE (b) |
|---|---|---|---|
| ABDOMINAL PAIN | 10( 4%) | 13( 5%) | 0.675 |
| ANEMIA | 2( 1%) | 3( 1%) | 1.000 |
| ANXIETY | 3( 1%) | 2( 1%) | 0.677 |
| ARTHRALGIA | 1( 0%) | 3( 1%) | 0.624 |
| BACK PAIN | 4( 1%) | 5( 2%) | 1.000 |
| BREAST FIBROADENOSIS | 0( 0%) | 3( 1%) | 0.249 |
| BRONCHOSPASM | 3( 1%) | 0( 0%) | 0.113 |
| CERVICITIS | 0( 0%) | 6( 2%) | 0.031 |
| CONSTIPATION | 3( 1%) | 4( 1%) | 1.000 |
| COUGHING | 4( 1%) | 3( 1%) | 0.717 |
| DEPRESSION | 4( 1%) | 1( 0%) | 0.203 |
| DIARRHEA | 11( 4%) | 3( 1%) | 0.029 |
| DIZZINESS | 11( 4%) | 3( 1%) | 0.029 |
| DYSMENORRHEA | 9( 3%) | 7( 2%) | 0.615 |
| DYSPEPSIA | 5( 2%) | 3( 1%) | 0.492 |
| DYSURIA | 2( 1%) | 5( 2%) | 0.452 |
| EMOTIONAL LABILITY | 4( 1%) | 1( 0%) | 0.203 |
| FATIGUE | 2( 1%) | 3( 1%) | 1.000 |
| FEVER | 1( 0%) | 3( 1%) | 0.624 |
| FLATULENCE | 5( 2%) | 1( 0%) | 0.112 |
| HEADACHE | 48( 18%) | 44( 15%) | 0.427 |
| HERPES SIMPLEX | 4( 1%) | 3( 1%) | 0.717 |
| HYPERGLYCEMIA | 3( 1%) | 3( 1%) | 1.000 |
| INFECTION | 0( 0%) | 6( 2%) | 0.031 |
| INFECTION BACTERIAL | 19( 7%) | 17( 6%) | 0.609 |
| INFECTION VIRAL | 2( 1%) | 4( 1%) | 0.687 |
| INFLUENZA-LIKE SYMPTOMS | 17( 6%) | 20( 7%) | 0.865 |
| INSOMNIA | 4( 1%) | 4( 1%) | 1.000 |
| INTERMENSTRUAL BLEEDING | 6( 2%) | 4( 1%) | 0.534 |
| LABORATORY TEST ABNORMAL | 0( 0%) | 6( 2%) | 0.031 |
| LEUKORRHEA | 2( 1%) | 8( 3%) | 0.108 |
| MALAISE | 0( 0%) | 3( 1%) | 0.249 |
| MENSTRUAL DISORDER | 4( 1%) | 4( 1%) | 1.000 |
| MIGRAINE | 3( 1%) | 3( 1%) | 1.000 |
| MONILIASIS | 9( 3%) | 8( 3%) | 0.807 |

Notes:
(a) Adverse event with incidence > 1% in at least one treatment group.
(b) P-value is from Fisher's exact test (two-tailed).

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 35

COMPARISON OF INCIDENCES OF ADVERSE EVENTS (a)

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| ADVERSE EVENT (WHO CODED TERM) | FLAGYL MR 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) | P-VALUE (b) |
|---|---|---|---|
| MOUTH DRY | 5( 2%) | 2( 1%) | 0.272 |
| MYALGIA | 2( 1%) | 3( 1%) | 1.000 |
| NAUSEA | 28( 10%) | 8( 3%) | 0.000 |
| NERVOUSNESS | 5( 2%) | 2( 1%) | 0.272 |
| PAIN | 4( 1%) | 6( 2%) | 0.753 |
| PERINEAL PAIN FEMALE | 6( 2%) | 16( 6%) | 0.051 |
| PHARYNGITIS | 8( 3%) | 4( 1%) | 0.249 |
| POLYURIA | 0( 0%) | 3( 1%) | 0.249 |
| PREGNANCY UNINTENDED | 3( 1%) | 1( 0%) | 0.358 |
| PRURITUS | 3( 1%) | 3( 1%) | 1.000 |
| PRURITUS GENITAL | 14( 5%) | 25( 9%) | 0.134 |
| RASH | 1( 0%) | 6( 2%) | 0.124 |
| RASH ERYTHEMATOUS | 4( 1%) | 6( 2%) | 0.753 |
| RHINITIS | 12( 4%) | 10( 4%) | 0.665 |
| SGOT INCREASED | 3( 1%) | 2( 1%) | 0.677 |
| SGPT INCREASED | 4( 1%) | 4( 1%) | 1.000 |
| SINUSITIS | 7( 3%) | 6( 2%) | 0.783 |
| SKIN ODOR ABNORMAL | 0( 0%) | 4( 1%) | 0.124 |
| TASTE PERVERSION | 23( 9%) | 1( 0%) | 0.000 |
| TONGUE DISCOLORATION | 3( 1%) | 0( 0%) | 0.113 |
| TOOTH DISORDER | 0( 0%) | 3( 1%) | 0.249 |
| UPPER RESP TRACT INFECTION | 11( 4%) | 10( 4%) | 0.825 |
| URINARY TRACT INFECTION | 6( 2%) | 16( 6%) | 0.051 |
| URINARY URGENCY | 3( 1%) | 1( 0%) | 0.358 |
| URINE ABNORMAL | 7( 3%) | 4( 1%) | 0.370 |
| URTICARIA | 4( 1%) | 1( 0%) | 0.203 |
| VAGINAL BURNING | 1( 0%) | 7( 2%) | 0.069 |
| VAGINAL DRYNESS | 1( 0%) | 3( 1%) | 0.624 |
| VAGINAL HEMORRHAGE | 0( 0%) | 3( 1%) | 0.249 |
| VAGINITIS | 39( 15%) | 33( 12%) | 0.313 |
| VOMITING | 6( 2%) | 4( 1%) | 0.534 |

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 36

INCIDENCE OF ADVERSE EVENTS(a) CAUSING WITHDRAWAL

PATIENTS WITH AT LEAST ONE DOSE OF STUDY MEDICATION/POOLED STUDIES

| SUMMARY (NUMBER OF PATIENTS) (a) | FLAGYL MR 750MG x 7 DAYS (N=267) | CLEOCIN (N=285) |
|---|---|---|
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT CAUSING WITHDRAWAL | 2( 1%) | 3( 1%) |
| PATIENTS WITH AT LEAST ONE ADVERSE EVENT NOT CAUSING WITHDRAWAL | 196( 73%) | 201( 71%) |
| PATIENTS WITH NO ADVERSE EVENTS | 69( 26%) | 81( 28%) |
| PATIENTS WITH NO ADVERSE EVENTS INFORMATION | 0( 0%) | 0( 0%) |
| ALL PATIENTS WITH AT LEAST ONE DOSE | 267(100%) | 285(100%) |
| ALL RANDOMIZED PATIENTS | 270 | 287 |

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

Table 36

LIST OF ADVERSE SIGNS AND SYMPTOMS CAUSING WITHDRAWAL

| PROTOCOL | PATIENT ID(a) | STUDY DRUG | AGE (Y) | ADVERSE EVENT (WHO TEXT/CRF TEXT) | SEVERITY | DATE STARTED | DATE STOPPED | CONTINUE | TIME TO ONSET (d) | DURATION (d/h) | POSSIBLE RELATION TO STUDY DRUG |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N13-95-02-015 | US0017-121 | FLAGYL MR 750 MG QD X 7 DAYS | 20 | PSYCHOSIS / PSYCHOSIS | MODERATE | 13OCT95 | | YES | 11 | | UNC |
| | US0024-341 | FLAGYL MR 750 MG QD X 7 DAYS | 30 | URTICARIA / HIVES | MODERATE | 08DEC95 | 09DEC95 | | 2 | 1 d | PROB |
| | | | | PRURITUS / ITCHINESS | MODERATE | 08DEC95 | 09DEC95 | | 2 | 1 d | PROB |
| N13-95-02-017 | US0007-102 | CLEOCIN 2% QD | 34 | PRURITUS GENITAL / VAGINAL IRRITATION | SEVERE | 30NOV95 | 07DEC95 | | 0 | 7 d | PROB |
| | | | | MICTURITION FREQUENCY / URINARY FREQUENCY | SEVERE | 01DEC95 | 09DEC95 | | 1 | 8 d | UNC |
| | US0008-020 | CLEOCIN 2% QD | 41 | RASH / VAGINAL RASH | MODERATE | 30OCT95 | 06NOV95 | | 3 | 7 d | UNC |
| | US0016-255 | CLEOCIN 2% QD | 32 | PERINEAL PAIN FEMALE / PELVIC PAIN | MODERATE | 19JAN96 | | YES | 9 | | UNC |

(a) Investigator number-patient number.

TREATMENT OF BACTERIAL VAGINOSIS WITH FLAGYL MODIFIED RELEASE TABLET

TABLE 37

YEAST SUPERINFECTION FROM BASELINE
NUMBER (%) OF PATIENTS WITH SUPERINFECTIONS
ALL RANDOMIZED PATIENTS/POOLED STUDIES

| | | FLAGYL MR 750MG X 7 DAYS (N=270) SUPERINFECTION (a) (b) | CLEOCIN (N=287) SUPERINFECTION (a) |
|---|---|---|---|
| PRESENCE OF BRANCHING PSEUDO HYPHAE ON WET MOUNT | -015 | 29/126 ( 23%) | 28/134 ( 21%) |
| | -017 | 24/118 ( 20%) | 20/116 ( 17%) |
| | POOLED | 53/244 ( 22%) | 48/250 ( 19%) |
| POSITIVE YEAST CULTURE | -015 | 43/105 ( 41%) | 46/111 ( 41%) |
| | -017 | 30/100 ( 30%) | 27/ 96 ( 28%) |
| | POOLED | 73/205 ( 36%) | 73/207 ( 35%) |
| POSITIVE CANDIDA ALBICANS CULTURE | -015 | 37/106 ( 35%) | 40/113 ( 35%) |
| | -017 | 23/102 ( 23%) | 25/100 ( 25%) |
| | POOLED | 60/208 ( 29%) | 65/213 ( 31%) |

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# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020868

## STATISTICAL REVIEW(S)

NOV 2 4 1997

# Statistical Review and Evaluation

| | |
|---|---|
| **NDA:** | 20-868 |
| **Drug Name:** | Flagyl MR®(metronidazole) 750 mg Tablets |
| **Applicant:** | G.D. Searle & Co. |
| **Indications:** | Treatment of bacterial vaginosis |
| **Documents Reviewed:** | NDA volumes 1.1, 1.27, 1.32 dated May 29, 1997. Electronic data submitted July 1, 1997 |
| **Medical Officer:** | Joseph Winfield, M.D., HFD-590 |

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## 1. Introduction

NDA 20-868 for Flagyl MR® (metronidazole) 750 mg tablets was submitted as a New Drug Application for the treatment of women with symptomatic and asymptomatic bacterial vaginosis (BV). It composed of two completed, randomized, single-blind, controlled clinical studies. Study N13-95-02-015 (referred as Study 015) had 445 women with a clinical diagnosis of BV who were enrolled into one of three treatment groups:

Treatment A: One Flagyl MR® 750 mg tablet daily x 5 days followed by two day placebo
Treatment B: One Flagyl MR® 750 mg tablet daily x 7 days
Treatment C: One applicator full of Cleocin® (clindamycin phosphate 2%) daily x 7 days

Study N13-95-02-017 (referred as Study 017) enrolled 264 women and had two active treatment groups:

Treatment A: One Flagyl MR® 750 mg tablet daily x 7 days
Treatment B: One applicator full of Cleocin® (clindamycin phosphate 2%) daily x 7 days

Aside from the number of treatment groups, the two studies were identical in population and design. Therefore, the design of these two studies will be summarized together.

2. Summary of Designs

2.1 Study 015 and Study 017

Protocol Title of Study 015: Treatment of Bacterial Vaginosis with Metronidazole Modified Release Tablet – A Dose Duration Study.

Protocol Title of Study 017: Treatment of Bacterial Vaginosis with Metronidazole Modified Release Tablet

The objectives of both trials were to demonstrate the equivalence in efficacy and safety between the metronidazole 750 mg MR tablet and the Cleocin® Vaginal Cream treatment of bacterial vaginosis. Study 015 was also designed to evaluate the safety and efficacy of two dose duration regimens of Flagyl® MR.

In Study 015, a total of 390 intent-to-treat patients was planned for entry into the study, and 260 patients planned for Study 017. Subjects must meet following criteria to be included in the studies: 1) females of age 15 or older; 2) vaginal discharge with (a) positive amine odor on alkalinization of vaginal fluid when mixed with 10% potassium hydroxide solution. (b) presence of at least one clue cell per field in 20 high power fields (x400) on direct wet mount examination of vaginal secretion. (c) pH of vaginal secretion > 4.5.

The primary efficacy endpoints were clinical outcomes at 4-7 days (visit 2) and 28-32 days (visit 3), and an overall outcome measure. For the primary analysis, the clinical outcome of interest was dichotomized as cure or not cure. Cure was defined as a return to normal of all 3 diagnostic criteria: pH of vaginal discharge ≤ 4.5, absence of a "fishy" amine odor when mixed with 10% KOH solution, and an absence of clue cells. An overall outcome was "cure" only if this subject was assessed as "cured" in both visit 2 and visit 3. Two-sided 95% confidence intervals for the difference in true cure rates were to be presented.

Statistical analyses were planned to be performed on both the intent-to-treat and evaluable cohorts of patients. All patients randomized to study medication will be included in the intent-to-treat population. A patient would be considered evaluable for efficacy if this patient met enrollment criteria and additionally, had a diagnosis of BV by the Spiegel criteria at entry, took no other antibacterial therapy, received a minimum of five days of therapy and completed assessments of clinical signs and symptoms.

The applicant made a post-hoc amendment on the evaluable population when they realized that the number of evaluable patients was not large enough for achieving statistical significance of comparison between Flagyl MR and Cleocin®. The new definition of evaluable population was called "clinically evaluable patients" which included all patients who met all evaluable criteria except the diagnosis of BV at study entry.

All adverse events occurring during the study were to be collected based upon the instruction for the standardized collection of this information.

3. Efficacy



3.1 Applicant's Results

Two hundred sixty-four patients in study 017 and four hundred fifty-five patients in study 015 were enrolled. The demographic(age, race) and baseline characteristics( gynecologic history such as method of contraception, reason for consultation and number of abortion and microbiological test such as GC test, Chlamydia test, Gardnerella culture, yeast culture and Candida albicans) were comparable among the treatment groups. (source: V.1.1, Table 1, Table 4 and V. 1.27 Table 23, Table 24.) Six hundred thirty three patients completed the study across the treatment groups. Among those who were withdrawn from studies, forty-four patients were lost to follow-up, 9(6%) in the 5 day Flagyl MR® group, 13 (5%) in the pooled 7 day Flagyl MR® group, and 22(8%) in the pooled Cleocin®

group. No more than 3% of patients in any treatment group were withdrawn for violation of entry criteria, pregnancy, or adverse events.

The number of patients included in the evaluable population is substantially lower than the number of patients in the intent-to-treat population. The majority of patients in all three treatment groups who were not evaluable did not have a confirmatory microbiological diagnosis of BV according to the Spiegel criteria for Gram stain of vaginal discharge. Clinically evaluable population was created for those who met all evaluability criteria with the exception of the bacteriological diagnosis of BV at study entry.

The applicant's clinical outcome are presented in the following table.

Table 1. Number (%) of Patients Cured

| | Flagyl MR 750mg x 5 days in Study 015 | Flagyl MR 750mg x 7 days | | Cleocin | |
|---|---|---|---|---|---|
| | | Study 015 | Study 017 | Study 015 | Study 017 |
| Intent-to-treat | N=152 | N=139 | N=131 | N=154 | N=133 |
| Visit 2 | 88 (58%) | 83 (60%) | 75 (57%) | 52 (34%) | 40 (30%) |
| Visit 3 | 77 (51%) | 77 (55%) | 75 (57%) | 81 (53%) | 53 (40%) |
| Overall | 57 (38%) | 55 (40%) | 54 (41%) | 31 (20%) | 23 (17%) |
| Evaluable | N=90 | N=74 | N=73 | N=78 | N=74 |
| Visit 2 | 57 (63%) | 51 (69%) | 48 (66%) | 28 (36%) | 25 (34%) |
| Visit 3 | 38 (58%) | 38 (56%) | 33 (59%) | 38 (64%) | 22 (39%) |
| Overall | 28 (42%) | 29 (43%) | 27 (48%) | 15 (25%) | 11 (20%) |
| Clinically evaluable | N=140 | N=123 | N=108 | N=124 | N=107 |
| Visit 2 | 85 (61%) | 79 (64%) | 68 (63%) | 45 (36%) | 34 (32%) |
| Visit 3 | 69 (63%) | 68 (61%) | 57 (66%) | 64 (63%) | 34 (41%) |
| Overall | 52 (48%) | 49 (44%) | 45 (52%) | 25 (25%) | 14 (17%) |

Source; V1.1 Table 3 and Table 6A.

*Note: The overall cure defined in the protocol was such that a patient was regarded as cured if she was a "cure" at both visit 2 and visit 3. However, based on the data in the submitted SAS datasets, the statistical reviewer found that the applicant's results of overall cure did not agree with this definition. Therefore, the results presented in the above table were produced by the statistical reviewer based on the applicant's data at visit 2 and visit 3.*

*Note: In both trials, the response rate of Flagyl MR was much better than Cleocin at visit 2. The response rate of Cleocin was higher in Study 015 than in Study 017 at visit 3. The reasons for this disparity were not discussed in the NDA.*

To compare the cure rates between Flagyl MR and Cleocin, 95% confidence intervals for the difference in clinical cure rates were calculated by the applicant and their results are presented in the following table.

Table 2. The 95 % Confidence Interval for the Difference in Clinical Cure Rates

| | Flagyl MR 750mg x 5 days - Cleocin Study 015 | Flagyl MR 750mg x 7 days - Cleocin Study 015 | Study 017 |
|---|---|---|---|
| Intent-to-treat | | | |
| Visit 2 | $_{152,154}$ (13%, 35%) $_{58\%,34\%}$ | $_{139,154}$ (15%, 37%) $_{60\%,34\%}$ | $_{131,133}$(16%, 39%)$_{60\%,30\%}$ |
| Visit 3 | $_{152,154}$ (-13%, 9%) $_{51\%,53\%}$ | $_{139,154}$(-9%, 14%) $_{55\%,53\%}$ | $_{131,133}$(6%; 29%)$_{57\%,40\%}$ |
| Overall | $_{152,154}$ (7%, 27%) $_{38\%,20\%}$ | $_{139,154}$(9%, 30%)$_{40\%,20\%}$ | $_{131,133}$(13%, 35%)$_{41\%,17\%}$ |
| Evaluable | | | |
| Visit 2 | $_{90,78}$ (13%, 42%) $_{63\%,36\%}$ | $_{74,78}$(18%, 48%) $_{69\%,36\%}$ | $_{73,74}$(17%, 47%)$_{66\%,34\%}$ |
| Visit 3 | $_{90,78}$ (-24%, 10%) $_{58\%,64\%}$ | $_{74,78}$(-26%, 9%) $_{56\%,64\%}$ | $_{73,74}$(2%, 38%)$_{59\%,39\%}$ |
| Overall | $_{90,78}$ (0.7%, 33%) $_{42\%,25\%}$ | $_{74,78}$(1%, 33%) $_{43\%,25\%}$ | $_{73,74}$(12%, 45%) $_{48\%,20\%}$ |
| Clinically evaluable | | | |
| Visit 2 | $_{140,124}$ (13%, 36%) $_{61\%,36\%}$ | $_{123,124}$ (16%, 40%) $_{64\%,36\%}$ | $_{108,107}$(19%, 44%)$_{63\%,32\%}$ |
| Visit 3 | $_{140,124}$ (-13%, 14%)$_{63\%,63\%}$ | $_{123,124}$(-15%, 12%)$_{61\%,63\%}$ | $_{108,107}$(10%, 39%)$_{66\%,41\%}$ |
| Overall | $_{140,124}$ (11%, 36%) $_{48\%,25\%}$ | $_{123,124}$(7%, 32%) $_{44\%,25\%}$ | $_{108,107}$(22%, 48%)$_{52\%,17\%}$ |

Source; V1.27 Table 18 A-C and V1.32 Table 18A-C.

The confidence interval was written as $_{Nt,Nc}$ (LB, UB) $_{Pt,Pc}$, where Nt= number of patients in treatment group, Nc= number of patients in control group, Pt = cure rate in treatment group, Pc= cure rate in control group.

According to the applicant's results, Flagyl MR® showed statistically significantly higher cure rates than Cleocin at visit 2 as well as judged by overall assessment by demonstrating positive lower bounds of the 95% confidence intervals. Flagyl MR® was still statistically superior to Cleocin at visit 3 in Study 017 but not in Study 015.

*Note: Reasons that caused superiority of Flagyl MR ® will be discussed in the Statistical Review later.*

*Note: The 95% confidence intervals were based on the proportion of cure in each treatment group. For such multi-center trials, patients were enrolled according to a stratified randomization scheme by centers. The stratified confidence interval should also be considered.*



3.2 Reviewer's Comments

3.2.1 Assessment by Each Criterion in Definition of Cure

As mentioned before, the applicant's results showed that Flagyl MR ® had a higher cure rate than Cleocin at visit 2 and judged by overall assessment. However, if patients are assessed by each of the criteria in the definition of Cure, it was found that the superiority of Flagyl MR ® over Cleocin is basically driven by the pH value. While the proportion of patients who had no fishy odor or who had no clue cells at visit 2 and visit 3 are comparable as shown in the following table, patients treated with Flagyl MR ® apparently are more likely to return to normal pH values and to reach normal pH values earlier.

It is also clearly shown in the table 3 that the 7-day treatment of Flagyl MR® demonstrated higher success rates than the 5-day Flagyl MR® treatment with respect to three individual criteria at both visit 2 and visit 3. For this reason, The treatment of 7-day Flagyl MR® is favored.

Table 3. Number (%) of Patients Cured by Criteria Breakdown

| | Flagyl MR 750mg x 5 days N=152 | Flagyl MR 750mg x 7 days Study 015 N=139 | Study 017 N=131 | Cleocin Study 015 N=154 | Study 017 N=133 |
|---|---|---|---|---|---|
| No Fishy Odor | | | | | |
| Visit 2 | 132 (87%) | 134 (96%) | 118 (90%) | 136 (88%) | 118 (89%) |
| Visit 3 | 119 (78%) | 115 (83%) | 116 (89%) | 131(85%) | 118 (89%) |
| No Clue Cells | | | | | |
| Visit 2 | 119 (78%) | 119 (86%) | 109 (83%) | 127 (82%) | 107 (80%) |
| Visit 3 | 112 (74%) | 116 (83%) | 111 (85%) | 129 (84%) | 110 (83%) |
| pH value ≤ 4.5 | | | | | |
| Visit 2 | 105 (69%) | 103 (74%) | 91 (69%) | 65 (42%) | 48 (36%) |
| Visit 3 | 99 (65%) | 99 (71%) | 96 (73%) | 112 (73%) | 77 (58%) |

3.2.2 Mean pH value at Each Visit

Although the percentage of patients whose pH value returned to normal(<4.5) were observed higher at visit 2 in both studies and also observed greater at visit 3 in study 017, the real change of pH value from the baseline was not so significant. The baseline pH values were around 5.4 to 5.6 cross the treatments and studies. The mean pH values returned to 4.5 ~ 4.8 at visit 2 or visit 3 with all treatment groups. (See Table 4.) The net changes were only about one unit. Because the net change of pH value from baseline was small and the mean pH value finally return to below 4.80 for both treatments, the role of pH value in comparison of Flagyl MR ® and Cleocin ® might not be clinically critical. It is reasonable to exclude pH value from the assessment of clinical result in both studies.

Table 4. Mean(s.d.) pH value at Each Visit in Intent-to-treat Population

| | Flagyl MR 750mg x 5 days | Flagyl MR 750mg x 7 days Study 015 | Study 017 | Cleocin Study 015 | Study 017 |
|---|---|---|---|---|---|
| Intent-to-treat | | | | | |
| Baseline | 5.51(0.54) | 5.46(0.50) | 5.49(0.62) | 5.40(0.61) | 5.58 (0.60) |
| Visit 2 | 4.55(0.72) | 4.55(0.75) | 4.60(0.68) | 4.91(0.70) | 5.08(0.77) |
| Visit 3 | 4.68(0.71) | 4.55 (0.77) | 4.55(0.69) | 4.60(0.69) | 4.80(0.75) |

3.2.3 Assessment of Cure Without pH value

To assess the effectiveness of Flagyl MR ® without being interfered by pH values, definition of cure in this section to be used is absence of fishy odor and clue cells. The results shown here were calculated by the Statistical Reviewer based on the applicant's SAS data sets, therefore, based on their evaluation of each patient. The Results in Table 5 show that 1) the cure rates of Flagyl MR ® and Cleocin are pretty much consistent cross the studies and patient populations; 2) the cure rates of Flagyl MR ® and Cleocin are higher at visit visit 3 than at visit 2 in both studies; 3) in both studies, the cure rate of Flagyl MR ® are comparable to Cleocin cross all patient populations investigated.

Table 5. Number (%) of Patients Cured (pH value requirement ignored)

| | Flagyl MR 750mg x 5 days | Flagyl MR 750mg x 7 days | | Cleocin | |
|---|---|---|---|---|---|
| | | Study 015 | Study 017 | Study 015 | Study 017 |
| Intent-to-treat | N=152 | N=139 | N=131 | N=154 | N=133 |
| Visit 2 | 92 (61%) | 90 (65%) | 90 (69%) | 91 (59%) | 83 (62%) |
| Visit 3 | 109 (72%) | 108 (78%) | 106 (81%) | 119 (77%) | 104 (78%) |
| Overall | 92 (61%) | 90 (65%) | 90 (69%) | 91 (59%) | 83 (62%) |
| Evaluable | N=90 | N=74 | N=73 | N=78 | N=74 |
| Visit 2 | 48 (53%) | 52 (70%) | 47 (64%) | 45 (58%) | 43 (58%) |
| Visit 3 | 59 (66%) | 57 (77%) | 56 (77%) | 61 (78%) | 55 (74%) |
| Overall | 48 (53%) | 52 (70%) | 47 (64%) | 45 (58%) | 43 (58%) |
| Clinically evaluable | N=140 | N=123 | N=108 | N=124 | N=107 |
| Visit 2 | 86 (61%) | 82 (67%) | 75 (69%) | 75 (60%) | 68 (64%) |
| Visit 3 | 103 (74%) | 95 (77%) | 88 (81%) | 97 (78%) | 85 (79%) |
| Overall | 86 (61%) | 82 (67%) | 75 (69%) | 75 (60%) | 68 (64%) |

In comparison of Flagyl MR ® and Cleocin, the 95% confidence intervals for the difference of cure rates between Flagyl MR ® and Cleocin were calculated based on a center stratified approach. In both studies, the lower bounds were no less than -15% for 7 day treatment of Flagyl MR ® compared to Cleocin. For visit 3 in Study 015, Flagyl MR ® ( 5 day regimen) failed to establish therapeutic equivalence with Cleocin in the evaluable patient group. In all other respective groups, Flagyl MR was therapeutically equivalent to Cleocin both on the 5-day regimen as well as the 7-day regimen.

Table 6.The 95 % Center-Adjusted Confidence Interval for the Difference in Clinical Cure Rates (pH value ignored)

| | Flagyl MR 750mg x 5 days - Cleocin | Flagyl MR 750mg x 7 days - Cleocin | |
|---|---|---|---|
| | Study 015 | Study 015 | Study 017 |
| Intent-to-treat | | | |
| Visit 2 | (-8%, 12%) | (-6%, 15%) | (-4%, 17%) |
| Visit 3 | (-15%, 4%) | (-10%, 9%) | (-7%, 13%) |
| Overall | (-8%, 12%) | (-6%,15%) | (-4%, 17%) |
| Evaluable | | | |
| Visit 2 | (-15%, 15%) | (-2%, 26%) | (-8%, 21%) |
| Visit 3 | (-21%, 6%) | (-15%, 12%) | (-12%,16%) |
| Overall | (-15%, 15%) | (-2%, 26%) | (-8%, 21%) |
| Clinically evaluable | | | |
| Visit 2 | (-9%, 13%) | (-7%, 16%) | (-7%, 17%) |
| Visit 3 | (-13%, 7%) | (-12%, 9%) | (-10%, 12%) |
| Overall | (-9%, 13%) | (-7%, 16%) | (-7%, 17%) |



3.2.4 Medical Officer's Assessment

To evaluate the applicant's analysis, the Medical Officer checked each patient's outcome and made some changes in patients' classifications. The major principles used by the Medical Officer are followings:

- A patient was considered Cured if she had (a) no fishy odor on alkalinization of vaginal fluid, (b) no presence of clue cells and (c) pH of vaginal secretion less or equal to 4.5.

- Evaluable population was defined as patients who met enrollment criteria and additionally, had a diagnosis of BV by the Nugent criteria (the applicant using Spiegel criteria) at entry, took no other antibacterial therapy, received a minimum of five days of therapy and completed assessments of clinical signs and symptoms.
- Clinically evaluable patients included all patients who met all evaluable criteria except the diagnosis of BV at study entry.

The detailed changes made by the Medical Officer on each patient might be found in the Medical Officer's review. The analyses in Table 7 and 8 were based on the Medical Officer's assessment. The results presented in Table 7 show that the cure rates of Flagyl MR® were similar to the rate of Cleocin in Study 015 while the cure rate of Cleocin was lower than all of the other three groups. The 95% confidence intervals of the difference in cure rates are presented in Table 8. Flagyl MR® was demonstrated therapeutically equivalent to Cleocin in Study 015 and statistically superior to Cleocin in Study 017.

Table 7. Number (%) of Patients Cured

| | Flagyl MR 750mg x 7 days | | Cleocin | |
|---|---|---|---|---|
| | Study 015 | Study 017 | Study 015 | Study 017 |
| Evaluable | N=103 | N=99 | N=113 | N=93 |
| Cured | 53 (51%) | 51 (52%) | 62 (55%) | 34 (37%) |
| Clinically evaluable | N=126 | N=119 | N=135 | N=117 |
| Cured | 77 (61%) | 74 (62%) | 80 (59%) | 50 (43%) |

Table 8. The 95% Confidence Interval of difference in Cure Rates

| | Flagyl MR 750mg x 7 days - Cleocin x 7 days | |
|---|---|---|
| | Study 015 | Study 017 |
| Evaluable | $_{103,\ 113}$(-17.7%, 10.8%)$_{51\%,55\%}$ | $_{99,93}$ (-3.3%, 26.8%) $_{52\%,\ 37\%}$ |
| Clinically evaluable | $_{126,\ 119}$ (-10.8%, 14.5%) $_{61\%,\ 59\%}$ | $_{119,\ 117}$ (6.1%, 32.8%) $_{62\%,\ 43\%}$ |

The confidence interval was written as $_{Nt,\ Nc}$ (LB, UB) $_{Pt,\ Pc}$, where Nt= number of patients in treatment group, Nc= number of patients in control group, Pt = cure rate in treatment group, Pc= cure rate in control group. Continuity correction was used in confidence interval calculation.

The center-adjusted 95% confidence intervals were also calculated and the results were presented in the following table. Centers with one of treatment group smaller than 4 patients were pooled together.

Table 9. The Center-adjusted 95% Confidence Interval of difference in Cure Rates

| | Flagyl MR 750mg x 7 days - Cleocin x 7 days | |
|---|---|---|
| | Study 015 | Study 017 |
| Evaluable | (-15%, 12%) | (0%, 27%) |
| Clinically evaluable | (-11%, 12%) | (7%, 30%) |

Based on the Medical Officer assessment, Flagyl MR is therapeutically equivalent to Cleocin with respect to both

evaluable and clinically evaluable patient population in Study 015. In Study 017, Flagyl MR is statistically superior to Cleocin for clinically evaluable patients.



4. Safety

When the data from Study 015 and Study 017 were pooled together, 67% and 74% of the 5 day and 7 day Flagyl MR® groups, respectively had at least one adverse event, compared with 72% of the Cleocin® group. The majority of adverse events were rated in severity as mild or moderate. The adverse events which happened to more than 2% of patients who took at least one dose of study drugs in either treatment group are presented in the table 10.

Table 10. Adverse Events Irrespective of Treatment Causality(> 2% incidence rate) in Either Group

| | Flagyl MR 5 days (N=151) | Flagyl MR 7 days (N=267) | Cleocin (N=285) |
|---|---|---|---|
| Mouth Dry | 4 (3%) | 5 (2%) | 2 (1%) |
| Influenza-like Symptoms | 10 (7%) | 17 (6%) | 20 (7%) |
| Pain in Body as a Whole | 7 (5%) | 4 (1%) | 6 (2%) |
| Headache | 22 (15%) | 48 (18%) | 43 (15%) |
| Dizziness | 2 (1%) | 11 (4%) | 3 (1%) |
| Nausea | 23 (15%) | 28 (10%) | 8 (3%) |
| Diarrhea | 6 (4%) | 11 (4%) | 3 (1%) |
| Abdominal Pain | 7 (5%) | 10 (4%) | 13 (5 %) |
| Vaginitis | 16 (11%) | 39 (15%) | 32 (11%) |
| Dysmenorrhea | 6 (4%) | 9 (3%) | 7 (2%) |
| Leukorrhea | 3 (2%) | 2 (1%) | 8 (3%) |
| Infection Bacterial | 12 (8%) | 19 (7%) | 17 (6%) |
| Moniliasis | 9 (6%) | 9 (3%) | 8 (3%) |
| Rhinitis | 6 (4%) | 12 (4%) | 10 (4%) |
| Upper Resp. Tract Infection | 8 (5%) | 11 (4 %) | 10 (4%) |
| Pharyngitis | 4 (3%) | 8 (3%) | 4 (1%) |
| Sinusitis | 4 (3%) | 7 (3%) | 6 (2%) |
| Pruritus Genital | 5 (3%) | 14 (5%) | 25 (9%) |
| Rash | 4 (3%) | 1 (0%) | 6 (2%) |
| Taste Perversion | 10 (7%) | 23 (9%) | 1 (0%) |
| Urine Abnormal | 6 (4%) | 7 (3%) | 4 (1%) |
| Urinary Tract Infection | 4 (3%) | 6 (2%) | 16 (6%) |

The most frequently reported adverse events were headache, yeast vaginitis, nausea and taste perversion. The incidence of headache is similar in the three groups (15% with the 5 days Flagyl MR, 18% with 7 days Flagyl MR and 15% with Cleocin). Vaginitis occurred in 11% and 15% of patients in the 5 day and 7 day Flagyl MR groups and 12% of patients in the Cleocin group. Nausea and taste perversion were the two most frequently reported adverse events related to Flagyl MR. The incidence of nausea was 15% and 10% for the five-day and seven-day Flagyl MR group, compared to 3% in the Cleocin group. Likewise, the incidence of taste perversion was 7% and 9% respectively in the two Flagyl MR groups and 0% in the Cleocin group. However, no patients withdrew from the study because of nausea and only patient withdrew from the study because of taste perversion.

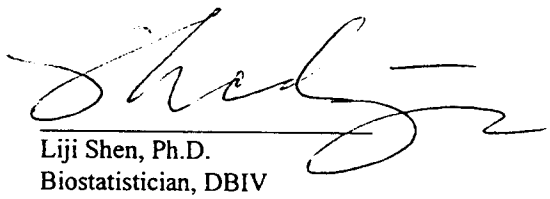
Two other adverse events, the incidence of which was not equally distributed across all three treatment groups, were genital pruritis and perineal pain. Genital pruritus was noticed in 9% of the Cleocin group, compared to only 3% and 5% in the 5 day and 7 day Flagyl MR groups respectively. Perineal pain was present in 6% of Cleocin treated

patients compared to 0% and 2% of the 5 day and 7 day Flagyl MR treated patients, respectively.

5. Statistical Reviewer's Overall Assessment and Conclusion

Based on the applicant's analysis and the Medical Officer's evaluation, the treatment of Flagyl MR ® by 7 days demonstrates statistically significantly higher cure rate than treatment by Cleocin for 7 days in Study 017 and is shown therapeutically equivalent to Cleocin in Study 015. (Tables 2, 8 and 9) However, The superiority of Flagyl MR ® is mainly driven by the one of three criteria in the assessment of cure, pH value. If pH values are taken out of requirement in assessing response of cure, Flagyl MR ® does not show statistically significantly higher cure rates than Cleocin and two treatments are equivalent if judged by the 95% confidence intervals in Tables 6.

The safety profile of Flagyl MR ® is very comparable to Cleocin ®. The most frequently reported adverse events were headache, yeast vaginitis, nausea and taste perversion.



Liji Shen, Ph.D.
Biostatistician, DBIV

Concur: Alaka Chakravarty 11/24/97
Alaka Chakravarty, Ph.D.
Acting Team Leader, DBIV

cc:
Archival: NDA 20-868
HFD-590
HFD-590/Dr. Winfield
HFD-590/Dr. Leissa
HFD-590 Dr. Albrecht
HFD-725/Dr. Chakravarty
HFD-725/Dr. Shen
HFD-725/Dr. Huque
HFD-725/Chron.
HFD-590/Dr. Goldberger
HFD-590/Ms.Fogarty
This review contains 9 pages.

APPEARS THIS WAY
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# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** 020868

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**Clinical Pharmacology/Biopharmaceutics Review**

| | |
|---|---|
| **NDA:** 20,868 | **Submission Dates:** 5/29/97, 10/27/97 |
| **Generic Name, Strength and Formulation:** (MR) Tablet | Metronidazole 750 mg Modified Release |
| **Brand Name:** Flagyl(TM) MR | **Date Assigned:** 6/16/97 |
| **Applicant:** G.D. Searle & Co. | **Final Review:** 11/24/97 |
| **Submission Code:** 3S | **Reviewer:** Kofi A. Kumi, Ph.D. |

**SYNOPSIS:**

The applicant submitted a new drug application (NDA) for Metronidazole 750 mg Modified Release (Flagyl(TM) MR) tablet for the treatment of symptomatic and asymptomatic women with bacterial vaginosis (BV). Metronidazole is a synthetic antiprotozoal and antibacterial agent that has been used for over 30 years. The oral formulations of Flagyl currently approved are 250, 375 and 500 mg immediate release (IR) tablets and are currently indicated for treatment of trichomoniasis, amebiasis and anaerobic bacterial infections. Metronidazole is also commercially available as an injectable solution, topical gel and cream.

In NDA 20,868 under section VI, the applicant resubmitted the same pivotal pharmacokinetic studies (Protocol S13-94-02-003, Report S13-95-06-003; Protocol S13-94-02-014, Report S13-95-06-014). In addition to the pivotal studies, the applicant submitted single dose pilot studies (Protocols S13-91-02-002 and S13-92-02-011) comparing the bioavailability from Flagyl(TM) 250 mg immediate release (IR) tablets with different formulations of Flagyl(TM) MR 750 mg

containing Based on the results of these pilot studies, . These pilot formulation development bioavailability studies were not reviewed. Also in this application, efficacy and safety studies were submitted to section VIII.

This reviewer agrees with the conclusions Dr. Pelsor reached in his review and supports the comments and recommendations made by him

**DISSOLUTION:**

**COMMENTS (To be forwarded to Sponsor):**
The following comments (#2 and 3 from Dr. Pelsor's original review) should be forwarded to the sponsor.

1. The dissolution method and specification recommended under the dissolution section should be incorporated into the manufacturing and controls specification for Flagyl MR 750mg.

2. The applicant should determine if the changes during dissolution testing.

3. The applicant is encouraged to evaluate the in vitro dissolution data and in vivo bioavailability data in their database to determine if there is a correlation. This information could be useful to evaluate SUPAC changes later.

**LABELING COMMENTS:**

The clinical pharmacology and dosage and administration sections of the label are recommended to be revised as follows:

**CLINICAL PHARMACOLOGY**

*Pharmacokinetics:*

Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of 8 hours. The major route of elimination of metronidazole and its metabolites is via the urine (60% to 80% of the dose), with fecal excretion accounting for 6% to 15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 mL/min/1.73m$^2$.(1)
Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the 2-hydroxymethyl metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria and *in vitro* trichomonacidal activity. Metronidazole appears in cerebrospinal fluid, saliva, and human milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.
Flagyl ER 750 mg Tablets contain 750 mg of metronidazole in an extended release formulation which allows for once-daily dosing. The steady state pharmacokinetics were *determined* in 24 healthy adult female subjects *with a mean±SD age of 28.8 ±8.8 (range: 19-46). The pharmacokinetic parameters of metronidazole after administration of Flagyl ER 750 mg under fed and fasting conditions are summarized in the following table.*

Pharmacokinetic Parameters of Metronidazole after Administration of Flagyl ER 750 mg Daily for 7 days

| Parameter | Flagyl ER 750 mg daily (fed) | Flagyl ER 750 mg daily (fasted) |
|---|---|---|
| | Mean ±SD (N=24) | |
| AUC(0-24)(μg*hr/mL) | 211±60.0 | 198±75.3 |
| Cmax (μg/mL) | 19.4±4.7 | 12.5±4.8 |
| Cmin (μg/mL) | 3.4±2.0 | 4.2±2.2 |
| Tmax (hrs) | 4.6±2.4 | 6.8±2.8 |
| T ½ (hrs) | 7.4±1.6 | 8.7±2.2 |

The rate of metronidazole absorption from the extended release tablet, under fasting conditions, *is* significantly decreased compared to fed conditions.

**DOSAGE AND ADMINISTRATION**

In elderly patients, the pharmacokinetics of metronidazole may be altered and therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

*Flagyl ER 750 mg tablets should be taken under fasting conditions, at least one hour before or two hours after meals.*

RECOMMENDATION:

The pharmacokinetic studies submitted under the Human Pharmacokinetics and Bioavailability Section of NDA 20,868 to fulfill sections 320 and 201.5 of 21 CFR demonstrated that the bioavailability of metronidazole from a single Flagyl ER 750 mg tablet or an every day regimen is not equivalent to the bioavailability of metronidazole from an equivalent dose of Flagyl 250 mg tablets or Flagyl 250 mg tablets every 8 hours, respectively. However, the studies have provided an understanding of the pharmacokinetics of Flagyl ER 750 mg and support a recommendation for approval if the clinical studies demonstrate that this dosing regimen is safe and efficacious for the treatment of the indication being sought.

11/24/97

Kofi A. Kumi, Ph.D.
Pharmacokinetics Reviewer (HFD 590)
Division of Pharmaceutical Evaluation III

Concurrence: 11/24/97

Funmi Ajayi, Ph.D.
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|---|---|---|
| CC: | HFD-590 | NDA: 50,740 |
| | | /MO/JWinfield |
| | | /PM/PFogarty |
| | HFD-340 | /Viswanathan |
| | HFD-880 | /TLDPEIII/FAjayi |
| | | /DPEIII/KKumi |
| | | /DPEIII Files ✓ |
| | CDR | /B.Murphy ✓ |

file:WP6.1/data/kumiwp/flagyl/overall
draft 1: 11/18/97

APPEARS THIS WAY
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# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020868

## ADMINISTRATIVE DOCUMENTS

## PATENT STATEMENT UNDER 21 CFR 314.53

Drug Product (Formulation) Patent

At this time there are no issued patents which claim the drug product that is the subject of this application. However, the following U. S. Patent Application contains allowed claims directed to formulation/dosage forms of the metronidazole product which is the subject of the present application:

| Patent Application Serial Number | Owner | Title | Expiration |
|---|---|---|---|
| 08/187,568 | G. D. Searle & Co. | Modified Release Metronidazole Compositions and Methods for Making and Using Same | |

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The undersigned declares that the above patent application has been allowed by the U. S. Patent and Trademark Office and contains claims that cover formulation/dosage forms of the metronidazole product which is the subject of this application for which approval is being sought. The patent number and expiration date will be submitted upon issuance of the patent by the U. S. Patent and Trademark Office.

Patent Owner

The undersigned certifies that the above listed U. S. Patent Application is assigned to G. D. Searle & Co.

EXCLUSIVITY SUMMARY for NDA # 20-868 SUPPL # _____

Trade Name FLAGYL® ER Generic Name metronidazole Extended Release Tablets 750 MG

Applicant Name G.D. Searle & Co. HFD-590

Approval Date November 26, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

APPEARS THIS WAY
ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 12-623 (Flagyl metronidazole) 250 500 tablets. _____

NDA # 20-334 (Flagyl metronidazole) 375 tab. _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 13-95-02-015

Investigation #2, Study # 13-95-02-017

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # 13-95-02-015

Investigation #__, Study # 13-95-02-017

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /X/ NO /___/ Explain: _____

Investigation #2

IND # YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____

Signature
Title: Regulatory Project Manager

11/26/97
Date

Signature of Division Director

12/2/97
Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

## CLAIMED PRODUCT EXCLUSIVITY - UNDER 21 CFR 314.50(j)

The present applicant, G. D. Searle & Co. is claiming exclusivity under 21 CFR §314.50(j) for the metronidazole sustained release product which is the subject of the present application.

New Clinical Investigations:

The undersigned certifies that to the best of applicant's knowledge that each of the clinical investigations included in the present application meets the definition of "new clinical investigation" set forth in §314.108(a).

Essential to Approval:

The undersigned certifies that the applicant has thoroughly searched the scientific literature and, to the best of applicant's knowledge, there are no published studies or publicly available reports of clinical investigations regarding the indications of the treatment of asymptomatic and symptomatic women with bacterial vaginosis for a sustained release product containing the active ingredient metronidazole. The clinical studies contained in the application were determined to be essential to approval of the metronidazole sustained release product.

Conducted or Sponsored by:

The undersigned certifies that the applicant was the sponsor named in the Form FDA-1571 for an investigational new drug application under which the new clinical investigations which are essential to approval were conducted.

**PEDIATRIC PAGE**

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA#**20-868** Supplement#_____Circle one:SE1 SE2 SE3 SE4 SE5 SE6

**HFD-590** Trade and generic names/dosage form : **FLAGYL®ER (metronidazole extended release tablets) 750 mg** Action: AP AE NA

Applicant **G.D. Searle & Co** Therapeutic Class **3/S**

Indication(s) previously approved_____
Pediatric information in labeling of approved indication(s)is adequate_
inadequate_

Indication in this application **Bacterial Vaginosis (BV)** (For supplement answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

   a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

   b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

   c. The applicant has committed to doing such studies as will be required.

      (1) Studies are ongoing,

      (2) Protocols were submitted and approved.

      (3) Protocols were submitted and are under review.

      (4) If no protocol has been submitted, attach memo describing status of discussions.

   d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. X **If none of the above apply,** attach an explanation, as necessary.

**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS. AS NECESSARY.**

**Safety and effectiveness in this dosage form of metronidazole in pediatric patients have not been established.**

Regulatory Project Manager.
Signature of Preparer and Title

November 26, 1997
Date

cc: Orig (NDA) PLA/PMA# 20-868
HFD/Div File
NDA/PLA Action Package
HFD-006/SOlmstead (plus, for CDER/CBER APs and Aes, copy of action letter and labeling)
**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.(revised)**

APPEARS THIS WAY
ON ORIGINAL

## DEBARMENT CERTIFICATION

Pursuant to section 306 (k) of the Federal Food, Drug and Cosmetic Act, the applicant did not and will not use in any capacity the services of any person disbarred under subsection (a) or (b), in connection with this application.

APPEARS THIS WAY
ON ORIGINAL