

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050680/S002

MEDICAL REVIEW(S)

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MEDICAL OFFICER'S REVIEW OF SUPPLEMENT 002 TO NDA 50-680

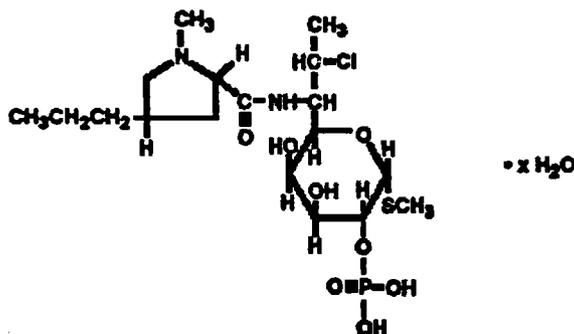
APPLICANT: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001-0199

GENERIC NAME: Clindamycin phosphate vaginal cream

TRADE NAME: Cleocin® Vaginal Cream

CHEMICAL NAME: methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo- α -D-galacto-octopyranoside 2-(dihydrogen phosphate).

CHEMICAL STRUCTURE:



MOLECULAR FORMULAR: C₁₈ H₃₄ ClN₂O₈ PS

MOLECULAR WEIGHT: 504.96

PHARMACOLOGIC CATEGORY : Anti-bacterial

DOSAGE FORM: Vaginal Cream

ROUTE OF ADMINISTRATION: Vaginal

PROPOSED INDICATION AND USAGE: Cleocin Vaginal Cream 2%, is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis or anaerobic vaginosis). Cleocin Vaginal Cream 2%, can be used to treat non-pregnant women and pregnant women during the second and third trimester.

PROPOSED DOSAGE AND ROUTE OF ADMINISTRATION: The recommended dose is one applicatorful of clindamycin phosphate vaginal cream 2%. (5 grams containing approximately 100 mg of clindamycin phosphate) intravaginally, preferably at bedtime, for three or seven consecutive days in non-pregnant patients and for seven consecutive days in pregnant patients.

RELATED DRUGS: IND:
NDAs 50-600, 50-615, 50-680

MATERIAL REVIEWED: 8 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[1,2]. It causes significant patient discomfort and has been implicated in several gynecologic diseases and obstetrical 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. Although generally regarded as a mild, non-life-threatening condition, treatment is recommended if symptoms are present[3,4].

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 [5]. The etiology of bacterial vaginosis (BV) is thought to be the result of a replacement of the normal, hydrogen peroxide-producing 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 bacteria-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 [6]. 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 [7], 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 [8] 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 [8,9]. 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. [10]. The "whiff" test for volatile amines has been described as a powerful predictor of BV by some, [8,11] but Eschenbach [7] 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 [7] found that the presence of clue cells correlated most highly with Gram stain criteria for BV.

Clindamycin is active against the organisms commonly associated with bacterial vaginosis: namely *Bacteroides* spp., *Peptococcus* spp., *Gardnerella vaginalis*, *Mobiluncus* spp., and *Mycoplasma hominis* [12]. The development of clindamycin as an intravaginal preparation was prompted by an investigator in the early 1980s who was searching for an effective topical therapy for the treatment of BV and treated 10 women with a 1% clindamycin cream administered twice daily. There was marked improvement or cure in all 10 patients. In 1988, another study reported that oral clindamycin hydrochloride 300 mg twice daily for 7 days was effective in the treatment of bacterial vaginosis.

Following these uncontrolled clinical experiences, the Upjohn Company initiated dose finding studies to determine the most appropriate concentration and frequency of administration for clindamycin in treating BV. These studies indicated that efficacy improved as the clindamycin concentration increased, and the once daily administration appeared to be comparable to twice daily administration. Therefore, clinical studies were designed to use 2% clindamycin cream administered once daily at bedtime for 7 days.[13,14,15,16].

NDA 50-680 provided the results of four Phase III efficacy and safety clinical trials which was the basis for approval of the 2% Clindamycin Vaginal Cream once-a-day dosage for the 7 day treatment for bacterial vaginosis and was approved in August, 1992. Supplement 001 to NDA 50-680 presented data from clinical trials that used the 2% Clindamycin vaginal cream once daily for 7 days in second trimester pregnant patients

and was the basis for its approval in October, 1995 for use in second trimester of pregnancy.

The Applicant is of the opinion that the treatment of bacterial vaginosis could be shortened to a 3-day regimen using clindamycin vaginal cream 2% which would potentially improve compliance and decrease the adverse events without decreasing efficacy. To support this hypothesis, the Upjohn company submitted Supplement 002 to NDA 50-580 that presented data from three Phase III clinical studies. Two of these studies (0021 and 0027) were placebo-controlled, randomized, double blind clinical trials that were conducted in the United Kingdom and compared a 3-day treatment with 2% clindamycin vaginal cream to placebo cream. A third study (0020) was an observer-blinded, controlled, multicenter study conducted in the United States and compared the 3-day treatment to the 7-day treatment. Efficacy results of studies are shown below.

	Clinical Cure Rates For Evaluable Patients					
	Clinical Cures Assessed By Applicant			Clinical Cures Assessed By Medical Officer		
	Cleocin	Placebo	Corrected 95% CI	Cleocin	Placebo	Corrected 95% CI
Study 0021	13/18 (72%)	2/9 (22%)	8, 92	12/18 (67%)	0/20 (0%)	40, 94
Study 0027	30/56 (54%)	1/41 (2%)	38, 69	38/71 (54%)	4/88 (5%)	35, 63
	Cleocin-3	Cleocin-7		Cleocin-3	Cleocin-7	
Study 0020*	94/131 (72%)	110/128 (86%)	-25, -4	124/167 (74%)	139/161 (86%)	-21, -3

*Cure defined as absence of clue cells and amine odor

In that supplemental application, the results from studies 0021 and 0027 which compare the shortened 3-day clindamycin phosphate cream 2% regimen to a placebo control demonstrated that the clindamycin cream regimen was superior to placebo.

However in Study 0020 which compared the shortened 3-day clindamycin phosphate vaginal cream 2% regimen to the standard 7-day clindamycin phosphate vaginal cream 2% regimen, the results obtained from the analyses of this study indicated that the 3-day clindamycin phosphate vaginal cream 2% regimen was statistically inferior to the 7-day regimen in the treatment of patient with BV. In addition, there was no statistical significant safety advantage observed with the shorter 3-day therapy when compared to the 7-day regimen.

The Applicant was advised on May 7, 1996 that Supplement 002 was "not approvable" for failure of the 3-day regimen of clindamycin vaginal cream 2% to demonstrate clinical and statistical equivalence to the 7-day regiment of clindamycin vaginal cream 2%. In response to the non-approval letter, the applicant agreed to conduct another study (0048)

that compared the 3-day regimen to the 7-day regimen in order to prove that the 3 day treatment was equivalent to the 7 day regimen..

Rationale for 3-Day Therapy

Clindamycin vaginal cream 2% is currently an approved treatment regimens for bacterial vaginosis as a once daily dose for 7 days. The Applicant states that improved compliance and convenience to the consumer can be obtained with a shorter course of therapy (3-days) thereby improving efficacy and decreasing the likelihood of adverse effects associated with systemic clindamycin administration

Clinical Study M/1115/0048

In an attempt to obtain approval for the use of once daily dosing of clindamycin vaginal cream 2% for 3 days in the treatment of BV, the applicant conducted a multicenter clinical trial under Protocol M/1115/0048 at 36 sites in Europe which compared the safety and efficacy of a 3-day treatment with a 7-day treatment of clindamycin vaginal cream 2%. This review will present the results of this clinical study as determined by the Applicant and the Reviewing Medical Officer.

Study Objectives

The Applicant states that the primary objective of the study was to determine if a 3-day regimen of clindamycin vaginal cream given once daily in therapeutically equivalent to a 7-day regimen given once daily in the treatment of BV. Secondary objectives included comparing the two regimens in the prevention of recurrence of BV after the successful treatment.

Study Design

This was a double-blind, multicenter, prospective, randomized study which compared a 3-day treatment regimen of clindamycin vaginal cream to a 7-day treatment regimen of clindamycin vaginal cream 2% in women with a diagnosis of Bacterial Vaginosis (BV). Patients were enrolled in a randomly assigned, 1:1 ratio per center to receive one of two treatment regimens:

Regimen A: Clindamycin phosphate vaginal cream (5g), inserted intravaginally, at bedtime, for 3 consecutive days, and matching placebo cream (5g), inserted intravaginally, at bedtime, for the next 4 days.

Regimen B: Clindamycin phosphate vaginal cream (5g), inserted intravaginally, at bedtime, for 7 consecutive days.

In this clinical trial, a diagnosis of bacterial vaginosis required all of the following criteria:

- a. Presence of an increased thin, homogenous, malodorous vaginal discharge.
- b. vaginal fluid pH >4.5;
- c. "fishy" amine odor after adding 10% KOH to vaginal fluid;
- d. "clue cells" in vaginal fluid on microscopic examination.

Patients were to have a pretreatment evaluation and three follow-up visits at Day 10, Day 30, and Day 90 after the start of study medication to assess resolution of BV and onset of recurrence. At the pretreatment examination, a pelvic examination and other tests were performed to determine study eligibility. These included determination of vaginal fluid pH, description of vaginal discharge, smear for clue cells, test of vaginal fluid for "fishy odor", and tests for microbial pathogens. At each follow-up visit, patients had a vulvovaginal assessment and tests to determine the presence of BV or concomitant illness. An assessment of medical events and concomitant medications was also completed.

Study Population

A total of 581 women who met the criteria for bacterial vaginosis (BV) was randomized to receive treatment with clindamycin vaginal cream (CVC) either for 3 days (288) or 7 days (293). Records of 47 randomized patients (27 in the CVC 3-day group and 20 in the CVC 7-day group) showed no evidence that study medication had been received. Therefore safety and efficacy analyses in this review will be based on a modified intent-to-treat population. Safety evaluation will be performed on all enrolled patients for whom there was either evidence of receipt of study medication or a record of post-baseline safety data. Efficacy evaluations will be performed on evaluable subgroups as determined by the Applicant and the Medical Officer as follows:

1. Patients who are determined to be evaluable based on the four diagnostic criteria as specified in the protocol
2. Patients who are determined as evaluable based on "clue" cells and odor as requested by the FDA.

Inclusion Criteria

Patients were included in the study if they were between the ages of _____ had a clinical diagnosis of BV according to the four criteria listed above, were using a medically recognized method of contraception (if of child-bearing potential), not menstruating and were capable of giving written informed consent.

Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

- Allergy to clindamycin or excipients of the cream.
- Pregnancy or breast feeding.
- Systemic or vaginal antimicrobial therapy within two weeks prior to study.
- Previous enrollment into this study.
- Positive culture for *Neisseria gonorrhoea*, *Candida albicans*, *Chlamydia trachomatis* or positive wet mount for *Trichomonas vaginalis*.
- Clinical evidence of genital Herpes virus infection
- A history of antibiotic-associated colitis, inflammatory bowel disease or frequent periodic diarrhea

Efficacy Determinations

In the Applicant's analyses, clinical efficacy was to be evaluated at the first follow-up visit (Day 10), while the incidence of recurrence of BV was to be evaluated at the second and third follow-up visits (Days 30 and 90) base on the clinical diagnostic criteria for BV as described in the protocol. Since the "Test of Cure" is based on the outcome of clinically evaluable patient at the 30 day follow-up visit, in this review only the results of the clinical outcome at the 30 day follow-up as determined by the Applicant and the Medical Officer will be considered as primary for determining efficacy of the 3-day treatment with clindamycin vaginal cream compared to the approved 7-day treatment.

Efficacy Analyses by Applicant

The primary efficacy measure as defined in the original protocol was derived based on clinical diagnostic criteria rather than the investigator assessment. The primary efficacy measure was clinical status (cured, improved, failed [recurred], or non-assessable at Day 30 for patients who were cured/improved at Day 10. Between-treatment comparisons at Day 30 were also measured carrying forward patients who had failed at Day 10. Clinical status was determined using the following four clinical diagnostic criteria: pH (resolved when ≤ 4.5 , failed when > 4.5), amine odor (resolved when absent, failed when present), clue cells (resolved when absent, failed when present), and thin vaginal discharge (resolved when absent, failed when present). Patients with resolution of at least 3 of the four criteria at the Day 30 were considered improved; those with resolution of fewer than three of the criteria at the Day 30 follow-up visit were considered failed (recurred). Outcome was considered non-assessable in the absence of adequate data to categorize an outcome as cured, improved or failed (recurred).

At the recommendation of the FDA, the Applicant also analyzed the overall clinical outcome at the Day 30 visit using clue cells and amine odor only as the only criteria in evaluation of clinical status. This recommendation was based on evidence that the

presence of clue cells plus the presence of amine odor more accurately predict BV (with about 98% accuracy) than vaginal fluid pH. Additionally, from a clinical perspective, patients would not be considered to have failed treatment or need further treatment if pH were the only abnormal diagnostic criterion observed. Resolution of both clue cells and amine odor at Day 10 and Day 30 was considered a cure, the absence of resolution of either clue cells or amine odor at either follow-up visit was considered a failure.

Clinical Assessment Based on All Four Criteria By Applicant

VISIT AT 10 DAYS	VISIT AT 30 DAYS	OVERALL OUTCOME
Cure	Cure	Cure
Improved	Improved	Improved
	Failed	Failed
Failed	Failed	Failed

Clinical Assessment Based on Clue Cells and Amine Odor By Applicant

VISIT AT 10 DAYS	VISIT AT 30 DAYS	OVERALL OUTCOME
Cure	Cure	Cure
Failed	Failed	Failed

Efficacy Analyses By Medical Officer

In the Medical Officer analyses, the primary efficacy end-point was performed on two groups of evaluable patients as was done in the Applicants analyses, however those patients that were considered as improved in the Applicants analyses were assessed as cures or failures by the medical officer. In the first determination of outcome by the medical officer, cures were considered as those evaluable patients at 30 day follow-up whose vaginal secretions had a pH of 4.7, the absence of clue cells and amine odor. All patients at the 30 day follow-up visit were reclassified as either a cure or a failure. There was no improved category in the Medical Officer analyses.

The medical officer also analyzed the overall clinical outcome at the Day 30 visit using the clue cells and amine odor as the endpoints for determining cure .

The outcome at the Day 30 follow-up visit as determined by the Applicant and the Medical Officer using both analyses as stated above is found in the Efficacy Results section of this review.

Safety Analyses

Safety analyses were performed on all randomized patients who had a recorded dosing start date or who had completed Day 10 follow up All safety data were reported by the Applicant and reviewed by the Medical Officer. Medical Events (MEs) and non-

investigational medication reports were used to assess safety. The medical event reporting period for the study began immediately after the first dose of investigational medication and ended at the final clinic visit.

A medical event (ME) was any untoward medical occurrence that happened during the protocol-specified medical event reporting period, regardless of whether it was considered related to a medication. In addition, any known untoward event that occurred subsequent to the medical event reporting period that the investigator assessed as possibly related to the investigational medication was considered a ME.

The investigator was to report all directly observed MEs and all MEs spontaneously reported by the study patient. Each study patient was questioned about MEs at each clinic visit after initiation of treatment. Each ME was to be classified by the investigator as serious or nonserious. The investigator was to use the adjectives mild, moderate, or severe to describe the maximum intensity of the ME. For purposes of consistency, these intensity grades were defined as follows:

- *Mild*: Does not interfere with patient's usual function
- *Moderate*: Interferes to some extent with patient's usual function
- *Severe*: Interferes significantly with patient's usual function

Serious medical events were defined as those that were fatal or life-threatening (i.e., resulted in an immediate risk of death); were permanently or substantially disabling; required or prolonged hospitalization; were any congenital anomaly, cancer, or medication overdose, or were judged by the investigator or monitor to be serious or suggestive of a significant hazard, contraindication, side effect, or precaution.

Investigators

A total of 36 investigators located in several European countries participated in this clinical study. Each investigator appears to be well qualified to conduct the investigation according to the protocol. A list of all investigators and study sites is located in Table 1..

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Table 1

List of Investigators and Study Sites

Dr. I Ahmed MB, ChB, MRCP, FRCP UNITED KINGDOM	Prof S Papp, PhD, MD, DSc HUNGARY
Prof U. Beller, MD ISRAEL	Dr E Pauwells, MD BELGIUM
J. Bornstein, MD ISRAEL	Prof J Peterek, PhD, MD POLAND
W. Brach, MD GERMANY	Dr. E. Peterson, MD GERMANY
Prof J Branco, MD PORTUGAL	Dr. J. Platz-Christensen, MD SWEDEN
Prof H. Cronje, BSc., MD SOUTH AFRICA	Prof V Prilepskaya, MD RUSSIA
Dr. V. Cupanik, PhD, MD SLOVAK REPUBLIC	Dr. P. Rosendranz, MD GERMANY
Dr. S Damm, MD SWEDEN	Prof A Schaetzing, PhD, MD FCOG, FRCOG, MRCOG SOUTH AFRICA
Prof J De Oliveira, MD PORTUGAL	Dr H Schmidt, MD DENMARK
Prof S Gardo, PhD, MD, DSc HUNGARY	Dr P. Schwaner, MD GERMANY
Dr. P Hay, MB, BS, MRCP UNITED KINGDOM	Dr M Shahmanesh, MB, BS, FRCP, MRCP, MRCS UNITED KINGDOM
Dr. K. Larkio-Miettinen, MD UNITED KINGDOM	Dr S. Sik, MD CZECHOSLOVAKIA REPUBLIC
Dr P. Larsson, PhD, MD. SWEDEN	Prof J. Stelmachow, PhD, MD POLAND
Dr P. Liukko, MD FINLAND	Prof I Szabo, PhD, MD HUNGARY
Dr P. Matthews, MB, ChB SOUTH AFRICA	Prof A Szczurowicz, PhD, MD, DSc POLAND
Prof J. Moodley, MD SOUTH AFRICA	Dr D. Tavares, MD, MS PORTUGAL
Dr P. Nel, Mpharm, MED, MD SOUTH AFRICA	Prof E. Vadora, MD ITALY
Dr B Norling, MD NORWAY	DR P Vosta, MD CZECHOSLOVAKIA REPUBLIC

Results

Objective: The objective of this study was to evaluate the efficacy and safety of a 3-day treatment of clindamycin vaginal cream 2% compared to a 7-day treatment of clindamycin vaginal cream 2% in patients with a clinical diagnosis of bacterial vaginosis.

Demographics

A total of 534 patients were randomized and received at least one dose of study drug, 261 in the 3-day clindamycin vaginal cream 2% group and 273 in the 7-day treatment group. There were no statistically significant differences between treatment groups with respect to demographics and baseline characteristics (age, weight and race). For all randomized patients, the mean age was 34.9 years, the mean weight was 62 kg. Approximately 87% of the patient were Caucasian, 10% were black, 2% Oriental/Asian and 1% other. See Table 2 below.

Table 2

**Demographics and Baseline Characteristics
Patient who Received At Least One Dose of Study Medication**

VARIABLE	STATISTIC	CVC 3-DAY	CVC 7-DAY	TOTAL
Age	N	261	273	534
	Median	34.0	35.0	34.0
	Mean	34.7	35.1	34.9
	Std Dev	9.4	10.2	9.8
	Min			
	Max			
Weight	N	261	273	534
	Not Reported	6	5	11
	Median	60.60	61.00	61.00
	Mean	62.32	62.89	62.61
	Std Dev	9.49	10.11	9.81
	Min			
	Max			
Race	N	261	272	533
	Not Reported	0	1	1
	Caucasian	226	240	466
	Black	28	26	54
	Oriental/Asian	5	2	7
	Other	2	4	6

Evaluable Patients

Clinically evaluable patients were those who met all of the criteria as described previously. In the Applicant's analyses, the evaluable population consisted of 420

patients : 70% (202/288) in the clindamycin vaginal cream 3-day group and 74% (218/293) in the 7-day treatment group. In the Medical Officer's analyses , the evaluable population consisted of 452 patients: 76% (219/288) in the 3-day treatment group and 79% (232/293) in the 7-day treatment group. There was no statistical significant difference among the evaluable patients as determined by the Applicant and the Medical Officer in the two treatment groups. Tables 3 and 4.

Table 3
Evaluable Patients Clindamycin Vaginal Cream 3-Day

Investigator	Number Enrolled	Applicant #Eval (%)	Medical Off #Eval (%)
Ahmed	4	1 (25)	0
Beller	2	0	0
Bornstein	9	6 (67)	5 (55)
Brach	10	9 (90)	10 (100)
Branco	0	0	0
Cronje	5	3 (60)	4 (80)
Cupanik	3	3 (100)	3 (100)
Damm	10	7 (70)	9 (90)
Gardo	8	6 (75)	6 (75)
Hay	6	0	1 (17)
Larkio-Miettinen	20	15 (75)	15 (75)
Larsson	9	7 (78)	7 (78)
Liukko	3	2 (66)	2 (66)
Mathews	8	7 (88)	7 (88)
Moodley	12	7 (58)	8 (66)
Nel	14	11 (79)	11 (79)
Norling	8	5 (63)	6 (75)
Oliveira	6	3 (50)	3 (50)
Papp	9	9 (100)	9 (100)
Pauwels	0	0	0
Peterek	10	10 (100)	10 (100)
Peterson	6	4 (67)	6 (100)
Platz-Christensen	10	8 (80)	9 (90)
Prilepskaya	10	7 (70)	7 (70)
Rosenkranz	12	9 (75)	11 (92)
Schaetzing	3	2 (66)	2 (66)
Schmidt	14	9 (64)	11 (79)
Schwaner	12	9 (75)	11 (92)
Shahmanesh	10	1 (10)	3 (30)
Sik	10	7 (70)	7 (70)
Stelmachow	10	8 (80)	9 (90)
Szabo	4	3 (75)	4 (100)
Szczurowicz	10	10 (100)	7 (70)
Tavares	10	5 (50)	6 (60)
Vadora	1	1 (100)	1 (100)
Vosta	10	8 (80)	9 (90)
All Investigators	288	202 (70)	219 (76)

Table 4
Evaluable Patients Clindamycin Vaginal Cream 7 Day

Investigator	Number Enrolled	Applicant # Eval (%)	Medical Off #Eval (%)
Ahmed	2	1 (50)	1 (50)
Beller	1	0	0
Bornstein	10	7 (70)	7 (70)
Brach	10	8 (80)	9 (90)
Branco	1	0	0
Cronje	6	1 (16)	1 (16)
Cupanik	2	1 (50)	1 (50)
Damm	10	6 (60)	8 (80)
Gardo	8	8 (100)	8 (100)
Hay	8	1 (13)	1 (13)
Larkio-Miettinen	20	15 (75)	17 (85)
Larsson	9	6 (66)	9 (100)
Liukko	4	3 (75)	4 (100)
Matthews	9	7 (78)	8 (88)
Moodley	11	7 (64)	7 (64)
Nel	14	12 (86)	13 (93)
Norling	7	5 (71)	5 (71)
Oliveira	7	4 (57)	3 (43)
Papp	9	8 (88)	8 (88)
Pauwels	2	1 (50)	1 (50)
Peterek	10	10 (100)	10 (100)
Peterson	6	6 (100)	6 (100)
Platz-Christensen	10	8 (80)	8 (80)
Prilepskaya	10	10 (100)	10 (100)
Rosenkranz	12	9 (75)	11 (92)
Schaetzing	2	0	0
Schmidt	13	8 (62)	10 (77)
Schwaner	12	10 (83)	10 (83)
Shahmanesh	11	7 (64)	7 (64)
Sik	12	11 (92)	10 (83)
Stelmachow	10	9 (90)	10 (100)
Szabo	3	3 (100)	3 (100)
Szczurowicz	10	9 (90)	7 (70)
Tavares	10	7 (70)	8 (80)
Vadora	1	0	1 (100)
Vosta	11	10 (91)	10 (91)
All Investigators	293	218 (74)	232 (79)

Non Evaluable Patients

In the Applicant's analyses, the most common primary reason for non-evaluability were failure to return within appropriate follow-up window (reported in 11%) of patients, study medication not being taken (8%) and dosing noncompliance (6%).

In the Medical Officer's analyses, the most common reasons for non-evaluability were lost to follow-up (13%) and failure to receive medication (8%).

The percentage of non-evaluable patients and the reasons for non-evaluability were similar in the analyses by the Applicant and the Medical Officer in each of the two treatment groups. Table 5

Table 5

Primary Reasons for Non-Evaluability at 30 Day Follow-up (Applicant Analyses)

PRIMARY REASON FOR NON-EVALUABILITY	NUMBER OF PATIENTS (% OF GROUP)		
	CVC 3-DAY (N = 288)	CVC 7-DAY (N = 293)	TOTAL (N = 581)
DID NOT RECEIVE ANY STUDY MEDICATION	27 (9.3)	20 (6.8)	47 (8.0)
DID NOT MEET INCLUSION/EXCLUSION CRITERIA	3 (1.0)	2 (0.6)	5 (0.9)
ADDITIONAL MICROBIAL THERAPY	7 (2.4)	6 (2.0)	13 (2.2)
DOSING NONCOMPLIANCE	22 (7.6)	10 (3.4)	32 (5.5)
FOLLOW-UP NOT WITHIN WINDOW	27 (9.3)	37 (12.6)	64 (11.0)
TOTAL	86 (29.9)	75 (25.6)	161(27.7)
Primary Reasons for Non-Evaluability at 30 Day Follow-up (Medical Officer's Analyses)			
DID NOT RECEIVE ANY STUDY MEDICATION	27 (9.3)	20 (6.8)	47 (8.0)
DID NOT MEET INCLUSION/EXCLUSION CRITERIA	3 (1.0)	2 (0.6)	5 (0.9)
LOST TO FOLLOW-UP	39 (13.5)	39 (13.3)	78 (13.4)
TOTAL	69 (23.9)	61 (20.8)	130 (22.4)

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Efficacy Results: The number of evaluable and cured patients as assessed by the Applicant and the Medical Officer is shown in Tables 8 and 9 for each treatment group.

Analyses Based on Four Diagnostic Criteria

A summary of treatment outcome at Day 30 for evaluable patients who were cured/improved at Day 10, as determined by the Applicant from tests of all four diagnostic criteria, is shown in Table 6.

Table 6

**Clinical Status at Day 30 (Carrying Forward Failures) for Evaluable patients
Based on Four Diagnostic Criteria (By Applicant)**

Outcome at Day 30	Number of Patients ()% of Group		[95% CI]
	CVC 3-Day N = 202	CVC 7-Day N = 218	
Cured	136 (67.3)	145 (66.5)	- 9, 10
Improved	32 (15.8)	45 (20.6)	
Failed at Day 10	21 (10.3)	16 (7.3)	
Failed at Day 30	13 (6.4)	12 (5.5)	

In the Applicant analyses, patients who were improved at the day 30 visit were assessed as having a successful outcome. Therefore based on the analysis of data from evaluable patients who failed at Day 10 and carried forward to Day 30, 83.2% (168/202) of patients in the 3-Day group and 87.2% (190/218) of patients in the 7-Day group were cured or improved at Day 30. The difference between the two groups was not statistically significant (95% CI= -3.3, 11.3).

In the Medical Officer's analyses, 74% (162/219) in the 3-day treatment group and 73% (170/232) in the 7-day treatment group were assessed as cures. Table 7

Table 7

**Clinical Status at Day 30 (Carrying Forward Failures) for Evaluable patients
Based on Four Diagnostic Criteria (By Medical Officer)**

Outcome at Day 30	Number of Patients ()% of Group		[95% CI]
	CVC 3-Day N = 219	CVC 7-Day N = 232	
Cured	162 (74)	170 (73)	-8, 9
Failed at Day 30	57 (26)	62 (27)	

Table 8
Clindamycin Vaginal Cream 3 Day All Four Criteria
Patients Cured (%)

Investigator	Applicant #Eval	Applicant #Cured (%)	MO #Eval	MO # Cured (%)
Ahmed	1	0	0	0
Beller	0	0	0	0
Bornstein	6	1 (17)	5	2 (40)
Brach	9	7 (78)	10	8 (80)
Branco	0	0	0	0
Cronje	3	1 (33)	4	1 (25)
Cupanik	3	1 (33)	3	3 (100)
Damm	7	5 (71)	9	6 (66)
Gardo	6	6 (100)	6	6 (100)
Hay	0	0	1	1 (100)
Larkio-Miettinen	15	12 (80)	15	12 (80)
Larsson	7	3 (43)	7	3 (43)
Liukko	2	0	2	1 (50)
Matthews	7	2 (29)	7	2 (29)
Moodley	7	2 (29)	8	3 (38)
Nel	11	6 (55)	11	7 (64)
Norling	5	5 (100)	6	6 (100)
Oliveira	3	1 (33)	3	1 (33)
Papp	9	9 (100)	9	9 (100)
Pauwels	0	0	0	0
Peterek	10	10 (100)	10	10 (100)
Peterson	4	3 (75)	6	4 (66)
Platz-Christensen	8	5 (63)	9	6 (66)
Prilepskaya	7	5 (71)	7	6 (86)
Rosenkranz	9	9 (100)	11	11 (100)
Schaetzing	2	0	2	0
Schmidt	9	5 (55)	11	8 (73)
Schwaner	9	9 (100)	11	11 (100)
Shahmanesh	1	1 (10)	3	3 (30)
Sik	7	2 (29)	7	3 (43)
Stelmachow	8	8 (100)	9	9 (100)
Szabo	3	3 (100)	4	4 (100)
Szczurowicz	10	5 (50)	7	5 (71)
Tavares	5	3 (60)	6	4 (66)
Vadora	1	1 (100)	1	1 (100)
Vosta	8	6 (75)	9	6 (66)
All Investigators	202	136 (67)	219	162 (74)

Table 9

Clindamycin Vaginal Cream 7 Day All Four Criteria
Patients Cured (%)

Investigator	Applicant #Eval	Applicant #Cured (%)	MO Eval	MO # Cured (%)
Ahmed	1	1 (100)	1	1 (100)
Beller	0	0	0	0
Bornstein	7	1 (14)	7	1 (14)
Brach	8	6 (75)	9	8 (89)
Branco	0	0	0	0
Cronje	1	0	1	0
Cupanik	1	1 (100)	1	1 (100)
Damm	6	2 (33)	8	4 (50)
Gardo	8	6 (75)	8	7 (88)
Hay	1	1 (100)	1	1 (100)
Larkio-Miettinen	15	12 (80)	17	15 (88)
Larsson	6	3 (50)	9	7 (78)
Liukko	3	0	4	3 (75)
Matthews	7	3 (43)	8	4 (50)
Moodley	7	1 (14)	7	0
Nel	12	7 (58)	13	8 (62)
Norling	5	5 (100)	5	5 (100)
Oliveira	4	1 (25)	3	1 (33)
Papp	8	7 (88)	8	7 (88)
Pauwels	1	1 (100)	1	1 (100)
Peterek	10	10 (100)	10	10 (100)
Peterson	6	5 (83)	6	5 (83)
Platz-Christensen	8	4 (50)	8	5 (63)
Prilepskaya	10	9 (90)	10	9 (90)
Rosenkranz	9	9 (100)	11	11 (100)
Schaetzing	0	0	0	0
Schmidt	8	2 (25)	10	4 (40)
Schwaner	10	9 (90)	10	9 (90)
Shahmanesh	7	2 (29)	7	3 (43)
Sik	11	6 (55)	10	6 (60)
Stelmachow	9	8 (89)	10	9 (90)
Szabo	3	3 (100)	3	3 (100)
Szczurowicz	9	6 (66)	7	6 (86)
Tavares	7	5 (71)	8	5 (63)
Vadora	0	0	1	1 (100)
Vosta	10	9 (90)	10	10 (100)
All Investigators	218	145 (67)	232	170 (73)

Analyses Based on Amine Odor and Clue Cells Only

A summary of treatment outcome at Day 30 for evaluable patients who were cured at Day 10, as determined by the Applicant and Medical Officer using amine odor and clue cells as the only criteria for cure and failures at Day 10 being carried forward, is shown in Tables 10 and 11 respectively.

Table 10

**Clinical Status at Day 30 (Carrying Forward Failures) for Evaluable patients
Based on Amine Odor and Clue Cells Only (By Applicant)**

Outcome at Day 30	Number of Patients ()% of Group		[95% CI]
	CVC 3-Day N = 202	CVC 7-Day N = 218	
Cured	161 (80)	181(83)	-11, 5
Failed at Day 30	41 (20)	37 (17)	

Table 11

**Clinical Status at Day 30 (Carrying Forward Failures) for Evaluable patients
Based on Amine Odor and Clue Cells Only (By Medical Officer)**

Outcome at Day 30	Number of Patients ()% of Group		[95% CI]
	CVC 3-Day N = 219	CVC 7-Day N = 232	
Cured	189 (86)	205(88)	-9, 5
Failed at Day 30	30 (14)	27 (12)	

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A summary of the clinical outcome by investigator as assessed by the Applicant and the Medical officer for the 3-day and 7-day treatment regimens based on clue cells and odor is shown in tables 12 and 13 respectively.

Table 12

Clindamycin Vaginal Cream 3 Day Odor and Clue Cells
Patients Cured

Investigator	Applicant #Eval	Applicant #Cured (%)	MO #Eval	MO # Cured (%)
Ahmed	1	0	0	0
Beller	0	0	0	0
Bornstein	6	4 (66)	5	5 (100)
Brach	9	9 (100)	10	10 (100)
Branco	0	0	0	0
Cronje	3	2 (66)	4	4 (100)
Cupanik	3	3 (100)	3	3 (100)
Damm	7	7 (100)	9	9 (100)
Gardo	6	6 (100)	6	6 (100)
Hay	0	0	1	1 (100)
Larkio-Miettinen	15	12 (80)	15	12 (80)
Larsson	7	4 (57)	7	4 (57)
Liukko	2	2 (100)	2	2 (100)
Matthews	7	7 (100)	7	7 (100)
Moodley	7	4 (57)	8	5 (63)
Nel	11	6 (55)	11	7 (64)
Norling	5	5 (100)	6	6 (100)
Oliveira	3	0	3	1 (33)
Papp	9	9 (100)	9	9 (100)
Pauwels	0	0	0	0
Petek	10	10 (100)	10	10 (100)
Peterson	4	3 (75)	6	5 (83)
Platz-Christensen	8	7 (88)	9	8 (89)
Prilepskaya	7	6 (86)	7	6 (86)
Rosenkranz	9	9 (100)	11	11 (100)
Schaetzing	2	0	2	0
Schmidt	9	6 (66)	11	9 (82)
Schwaner	9	9 (100)	11	11 (100)
Shahmanesh	1	1 (100)	3	3 (100)
Sik	7	4 (57)	7	4 (57)
Stelmachow	8	8 (100)	9	9 (100)
Szabo	3	3 (100)	4	4 (100)
Szczurowicz	10	5 (50)	7	5 (71)
Tavares	5	2 (40)	6	4 (66)
Vadora	1	1 (100)	1	1 (100)
Vosta	8	7 (88)	9	8 (89)
All Investigators	202	161 (80)	219	189 (86)

Table 13
Clindamycin Vaginal Cream 7 Day Clue Cells and Odor
Patients Cured

Investigator	Applicant		MO	
	#Eval	#Cured (%)	#Eval	#Cured (%)
Ahmed	1	1 (100)	1	1 (100)
Beller	0	0	0	0
Bornstein	7	6 (86)	7	6 (86)
Brach	8	8 (100)	9	9 (100)
Branco	0	0	0	0
Cronje	1	1 (100)	1	1 (100)
Cupanik	1	1 (100)	1	1 (100)
Damm	6	2 (33)	8	5 (63)
Gardo	8	7 (88)	8	7 (88)
Hay	1	1 (100)	1	1 (100)
Larkio-Miettinen	15	13 (87)	17	16 (94)
Larsson	6	6 (100)	9	9 (100)
Liukko	3	2 (66)	4	3 (75)
Mathews	7	7 (100)	8	8 (100)
Moodley	7	4 (57)	7	4 (57)
Nel	12	7 (58)	13	8 (62)
Norling	5	5 (100)	5	5 (100)
Oliveira	4	1 (25)	3	1 (33)
Papp	8	7 (88)	8	7 (88)
Pauwels	1	1 (100)	1	1 (100)
Peterek	10	10 (100)	10	10 (100)
Peterson	6	5 (83)	6	5 (83)
Platz-Christensen	8	8 (100)	8	8 (100)
Prilepskaya	10	10 (100)	10	10 (100)
Rosenkranz	9	9 (100)	11	11 (100)
Schaetzing	0	0	0	0
Schmidt	8	4 (50)	10	8 (80)
Schwaner	10	10 (100)	10	10 (100)
Shahmanesh	7	4 (57)	7	4 (57)
Sik	11	8 (73)	10	8 (80)
Stelmachow	9	9 (100)	10	10 (100)
Szabo	3	3 (100)	3	3 (100)
Szczurowicz	9	7 (78)	7	7 (100)
Tavares	7	5 (71)	8	7 (86)
Vadora	0	0	1	1 (100)
Vosta	10	9 (90)	10	10 (100)
All Investigators	218	181 (83)	232	205 (88)

Safety results

The proportion of patients who reported at least one medical event (ME) was similar for the two treatment groups, with 30.7% (80/261) of patients in the CVC 3-day group experiencing at least one ME compared to 32.6% (89/273) in the CVC 7-day group (Table 15).

MEs affecting the urogenital system and the body as a whole were the most common MEs by body system for both treatment groups, and were reported in a similar percentage of patients in each treatment group (Table 14).

MEs are presented by body system and COSTART description in Table 15. Overall, the most common MEs reported were vaginal moniliasis, moniliasis, vulvovaginal disorder, and BV. These MEs were reported by 9%, 3.1%, 3.8%, and 2.7% of patients, respectively in the CVC 3-day treatment group and 8.8%, 4.8%, 3.7%, and 2.9% of patients respectively in the CVC 7-day treatment group.

In general, the percentage of patients reporting each event was small and was similar for the two treatment groups, with many events reported by only one patient in one or other of the treatment groups. A higher percentage of patients in the 3-day group reported MEs of generalized abdominal pain, headache, trauma, and upper respiratory tract infection than in the 7-day group, while menopause was more commonly reported for patients treated for 7 days than for 3-day patients.

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TABLE 14

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Medical Events by Body System
Patients who Receive at Least one Dose of Medication

BODY SYSTEM	CVC 3-DAY		CVC 7-DAY		TOTAL	
	N	%	N	%	N	%
BODY	34	13.0	29	10.6	63	11.8
CARDIOVASCULAR	3	1.1	2	0.7	5	0.9
DIGESTIVE	9	3.4	8	2.9	17	3.2
ENDOCRINE	1	0.4			1	0.2
HEMIC AND LYMPHATIC	1	0.4	1	0.4	2	0.4
MUSCULO-SKELETAL			3	1.1	3	0.6
NERVOUS			1	0.41	1	0.2
RESPIRATORY	4	1.5	3	1.1	7	1.3
SKIN	3	1.1	6	2.2	9	1.7
UROGENITAL	53	20.3	56	20.5	109	20.4
NUMBER OF PATIENTS ON WHICH % IS BASED	261		273		534	

TABLE 15

MEDICAL EVENTS BY BODY SYSTEM AND COSTART DESCRIPTION (MET)

BODY SYSTEM	COSTART DESCRIPTION (MET)	CVC 3-DAY		CVC 7-DAY		TOTAL	
		N	%	N	%	N	%
PATIENTS WITH NO MEDICAL EVENTS		181	69.3	184	67.4	365	68.4
PATIENTS WITH AT LEAST ONE MEDICAL EVENT		80	30.7	89	32.6	169	31.6
BODY	ABDOMINAL CRAMP			1	0.4	1	0.2
	ABDOMINAL PAIN GENERALIZED	4	1.5	1	0.4	5	0.9
	ABDOMINAL PAIN LOCALIZED	2	0.8			2	0.4
	ALLERGIC REACTION	1	0.4			1	0.2
	BACK PAIN	1	0.4	1	0.4	2	0.4
	ENVIRONMENTAL ALLERGY	1	0.4	1	0.4	2	0.4
	FEVER			1	0.4	1	0.2
	FLU SYNDROME	5	1.9	2	0.7	7	1.3
	HEADACHE	5	1.9	1	0.4	6	1.1
	INFECTION BACTERIAL NOS			1	0.4	1	0.2
	INFECTION PARASITIC NOS			1	0.4	1	0.2
	INFECTION VIRAL NOS			1	0.4	1	0.2
	INFLAMMATORY SWELLING			1	0.4	1	0.2
	LOCALIZED PAIN			1	0.4	1	0.2
	MICROBIOLOGICAL TEST ABNORMAL NOS	2	0.8	5	1.8	7	1.3
	MONILIASIS	8	3.1	13	4.8	21	3.9
	RECTION UNEVALUABLE	1	0.4	1	0.4	2	0.4
	TRAUMA	5	1.9			5	0.9
	UPPER RESPIRATORY INFECTION	3	1.1			3	0.6
CARDIOVASCULAR	HEMORRAGE	1	0.4			1	0.2
	HYPERTENSION			1	0.4	1	0.2
	MIGRAINE	2	0.8			2	0.4
	VASODILATATION			1	0.4	1	0.2
DIGESTIVE	CONSTIPATION			1	0.4	1	0.2
	DIARRHEA	2	0.8	3	1.1	5	0.9
	ENTERITIS			1	0.4	1	0.2
	ENTEROCOLITIS			1	0.4	1	0.2
	FLATULENCE	1	0.4			1	0.2
	GASTRITIS	1	0.4			1	0.2
	GASTROENTERITIS	2	0.8	2	0.7	4	0.7
	NAUSEA	2	0.8			2	0.4
	VOMITING	1	0.4			1	0.2
ENDOCRINE	HYPERTHYROIDISM	1	0.4			1	0.2
HEMIC AND LYMPHATIC	ANEMIA			1	0.4	1	0.2
	LYMPHADENITIS	1	0.4			1	0.2
MUSCULO-SKELETAL	FIBROSIS TENDINOUS			1	0.4	1	0.2
	MYALGIA			1	0.4	1	0.2
	MYOSITIS			1	0.4	1	0.2

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TABLE 15 CONTINUED
 MEDICAL EVENTS BY BODY SYSTEM AND COSTART DESCRIPTION (MET)

BODY SYSTEM	COSTART DESCRIPTION (MET)	CVC 3-DAY		CVC 7-DAY		TOTAL	
		N	%	N	%	N	%
NERVOUS	ANXIETY			1	0.4	1	0.2
RESPIRATORY	BRONCHITIS			1	0.4	1	0.2
	COUGH	1	0.4			1	0.2
	PHARYNGITIS	3	1.1	1	0.4	4	0.7
	SINUSITIS			1	0.4	1	0.2
SKIN	ECZEMA			2	0.7	2	0.4
	ERYTHEMA			1	0.4	1	0.2
	MONILIASIS SKIN	1	0.4			1	0.2
	PRURITUS NON-APPLICATION SITE	2	0.8	1	0.4	3	0.6
	RASH			2	0.7	2	0.4
	AMENORRHEA	1	0.4			1	0.2
UROGENITAL	BACTERIAL VAGINOSIS	7	2.7	8	2.9	15	2.8
	BREAST PAIN	1	0.4			1	0.2
	CYSTITIS	3	1.1	1	0.4	4	0.7
	DISORDER VULVOVAGINAL	10	3.8	10	3.7	20	3.7
	DYSMENORRHEA			1	0.4	1	0.2
	ENDOMETRIOSIS			1	0.4	1	0.2
	HEMORRRHAGE UTERINE			1	0.4	1	0.2
	HEMORRAGE VAGINAL			2	0.7	2	0.4
	INFECTION URINARY TRACT	5	1.9	6	2.2	11	2.1
	LEUKORRHEA	2	0.8			2	0.4
	MASTITIS	1	0.4			1	0.2
	MENOPAUSE			3	1.1	3	0.6
	MENORRHAGIA			2	0.7	2	0.4
	METRORRHAGIA	1	0.4	3	1.1	4	0.7
	MONILIASIS VAGINAL	18	6.9	24	8.8	42	7.9
	NEOPLASM UROGENITAL	1	0.4			1	0.2
	PREGNANCY UNINTENDED	3	1.1	1	0.4	4	0.7
	VAGINAL DISCHARGE NOS	1	0.4	2	0.7	3	0.6
	VAGINAL PAIN	1	0.4			1	0.2
	VAGINITIS TRICHOMONAL	2	0.8	1	0.4	3	0.6
VAGINITIS/VAG INFECTION	3	1.1	2	0.7	5	0.9	
TOTAL NUMBER OF MEDICAL EVENTS		119		124		243	
TOTAL NUMBER OF PATIENTS ON WHICH % IS BASED		261		273		534	

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Medical Events Reported in ≥1% of Patients

Table 16 summarize MEs reported in 1% or more of patients in either treatment group based on the COSTART description, and also shows, for each event, the number of patients in whom the investigators considered the event to be related to the study drug

Table 16
Medical Events Reported in ≥1% of Patients

BODY SYSTEM	EVENT	NUMBER OF PATIENTS (% OF GROUP) [NUMBER OF DRUG-RELATED EVENTS]*		
		CVC 3-DAY N = 261	CVC 7-DAY N = 273	TOTAL N = 534
BODY	GENERALIZED ABDOMINAL PAIN	4 (1.5) [1]	1 (0.4) [0]	5 (0.9) [1]
	FLU SYNDROME	5 (1.9) [0]	2 (0.7) [0]	7 (1.3) [0]
	HEADACHE	5 (1.9) [0]	1 (0.4) [0]	6 (1.1) [0]
	ABNORMAL MICRO TEST NOS	2 (0.8) [0]	5 (1.8) [1]	7 (1.3) [1]
	MONILIASIS	8 (3.1) [7]	13 (4.8) [1]	21 (3.9) [8]
	TRAUMA	5 (1.9) [0]	0	5 (0.9) [0]
	UPPER RESPIRATORY INFECTION	3 (1.1) [0]	0	3 (0.6) [0]
DIGESTIVE	DIARRHEA	2 (0.8) [1]	3 (1.1) [2]	5 (0.9) [3]
RESPIRATORY	PHARYNGITIS	3 (1.1) [0]	1 (0.4) [0]	4 (0.7) [0]
UROGENITAL	BACTERIAL VAGINOSIS	7 (2.7) [0]	8 (2.9) [0]	15 (2.8) [0]
	CYSTITIS	3 (1.1) [0]	1 (0.4) [0]	4 (0.4) [0]
	VULVOVAGINAL DISORDER	10 (3.8) [8]	10 (3.7) [6]	20 (3.7) [14]
	URINARY TRACT INFECTION	5 (1.9) [0]	6 (2.2) [0]	11 (2.1) [0]
	MENOPAUSE	0	3 (1.1) [0]	3 (0.6) [0]
	METRRORRHAGIA	1 (0.4) [0]	3 (1.1) [0]	4 (0.7) [0]
	VAGINAL MONILIASIS	18 (6.9) [6]	24 (8.8) [9]	42 (7.9) [15]
	UNINTENDED PREGNANCY	3 (1.1) [0]	1 (0.4) [0]	4 (0.7) [0]
	VAGINITIS/VAGINAL INFECTION	3 (1.1) [0]	2 (0.7) [0]	5 (0.9) [0]

*PATIENTS REPORTING EVENTS JUDGED BY THE INVESTIGATOR TO BE DRUG RELATED

CVC 3-DAY - CLINDAMYCIN VAGINAL CREAM 3-DAY TREATMENT

CVC 7-DAY - CLINDAMYCIN VAGINAL CREAM 7-DAY TREATMENT

Only moniliasis, BV, vulvovaginal disorder, urinary tract infection, and vaginal moniliasis were reported in either treatment group at frequencies greater than 2%. Frequencies of all events were generally similar between treatment groups.

Medical Event Frequencies by Maximum Intensity

A tabulation of MEs by maximum intensity is presented in Table 17. Of the 243 events reported, 235 (96.7%) were of mild or moderate intensity. There was no clinically important differences between the two treatment groups with respect to the overall intensity of events reported, with 95.8% of MEs in the 3-day group of mild or moderate intensity compared to 97.6% of those in the 7-day group. Seven (2.9%) of 248 events were related as severe. These were moniliasis, hyperthyroidism, vulvovaginal disorder, and mastitis experienced by patients in the 3-day treatment group and hypertension, an unintended pregnancy, and endometriosis for patients in the 7-day treatment group. There was one ME (unintended pregnancy) experienced by a patient in the CVC 3-day group for which the intensity was not reported.

TABLE 17

MEDICAL EVENTS BY BODY SYSTEM, COSTART DESCRIPTION (MET)
 MAXIMUM INTENSITY
 PATIENTS WHO RECEIVED AT LEAST ONE DOSE OF MEDICATION

BODY SYSTEM	COSTART DESCRIPTION (MET)	CVC 3-DAY			CVC 7-DAY		
		MILD	MOD	SEV	MILD	MOD	SEV
BODY	ABDOMINAL CRAMP				1		
	ABDOMINAL PAIN GENERALIZED	4			1		
	ABDOMINAL PAIN LOCALIZED	2					
	ALLERGIC REACTION		1				
	BACK PAIN		1		1		
	ENVIRONMENTAL ALLERGY	1			1		
	FEVER					1	
	FLU SYNDROME	3	2		1	1	
	HEADACHE	2	3			1	
	INFECTION BACTERIAL NOS				1		
	INFECTION PARASITIC NOS				1		
	INFECTION VIRAL NOS				1		
	INFLAMMATORY SWELLING					1	
	LOCALIZED PAIN				1		
	MICRO TEST ABNORMAL NOS	1	1		5		
	MONILIASIS	3	4	1	10	3	
	REACTION UNEVALUABLE	1			1		
	TRAUMA	4	1				
	UPPER RESPIRATORY INFECTION	2	1				
CARDIOVASCULAR	HEMORRHAGE	1					
	HYPERTENSION						1
	MIGRAINE	2					
	VASODILATION				1		
DIGESTIVE	CONSTIPATION				1		
	DIARRHEA	2			2	1	
	ENTERITIS				1		
	ENTEROCOLITIS				1		
	FLATULENCE	1					
	GASTRITIS	1					
	GASTROENTERITIS	1	1		1	1	
	NAUSEA	1	1				
VOMITING		1					
ENDOCRINE	HYPERTHYROIDISM			1			
HEMIC AND LYMPHATIC	ANEMIA				1		
	LYMPHADENITIS	1					
MUSCULO-SKELETAL	FIBROSIS TENDINOUS				1		
	MYALGIA					1	
	MYOSITIS					1	
NERVOUS	ANXIETY					1	
RESPIRATORY	BRONCHITIS					1	
	COUGH	1					
	PHARYNGITIS	2	1			1	
	SINUSITIS					1	
SKIN	ECZEMA				2		
	ERYTHEMA				1		
	MONILIASIS SKIN		1				
	PRURITUS NON-APPLICATION SITE	1	1		1		
	RASH					2	
UROGENITAL	AMENORRHEA	1					
	BACTERIAL VAGINOSIS	4	3		6	2	
	BREAST PAIN	1					
	CYSTITIS	3				1	
	DISORDER VULVOVAGINAL	6	3	1	6	4	

TABLE 17 CONTINUED

MEDICAL EVENTS BY BODY SYSTEM, COSTART DESCRIPTION (MET)
 MAXIMUM INTENSITY
 PATIENTS WHO RECEIVED AT LEAST ONE DOSE OF MEDICATION

BODY SYSTEM	COSTART DESCRIPTION (MET)	CVC 3-DAY			CVC 7-DAY		
		MILD	MOD	SEV	MILD	MOD	SEV
UROGENITAL	DYSMENORRHEA					1	
	ENDOMETRIOSIS						1
	HEMORRHAGE UTERINE					1	
	HEMORRHAGE VAGINAL				1	1	
	INFECTION URINARY TRACT	4	1		3	3	
	LEUKORRHEA	1	1				
	MASTITIS			1			
	MENOPAUSE				1	2	
	MENORRHAGIA					2	
	METORRHAGIA		1		2	1	
	MONILIASIS VAGINAL	12	6		14	10	
	NEOPLASM UROGENITAL	1					
	PREGNANCY UNINTENDED*	2					
	VAGINAL DISCHARGE NOS		1		1	1	
	VAGINAL PAIN		1				
	VAGINITIS TRICHOMONAL	2				1	
	VAGINITIS/VAG INFECTION	1	2		1	1	
*1 NOT REPORTED							
TOTAL EVENTS		75	39	4	73	48	3

APPEARS THIS WAY
 ON ORIGINAL