Based on the p-value of the evaluable patient population reporting Gram stain, there was a statistically significant difference between treatments regarding the distribution among Gram stain results categories, at each follow-up visit. At the first visit, although the majority of patients in both treatment groups had normal Gram stain results (73.1% [79/108] for the clindamycin VO and 76.1% [86/113] for the metronidazole), a greater percentage of patients in the metronidazole group had Gram stain results compatible with BV (22.1%, vs 9.3% in the clindamycin VO group. At the second visit, the majority of patients also had normal Gram stain results in both treatment groups, with a somewhat larger percentage in the metronidazole group 72.1% [80/111] than in the clindamycin VO group 59.8% [61/102]; but a greater percentage of clindamycin VO patients than metronidazole patients (14.7% vs 4.5%), respectively had intermediate Gram stain results.

SAFETY RESULTS

All patients enrolled in the study and who received any study drug were included in the safety analyses. Evaluation for safety was based on all reported medical event data. Table 39 summarizes the number of patients who reported medical events by investigator. There is no significant difference between groups for the percentage of patients reporting al least one medical event (ovule group 33% [67/203]; metronidazole group, 34% [67/196]).

Table 39

Number of patients who Reported Medical Events by Investigator – ITT Patients
Protocol 0002 All Causality

INVESTIGATOR	Medical Events – Intent-To-Treat (ITT) Patients					
	Cleocin Ovule			Metronidazole		
	ITT	ME	%	ITT	ME	%
Ahmed	24	12	50	23	9	39
Arya	7	3	43	6	5	83
Capetta	4	4	100	5	2	40
Christoffersen	8	1	13	6	1	17
Cianci	1	0	0	0	0	0
Creatsas	8	0	0	8	0	0
Dellenbach	2	1	50	1	1	100
Dhont	4	1	25	4	1	25
Judlin	2	0	0	4	1	25
Kolben	7	1	14	6	2	33
Mangioni	3	0	0	2	0	0
Moi	5	3	60	6	3	60
Neuer	6	4	67	6	2	33
Paavonen	31	13	42	31	16	52
Peterek	8	0	0	8	0	0
Radcliffe	17	8	47	18	11	61
Schmidt	13	0	0	10	0	0
Schnittger	15	6	40	16	8	50
Szczurowicz	8	2	25	7	0	0
Thoren	10	4	40	10	2	20
Ungar	8	0	0	8	0	0
Wilson	11	4	37	11	3	27
Xercavins	1	0	0	0	0	0
Total	203	67	33	196	67	34

The percentages of patients reporting medical events in the digestive and special-senses body systems were each about 3-fold lower for the clindamycin VO patients compared to metronidazole patients; otherwise, events within body systems were reported in similar percentages of patients in each treatment group (Table 40). Other frequently reported medical events occurred in the "urogenital" and "body" (as a whole) categories.

TABLE 40
Medical Events by Body System ITT Patients All Causality

BODY SYSTEM	CLEOCIN OVULE		METRONIDAZOLE		TOTAL	
	Number	%	Number	%	Number	%
Body as Whole	26	12.8	22	11.2	48	12.0
Digestive	8	3.9	25	12.8	33	8.3
Metabolic & Nutritional			1	0.5	1	0.3
Musculo-Skeletal	1	0.5			1	0.3
Nervous	2	1.0	5	2.6	7	1.8
Respiratory	7	3.4	4	2.0	11	2.8
Skin	7	3.4	7	3.6	14	3.5
Special Senses	2	1.0	7	3.6	9	2.3
Urogenital	30	14.8	25	12.8	55	13.8
No of Patients % is Based	203		196		399	

Medical Events Reported in ≥ 1% of Patients

Table 17 summarizes medical events reported in 1% or more of either clindamycin VO or metronidazole patients and shows, for each event, the number of patients for whom the investigators considered the event to be related to the study drug. Vaginal moniliasis was reported more frequently in clindamycin VO patients compared with metronidazole patients. However, due to COSTART coding rules, investigator descriptions of candidiasis or moniliasis were coded as either "moniliasis" (under the Body as a Whole system) or "vaginal moniliasis" (under the Urogenital system). The combined frequency of events coded as either of these descriptions was similar for both treatment groups: 6.9% (2.0% + 4.9%) of clindamycin VO patients and 5.1% (2.0% + 3.1%) of metronidazole patients. In this instance no patient reported both events; therefore, the combined frequencies are equal to the sums of the individual frequencies.

A higher percentage of metronidazole patients than clindamycin VO patients reported vulvovaginal irritation or soreness. Most medical event descriptions by investigators that included these or similar terms were coded as "vulvovaginal disorder" in COSTART; this was reported in 2.0% of clindamycin VO patients and 6.1% of metronidazole patients (Table 41). The incidence of systemic medical events (e.g., nausea, vomiting, and taste alteration) was higher in the metronidazole group. Few events were reported in either group at frequencies greater than 2%.

Table 41. Medical Events Reported by ≥ 1% of Clindamycin VO or Metronidazole Patients

Body System	Event (COSTART Description)	No. Patients (% of Group) [No. Drug-Related*]		
		CVO N=203	MET N=196	Total N=399
Body as a Whole	Abdominal cramp	2 (1.0) [1]	0 (0.0)	2 (0.5) [1]
	Localized abdominal pain	1 (0.5)	2 (1.0) [1]	3 (0.8) [1]
	Flu syndrome	3 (1.5)	2 (1.0)	5 (1.3)
	Headache	4 (2.0)	3 (1.5) [1]	7 (1.8) [1]
	Bacterial infection	3 (1.5)	2 (1.0)	5 (1.3)
	Infection	1 (0.5)	2 (1.0)	3 (0.8)
	Microbiological test abnormality	3 (1.5)	3 (1.5)	6 (1.5)
	Moniliasis	4 (2.0) [1]	4 (2.0) [2]	8 (2.0) [3]
	Upper respiratory infection	0 (0.0)	3 (1.5)	3 (0.8)
Digestive	Diarrhea	2 (1.0) [2]	4 (2.0) [3]	6 (1.5) [5]
	Increased thirst	0 (0.0)	2 (1.0) [2]	2 (0.5) [2]
	Nausea	2 (1.0) [2]	14 (7.1) [11]	16 (4.0) [13]
	Vomiting	1 (0.5)	2 (1.0) [1]	3 (0.8) [1]
Nervous	Dizziness	0 (0.0)	2 (1.0) [2]	2 (0.5) [2]
Respiratory	Bronchitis	2 (1.0)	2 (1.0)	4 (1.0)
	Pharyngitis	2 (1.0)	1 (0.5)	3 (0.8)
Skin	Herpes simplex (derm.)	1 (0.5)	2 (1.0)	3 (0.8)
	Pruritus (non-application site)	3 (1.5) [2]	2 (1.0) [1]	5 (1.3) [3]
Special Senses	Otitis media	2 (1.0)	0 (0.0)	2 (0.5)
	Taste perversion	0 (0.0)	7 (3.6) [6]	7 (1.8) [6]
Urogenital	Bacterial vaginosis	5 (2.5)	3 (1.5)	8 (2.0)
	Cystitis	2 (1.0)	1 (0.5)	3 (0.8)
	Menstrual disorder	2 (1.0) [2]	1 (0.5)	3 (0.8) [2]
	Vulvovaginal disorder	4 (2.0) [4]	12 (6.1) [7]	16 (4.0) [11]
	Dysuria	0 (0.0)	2 (1.0) [2]	2 (0.5) [2]
	Urinary tract infection	3 (1.5)	2 (1.0)	5 (1.3)
	Vaginal moniliasis	10 (4.9) [6]	6 (3.1) [4]	16 (4.0) [10]
	Vaginal discharge	2 (1.0) [1]	1 (0.5) [1]	3 (0.8) [2]
	Vaginitis/vaginal infection	2 (1.0)	1 (0.5)	3 (0.8)

CVO – clindamycin vaginal ovule, 3-day treatment
MET – metronidazole, 7-day treatment
* Patients reporting events judged by investigator to be related to study drug

Medical Event Frequencies by Maximum Intensity

A tabulation of medical events by maximum intensity is in Table 42. Of the 203 events reported, 197 (97%) were of mild to moderate intensity. Five events (2.5%) were rated as severe. These included localized abdominal pain, emotional lability, and vulvovaginal disorder in the metronidazole group, and diarrhea and vaginal moniliasis in the clindamycin VO group. There were no apparent differences between the two treatment groups with regard to the intensity of the events reported.

Table 42
Medical Events by Body System, COSTART Description Term, and Maximum Intensity – ITT Patients Protocol 0002 All Causality

BODY SYSTEM	COSTART DESCRIPTION	CLEOCIN OVULE				METRONIDAZOLE				TOTAL			
		Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot
BODY	Abdominal Cramp	2			2					2			2
	Abdominal Distention	1			1					1			1
	Abdominal Pain Gen					1			1	1			1
	Abdominal Pain Loc	1			1		1	1	2	1	1	1	3
	Disorder mucous Mem		1		1						1		1
	Fatigue					1			1	1			1
	Flu Syndrome		3		3		2		2		5		5
	Headache	4			4	3			3	7			7
	Infection Bacterial Nos	3			3	2			2	5			5
	Infection Nec	1			1	1	1		2	2	1		3
	Infection Viral Nos		1		1						1		1
	Localized Pain	1			1					1			1
	Micro Test Abn Nos	3			3	3			3	6			6
	Monialiasis	2	2		4	4			4	6	2		8
	Neck Pain	1			1					1			1
	Pelvic Pain	1			1					1			1
	Perioperative Event					1			1	1			1
	Trauma		1		1						1		1
	Upper Resp Inf					1	2		3	1	2		3
DIGESTIVE	Constipation	1			1					1			1
	Diarrhea	1		1	2	2	2		4	3	2	1	6
	Disorder GI Nos						1		1		1		1
	Dry Mouth					1			1	1			1
	Dysphagia	1			1					1			1
	Flatulence					1			1	1			1
	Increased Thirst					1	1		2	1	1		2
	Leukoplakia Oral					1			1	1			1
	Monilia Oral					1			1	1			1
	Nausea	1	1		2	12	2		14	13	3		16
	Tooth Abscess		1		1						1		1
	Vomiting	1			1	2			2	3			3

Table 42, Continued
Medical Events by Body System, COSTART Description Term, and Maximum Intensity – ITT Patients Protocol 0002

BODY SYSTEM	COSTART DESCRIPTION	CLEOCIN OVULE				METRONIDAZOLE				TOTAL			
		Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot
Metabolic and Nutritional	Hyperglycemia					1			1	1			1
Musculo-Skeletal	Mvalgia	1			1					1			1
Nervous	Dizziness					2			2	2			2
	Emotional Lability							1	1			1	1
	Halluniciation					1			1	1			1
	Insomia	1			1	1			1	2			2
	Nervousness		1		1						1		1
Respiratory	Bronchitis		2		2	1	1		2	1	3		4
	Cough	1			1					1			1
	Pharyngitis		2		2	1			1	1	2		3
	Pneumonia	1			1					1			1
	Sinusitus		1		1	1			1	1	1		2
Skin	Dermatitis Fungal					1			1	1			1
	Disorder Nail						1		1		1		1
	Herpes Simples Derm		1		1	2			2	2	1		3
	Irritated Scalp					1			1	1			1
	Pruritus	2	1		3	1	1		2	3	2		5
	Rash	1			1					1			1
	Topical Appl Site Pain		1		1						1		1
	Topical Appl Site Pruritus	1			1					1			1
Special Senses	Otitis Media	2			2					2			2
	Taste Perversion					5	2		7	5	2		7
UROGENITAL	Bacterial Vaginosis	3	2		5	3			3	6	2		8
	Breast Pain	1			1					1			1
	Carcinoma Cervix					1			1	1			1
	Cervicitis	1			1					1			1
	Chromaturia	1			1					1			1
	Contraception Failure	1			1					1			1
	Cystitis	2			2		1		1	2	1		3
	Disorder Menstrual Nec	2			2	1			1	3			3
	Disorder Vulvovaginal	2	2		4	8	3	1	12	10	5	1	16
	Dysmenorrhea					1			1	1			1
	Dyspareunia					1			1	1			1
	Dysuria					2			2	2			2
	Frequency Urinary						1		1		1		1
	Hemorrhage Vaginal						1		1		1		1
	Infection Urinary Tract	1	2		3		2		2	1	4		5
	Leukorrhea					1			1	1			1
	Moniliasis Vaginal	8	1	1	10	4	2		6	12	3	1	16
	Neoplasm Urogenital		1		1						1		1
	Pregnancy Unintended*				1								1
	Vaginal Discharge Nos	1	1		2	1			1	2	1		3
	Vaginal Pain	1			1		1		1	1	1		2
	Vaginitis/Vaginal Inf		2		2		1		1		3		3
Total Number of Medical Events		59	30	2	92	79	29	3	111	138	59	5	203

*Medical Event Reported but not Intensity

Drug-Related Medical Events

The investigators assessed the relatedness of the medical events to the use of study drug. Medical events considered drug-related were reported by more patients in the metronidazole group (32/196; 16.3%) than in the clindamycin VO group (21/203; 10.3%); however, this difference was not statistically significant (95% CI [-12.6, 0.7]). Drug-related medical events reported at higher frequencies in metronidazole patients than in clindamycin VO patients included the following: nausea, 1.0% (2/203) clindamycin VO versus 5.6% (11/196) metronidazole; and altered taste, 0% clindamycin VO versus 3.1% (6/196) metronidazole. Drug-related medical events that occurred at a higher frequency in clindamycin VO patients compared to metronidazole patients included vaginal moniliasis: 3.0% (6/203) clindamycin VO versus 2.0% (4/196) metronidazole. The majority of medical events that occurred in this study (127/203; 62.5%) were not considered drug-related.

TABLE 43
DRUG-RELATED MEDICAL EVENTS BY BODY SYSTEM ITT PATIENTS
PROTOCOL 0002

BODY SYSTEM	CLEOCIN OVULE		METRONIDAZOLE		TOTAL	
	Number	%	Number	%	Number	%
Patients with no Medical Event	182	89.7	164	93.7	346	86.7
Patients with at Least One Medical Event	21	10.3	32	16.3	53	13.3
Body as Whole	2	1.0	6	3.0	8	2.0
Digestive	4	2.0	19	9.7	23	5.8
Nervous	0	0	4	2.0	4	1.0
Skin	4	2.0	1	0.5	5	1.3
Special Senses	0	0	6	3.1	6	1.5
Urogenital	13	6.4	16	8.2	29	7.3
Total No of Med Event	23		53		76	
No of Patients % is Based	203		196		399	

Of the 76 drug-related events, 72 (95%) were of mild or moderate intensity. Four of the 5 severe medical events reported were considered drug-related by the investigators. Table 44.

Table 44
Drug-Related Medical Events by Body System, COSTART Description, and Maximum Intensity – ITT Patients

BODY SYSTEM	COSTART DESCRIPTION	CLEOCIN OVULE				METRONIDAZOLE				TOTAL			
		Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot
BODY	Abdominal Cramp	1			1					1			1
	Abdominal Pain Gen					1			1	1			1
	Abdominal Pain Loc							1	1			1	1
	Fatigue					1			1	1			1
	Headache					1			1	1			1
	Moniliasis		1		1	2			2	2	1		3
DIGESTIVE	Diarrhea	1		1	2	2	1		3	3	1	1	5
	Disorder GI Nos						1		1		1		1
	Flatulence					1			1	1			1
	Increased Thrist					1	1		2	1	1		2
	Leukoplakia Oral					1			1	1			1
	Nausea	1	1		2	10	1		11	11	2		13
	Vomiting					1			1	1			1
NERVOUS	Dizziness					2			2	2			2
	Emotional Liability							1	1			1	1
	Hallucination					1			1	1			1
SKIN	Pruritus non-applic site	1	1		2	1			1	2	1		3
	Topical Application Site Pain		1			1					1		1
	Topical Application Site Pruritus	1			1					1			1
Special Senses	Taste Perversion					4	2		6	4	2		6
UROGENITAL	Disorder Menstrual Nec	2			2					2			2
	Disorder Vulvovaginal	2	2		4	4	2	1	7	6	4	1	11
	Dyspareunia					1			1	1			1
	Dysuria					2			2	2			2
	Leukorrhea					1			1	1			1
	Moniliasis Vaginal	5	1		6	3	1		4	8	2		10
	Vaginal Discharge Nos		1		1	1			1	1	1		2
Total Number of Med Events		14	8	1	23	41	9	3	53	55	17	4	76

Dropouts Due to Medical Events

Three patients dropped out due to non-serious medical events, one in the clindamycin VO group and two in the metronidazole group. The patient who dropped out in the clindamycin VO group reported influenza 33 days after discontinuing treatment; of the two in the metronidazole group, one dropped out due to nausea and the other due to vulva itching and swelling. These patients and their medical events are summarized in Table 45 and detailed in the narrative summaries following.

Table 45. Medical Events for Patients Who Dropped Out Due to Medical Events

Patient No.	Investigator	Event (Investigator Description)	Intensity	Study Day	Drug-Related*
CLINDAMYCIN VO					
772	Ahmed-Jushuf	Influenza	Moderate	+33†	No
Metronidazole					
4	Paavonen	Itching/Swelling of Vulva	Severe	1	Yes
706	Capetta	Nausea	Moderate	1	No

* Investigator's opinion

† Days after treatment discontinued

Narrative for Patient #4

Investigator / Country: Paavonen / Finland

Reason for Narrative: Dropout due to Medical Event (Itching/Swelling of Vulva)

This 39-year-old, 64-kg white woman had a diagnosis of BV, and started study medication (metronidazole) on 30 May 1995. Her medical history included bronchial asthma since 1992. She applied one placebo ovule and took 4 capsules. On 31 May 1995 she reported swelling, itching, and blistering of the vulva. She discontinued medication and fully recovered within 3 weeks without sequelae. The event was considered nonserious and related to medication.

Narrative for Patient #706

Investigator / Country: Capetta / Italy

Reason for Narrative: Dropout due to Medical Event (Nausea)

This 31-year-old, 57-kg Hispanic woman had a diagnosis of BV, and started study medication (metronidazole) on 9 November 1995. Her medical history did not mention any disorders. She discontinued on her own request after taking 2 full days of medication; during these 2 days she complained of nausea of moderate intensity. The investigator did not consider the event related to study medication.

Narrative for Patient #772

Investigator / Country: Ahmed / UK

Reason for Narrative: Dropout due to Medical Event (Influenza)

This 18-year-old, 65-kg white woman had a diagnosis of BV, and started study medication (clindamycin VO) on 12 October 1995. Her medical history included genital warts. She completed the full course of medication on 18 October 1995, but did not return for any of the follow-up visits. Through a relative, she reported influenza from 20 November through 4 December 1995; this event was not considered drug related.

Deaths and Serious Medical Events

There were no deaths during the study. One metronidazole patient had a serious medical event during the study. This patient was diagnosed as having microinvasive carcinoma of the cervix post-treatment, which was not considered to be drug-related. Details of the event are given in Table 46 and the narrative summary following.

Table 46. Summary Table of Patients with Serious Medical Events

Patient No.	Event (Verbatim)	Study day	Duration (Days)	Drug-Related*	Outcome†	Action Taken with Study Drug
Metronidazole						
1302	Microinvasive cervical cancer	23 days after drug stopped	19	No	Recovered	None

* Investigator's opinion

† Outcome: recovered, not yet recovered, recovered with sequelae

Narrative for Patient #1302

Investigator / Country: Wilson / UK

Reason for Narrative: Serious Medical Event (Microinvasive Carcinoma of the Cervix)

This 31-year-old, 70-kg white woman was admitted to the study on 6 September 1995. She had been recruited within a department of genitourinary medicine. She had no relevant medical history abnormalities reported at baseline. She received metronidazole 500 mg BID for 7 days, beginning on 6 September 1995 and ending on 13 September 1995. She had no symptoms at her first follow-up visit on 19 September 1995. On the second follow-up visit (6 October 1995) she complained of vulvitis, which was thought to be due to candidal infection. At this visit she underwent colposcopy, and a microinvasive carcinoma of the cervix was diagnosed. She underwent cone biopsy of the cervix on 24 October 1995, and the lesion was fully excised at that time.

Exposure In Utero

One unintended pregnancy occurred during the study. This event was reported for a clindamycin VO patient on study day 4. The patient received a full course of treatment. The reported pregnancy outcome was a single live birth with no observed abnormalities.

Study 0002 Summary

This study indicates that a 3-day course of clindamycin vaginal ovules (clindamycin VO) is comparable in effectiveness to a 7-day course of metronidazole in the treatment of bacterial vaginosis (BV). The overall cure rate by the primary efficacy analysis for the intent-to-treat population was 57.7% in the clindamycin VO patients, compared to 60.0% in the metronidazole patients (95% confidence interval =[-13.2, 8.6] for the difference between cure rates). Similar results were observed in the evaluable population (50.4% versus 58.3%, respectively; 95% CI=[-20.7%, 4.9%]).

The secondary efficacy analysis (based on only clue cells and odor) showed higher overall cure rates than the primary analysis for both the ITT population (clindamycin VO 73.1%, metronidazole 68.6%) and the evaluable population (clindamycin VO 68.1%, metronidazole 66.7%), with no statistically significant differences between treatment

groups (95% CI=[-5.6, 14.6] for ITT patients; 95% CI=[-10.6, 13.5] for evaluable patients).

The predominant reason for classification of patients as nonevaluable in both analyses was failure to return for follow-up, or follow-up visits occurring outside the desired windows. The distribution of reasons for nonevaluability was similar between treatment groups.

As a secondary endpoint, this study investigated the use of the Gram stain, using the criteria described in 1991 by Nugent and co-workers [41]. These results, which are based upon a subjective assessment of the presence or absence of abnormal bacterial colonization and the presence or absence of lactobacilli, are not fully compatible with a clinical diagnosis of cure utilizing the [redacted] In this study, the rate of concordance of the Gram stain with the clinical definition of cure was at best 77.2% in the clindamycin group and 93.1% in the metronidazole group. Similar rates of concordance (at best 80.7% for clindamycin VO and 92.6% for metronidazole) were observed when this analysis was performed with the ITT patient population. These differences in concordance may reflect the difference between these two treatments in their effect on vaginal lactobacilli.

The number of patients reporting medical events was similar between treatment groups. More metronidazole patients than clindamycin VO patients reported vulvovaginal irritation or soreness. The incidence of events described by investigators as candidiasis or moniliasis, represented by the combined frequency of events coded by COSTART as moniliasis and vaginal moniliasis, was similar between the two treatment groups. The incidence of systemic medical events (e.g., nausea, vomiting, and taste alteration) was higher in the metronidazole group, while the incidence of diarrhea was similar in both groups. No serious drug-related medical events were reported during this study.

CONCLUSIONS

Clindamycin 100 mg vaginal ovules given once nightly for 3 consecutive nights appear to be as effective a therapy for bacterial vaginosis as oral metronidazole 500 mg BID given for 7 days. While the incidence of vaginal symptoms following therapy was similar between the two treatment groups, treatment with clindamycin vaginal ovules was associated with a lower incidence of systemic adverse effects. This may suggests that this treatment is more likely to be acceptable to patients affected by this condition.

15. NDA SUMMARY

The Applicant, Pharmacia & Upjohn, submitted this NDA (50-767) for the purpose of obtaining approval for the use of clindamycin vaginal ovule (CVO) once daily for three (3) consecutive days in treating patients with bacterial vaginosis. Presently the sponsor has approval to market clindamycin 2% vaginal cream for 3 and /or 7 days, however, it is of the opinion that a solid dose form of intravaginal clindamycin will be more convenient, provide an exact unit dose and will actually be the preferred dosage form by the consumer and physician. The proposed formulation (ovule) contains 100 mg of clindamycin per ovule, which is the same concentration of clindamycin per applicator approved as 3 and 7-day products.

In this NDA, the applicant submitted the results of 3 clinical trials that were conducted to examine the safety and efficacy of clindamycin VO in the treatment of BV. They comprise a Phase II placebo-controlled pilot study and two adequate and well-controlled Phase III studies, one using clindamycin vaginal cream (CVC) as the control treatment and the other using oral metronidazole(MET). The safety and efficacy studies were multicenter, randomized, blinded trials, using 100 mg clindamycin ovules versus a control (placebo or active comparator); they also used identical criteria for determining the efficacy of the study drugs. Study M/1100/0283 was a placebo controlled, double-blind, dose-duration study using a parallel design. Study M/1114/0001 was an active-controlled, observer-blind study comparing a 3-day clindamycin vaginal ovule regimen to the approved 7-day regimen of clindamycin vaginal cream. Study M/1114/0002 was an active-controlled, double-blind, double-dummy study comparing clindamycin vaginal ovule to oral metronidazole. Patients received either clindamycin vaginal ovule for 3 days plus oral placebo for 7 days or oral metronidazole for 7 days plus placebo suppositories for 3 days. Subsequently, the studies will be referred to by the last four digits of the protocol number.

For all studies, women were required to be 16 to 60 years old. The required clinical diagnosis of BV was based on three criteria: vaginal fluid with pH >4.5, presence of clue cells in the vaginal discharge, and an amine odor after adding 10% potassium hydroxide (KOH) to the vaginal discharge. In addition, for studies 0001 and 0002 a Gram stain of vaginal fluid was required to be compatible with a diagnosis of BV.

Patients were excluded for any of the following reasons: known allergy to clindamycin or lincomycin; pregnancy or breast feeding; systemic or vaginal antimicrobial therapy within the previous 2 weeks; previous enrollment in the study; need for non-protocol antibiotic therapy; positive test for *Neisseria gonorrhea*, *Candida albicans*, *Trichomonas vaginalis*, or (for studies 0001 and 0002) *Chlamydia trachomatis*; atrophic vaginitis; clinical evidence of genital herpes infection; anticipation of menses during treatment or follow-up visit; or any other condition judged by the investigator to be cause for exclusion.

Patients were randomized to the following treatment regimens:

- Clindamycin VO (all studies): one 100-mg ovule (or placebo ovule in study 0283) inserted intravaginally at bedtime for 3 consecutive days (or 5 days in study 0283);

study 0002 patients also took 2 placebo capsules orally twice daily for 7 consecutive days.

- Clindamycin VC (study 0001): 5 g (one applicatorful) of 2% cream (equivalent to 100 mg clindamycin) applied intravaginally at bedtime for 7 consecutive days
- Metronidazole (study 0002): 500 mg (two 250-mg capsules) orally twice daily for 7 consecutive days, plus 1 placebo vaginal ovule inserted intravaginally at bedtime for 3 consecutive days

Regimens of the comparator drugs (clindamycin VC and metronidazole) were those recommended for treatment of BV. The 100-mg clindamycin dose in the vaginal ovule is equivalent to the recommended dose of clindamycin VC. The selection of a 3-day course for the first clindamycin VO study (0283) was supported by results of an earlier study [38] showing that the efficacy of a 3-day regimen of clindamycin VC is comparable to that seen after 7 days of treatment. After the 3-day regimen was shown to be effective in study 0283, it was adopted for the subsequent studies.

Patients were required to return for two follow-up visits in all studies. For study 0283, the scheduled visit windows (per protocol) were 4 to 7 days and 21 to 35 days after completion of treatment (corresponding to 7 to 10 days and 24 to 38 days after the start of treatment for the 3-day regimen); for studies 0001 and 0002, the scheduled windows (per protocol) were 12 to 16 days and 28 to 42 days after the start of treatment. At each of these visits, tests were performed for the three key diagnostic criteria: vaginal fluid pH; amine odor when vaginal fluid was mixed with 10% KOH; and clue cells in vaginal fluid.

Clinical status (cured, failed, or non-assessable) was determined at each visit based on the number of diagnostic criteria that had resolved, i.e., returned to normal values (vaginal fluid pH ≤4.5, absence of odor, absence of clue cells). At the first visit, cure was defined as the return to normal of at least two criteria; at the second visit, cure was defined as the return to normal of all three criteria. All other outcomes were defined as failures or were considered non-assessable in the absence of available data. Patients who did not complete a full course of active drug (i.e., those receiving clindamycin VO for fewer than the assigned 3 or 5 days, or receiving clindamycin VC or metronidazole capsules for fewer than 6 days) because of an adverse event were designated side-effect failures. Patients whose status was failed at the first visit were not required to return for the second visit, were carried forward as failures and treated at the discretion of the investigator.

Patient Evaluability

Patients were considered fully evaluable for efficacy unless any of the following occurred: failure to meet selection criteria; inadequate dosing (clindamycin VO used for <3 days, clindamycin VC applied for <6 days or >9 days, or oral metronidazole taken for <6 days or >8 days and/or fewer than 21 capsules taken); any lapse in dosing of clindamycin VO (or placebo ovule in study 0283) or a lapse of >1 day in dosing of clindamycin VC or metronidazole; menses during therapy or at a follow-up visit; non-protocol systemic or vaginal antimicrobial treatment during study participation (unless given after failure assessed at first visit); failure to return for second follow-up visit if visit was required; or development of a concomitant genital infection (or discharge of unknown etiology in studies 0001 and 0002; in study 0283, patient deemed nonevaluable

if concomitant infection required treatment during study or compromised diagnostic criteria). In study 0001, an additional study-specific reason for judging patients to be nonevaluable was douching during protocol therapy or within 2 days prior to a follow-up visit. Although not specified in the study protocols, an exception was imposed for clinical and side-effect failures for all evaluability criteria except for those relating to data derived prior to initiation of treatment.

In all the studies, there were a number of patients who did not return for follow-up visits within the time windows defined by the protocols. The frequent failure to return within protocol-defined windows affected the determination of evaluability. Therefore, for the purpose of determining evaluability, wider windows were used for the second follow-up visit: the protocol-specified intervals were increased by 10 days before and after, to 14 to 48 days (study 0283) or 18 to 52 days (studies 0001 and 0002) after start of treatment. The primary efficacy analyses presented in the reports of the studies are based on these windows, which are hereafter referred to as the study report windows. Subsequent analyses were also performed using the protocol-specified windows for the second follow-up visit and using a window recommended by the FDA: 28 to 52 days after start of treatment (24 to 48 days for study 0283), with a minimum of 14 days between the first and second follow-up visits.

Intent-to-Treat Analysis

For each study, analysis of efficacy was performed for an intent-to-treat (ITT) population comprising all enrolled patients except those who were explicitly reported to have taken no study drug. The ITT population in each study included patients for whom no information was available on study drug administration, since in these cases there were no data explicitly indicating that drug had not been administered.

Primary Efficacy Measures

The primary efficacy measure was overall clinical outcome among evaluable patients. An overall outcome rating of cure, failure, or non-assessable, based on clinical status at both visits, was determined for each patient as defined in Table 47.

Table 47. Algorithm for Overall Clinical Outcome

Status at First Follow-up Visit	Status at Second Follow-up Visit	Overall Outcome
Cure (at least 2 of 3 criteria normal)	Cure (3 of 3 criteria normal)	Cure
	Failure (fewer than 3 criteria normal)	Failure
	Non-assessable	Non-assessable
Failure (fewer than 2 criteria normal)	Not applicable (Patients not required to return for visit.)	Failure
Side-effect failure		
Non-assessable	Cure	Non-assessable
	Failure	Failure
	Non-assessable	Non-assessable

The FDA also recommended that the efficacy data be analyzed using tests for vaginal fluid odor and clue cells as the only criteria for evaluation of clinical status. This analysis is based on evidence that the presence of clue cells plus the presence of amine odor alone can more accurately predict BV (with about 99% accuracy) than can these 2 criteria in combination with data on vaginal fluid pH. Furthermore, from a clinical perspective,

patients would not be considered to have failed treatment or to need further treatment if pH was the only abnormal diagnostic criterion observed. This supplementary analysis defines cure at either follow-up visit as resolution of both clue cells and odor and failure as resolution of one or fewer of these criteria. This analysis of overall outcome was performed for the evaluable populations based on both sets of widened allowable windows for the second visit and for evaluable patients based on the protocol-defined windows for the second visit.

Secondary Efficacy Measures

Secondary efficacy measures included determing the overall clinical outcome for ITT patients using the study report (SR) windows in each study and for Gram stain results of evaluable patients in studies 0001 and 0002.

Analysis of Results of All Controlled Studies

The intent-to-treat (ITT) population comprised 662 patients in study 0001 (clindamycin VO, 327 patients; clindamycin VC, 335 patients), 399 patients in study 0002 (clindamycin VO, 203 patients; metronidazole, 196 patients) and 116 patients on 3-day regimens in study 0283 (clindamycin VO, 59 patients; placebo, 57 patients). Enrollment for the 5-day arm of study 0283 was limited to 14 patients; due to the small sample size, efficacy data for these patients were not analyzed. All enrolled 3-day patients were included in the ITT population except 8 patients in study 0001 (4 from each group) reported to have taken no study medication. The number and percent of patients returning for each study visit are shown in Table 48.

Table 48. Disposition of Patients—ITT Patients

Study Visit	No. of Patients (% of Category)					
	Study 0283		Study 0001		Study 0002	
	CVO N=59	Placebo N=57	CVO N=327	CVC N=335	CVO N=203	MET N=196
Pretreatment	59 (100)	57 (100)	327 (100)	335 (100)	203 (100)	196 (100)
First Follow-Up	53 (89.8)	53 (93.0)	283 (86.5)	285 (85.1)	184 (90.6)	172 (87.8)
Second Follow-Up	46 (78.0)	31 (54.4)	229 (70.0)	206 (61.5)	150 (73.9)	146 (74.5)

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
MET – metronidazole, 7-day treatment

Approximately 9% to 14% of the total ITT population within each study did not return for the first follow-up visit, and 26% to 34% did not return for the second visit (including patients who failed treatment at the first visit and were therefore not required by protocol to return). The proportion of patients returning for each visit was similar for all treatment groups except the study 0283 placebo group and the study 0001 clindamycin VC group, in which the percentage returning for the second visit was comparatively small.

Patient Discontinuations

The primary reasons for study discontinuation assigned by the investigators are shown for the ITT population in Table 49.

Table 49. Primary Reasons for Discontinuation—ITT Patients

Reason for Discontinuation	No. of Patients (% of Group)					
	Study 0283		Study 0001		Study 0002	
	CVO N=59	Placebo N=57	CVO N=327	CVC N=335	CVO N=203	MET N=196
Lack of Efficacy	1 (1.7)	13 (22.8)	16 (4.9)	23 (6.9)	2 (1.0)	4 (2.0)
Serious Medical Event	0	0	1 (0.3)	0	0	0
Nonserious Medical Event	2 (3.4)	4 (7.0)	22 (6.7)	32 (9.6)	1 (0.5)	2 (1.0)
Found Ineligible after Medication Started	2 (3.4)	2 (3.5)	44 (13.5)	62 (18.5)	16 (7.9)	16 (8.2)
Protocol Noncompliance	16 (27.1)	10 (17.5)	71 (21.7)	77 (23.0)	7 (3.4)	3 (1.5)
Patient Request	1 (1.7)	3 (5.3)	1 (0.3)	2 (0.6)	5 (2.5)	2 (1.0)
Lost to Follow-up	6 (10.2)	4 (7.0)	27 (8.3)	27 (8.1)	19 (9.4)	24 (12.2)
Other	0	0	2 (0.6)	3 (0.9)	5 (2.5)	1 (0.5)
Total Discontinued	28 (47.5)	36 (63.2)	184 (56.3)	226 (67.5)	55 (27.1)	52 (26.5)
Completed Planned Visits	31 (52.5)	21 (36.8)	143 (43.7)	109 (32.5)	148 (72.9)	144 (73.5)

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
MET – metronidazole, 7-day treatment

A total of 55.2% (64/116) of study 0283 patients, 61.9% (410/662) of study 0001 patients, and 26.8% (107/399) of study 0002 patients discontinued study participation. In study 0283, the frequency distribution of reasons for discontinuation differed between treatment groups; the most common reason for clindamycin VO patients was protocol noncompliance (27.1%), and the most common reason for placebo patients was lack of efficacy (22.8%). In study 0001, the most common reasons for discontinuation were protocol noncompliance and evaluation of patients as ineligible after treatment was started; clindamycin VC patients had a slightly higher discontinuation rate than clindamycin VO patients overall and for every primary reason except loss to follow-up. The most common primary reason for discontinuation in study 0002 was loss of patients to follow-up (reported for 10.8% of all ITT patients). The percentage of patients in study 0002 discontinuing for each primary reason, as well as the total percentage discontinuing, was similar for the two treatment groups.

Patient Demographic and Baseline Characteristics
Table 50 summarizes demographic data for the ITT patients.

Table 50 Demographics—ITT Patients

Demographic Variable		Study 0283		Study 0001		Study 0002	
		CVO N=59	Placebo N=57	CVO N=327	CVC N=335	CVO N=203	MET N=196
Mean Age, yr ± SD [Range]		29.4 ± 9.7	27.8 ± 8.4	29.5 ± 8.3†	29.5 ± 8.0	33.0 ± 10.4	33.7 ± 10.7
Mean Weight, kg ± SD [Range; No. Patients Reporting]		75.0 ± 20.1 [N=59]	68.9 ± 13.2 [N=56]	69.0 ± 19.4 [N=314]	69.3 ± 17.5 [N=329]	63.3 ± 11.4 [N=197]	61.8 ± 9.6 [N=187]
Race, n (%)	White	10 (16.9%)	11 (19.3%)	113 (34.6%)	112 (33.4%)	185 (91.1%)	178 (90.8%)
	Black	44 (74.6%)	43 (75.4%)	148 (45.3%)	149 (44.5%)	16 (7.9%)	14 (7.1%)
	Oriental/Asian	0	0	3 (0.9%)	2 (0.6%)	2 (1.0%)	1 (0.5%)
	Hispanic	5 (8.5%)	3 (5.3%)	61 (18.7%)	68 (20.3%)	Not asked	Not asked
	Other	0	0	2 (0.6%)	4 (1.2%)	0	3 (1.5%)

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
MET – metronidazole, 7-day treatment
† N=326

The ITT treatment groups were balanced within all the studies at baseline with regard to age, weight, and race. The European patients in study 0002 were generally older and of lower mean weight than the North American patients in studies 0283 and 0001. The racial makeup of the three study populations differed considerably: a majority of study 0283 patients (75.0%; 87/116) were black; although black patients were the largest racial group in study 0001 (44.9%; 297/662), no single group comprised a majority of patients; and a large majority of study 0002 patients (91.0%; 363/399) were white. Within each study, the demographic profiles of patients evaluable by the study report windows were generally similar to that of ITT patients.

Patient Evaluability

Table 51 summarizes the primary reasons for nonevaluability assigned by the sponsor. The order of reasons shown in the table reflects the priority order used to select the primary reason for patients meeting more than one of the criteria for nonevaluability.

TABLE 51. PRIMARY REASONS FOR NONEVALUABILITY

Primary Reason for Nonevaluability	No. Patients (% of Group)					
	Study 0283		Study 0001		Study 0002	
	CVO N=59	Placebo N=57	CVO N=327	CVC N=335	CVO N=203	MET N=196
Did not have clinical BV	0 (0.0)	1 (1.8)	6 (1.8)	7 (2.1)	2 (1.0)	1 (0.5)
Did not meet inclusion criteria	2 (3.4)	1 (1.8)	41 (12.5)	51 (15.2)	38 (18.7)	37 (18.9)
Additional antimicrobial therapy given	4 (6.8)	2 (3.5)	14 (4.3)	8 (2.4)	13 (6.4)	10 (5.1)
Did not comply with dosing regimen	3 (5.1)	3 (5.3)	35 (10.7)	52 (15.5)	2 (1.0)	3 (1.5)
Follow-up not within required window*: Study report window	5 (8.5)	5 (8.8)	18 (5.5)	28 (8.4)	29 (14.3)	24 (12.2)
FDA-recommended window	7 (11.9)	5 (8.8)	23 (7.0)	36 (10.7)	32 (15.8)	28 (14.2)†
Protocol-defined window	10 (16.9)	6 (10.5)	28 (8.6)	36 (10.7)	37 (18.2)	34 (17.3)†
Menses during treatment or follow-up visit	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Douche during treatment or within 2 days of follow-up	Not applicable		0 (0.0)	1 (0.3)	Not applicable	
Had symptomatic concomitant vaginal infection	0 (0.0)	0 (0.0)	8 (2.4)	4 (1.2)	6 (3.0)	0 (0.0)
No information available on study drug administration	2 (3.4)	2 (3.5)	1 (0.3)	4 (1.2)	0 (0.0)	1 (0.5)
Not assessable (incomplete data)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	0 (0.0)	0 (0.0)
Total nonevaluable: Study report window	17 (28.8)	14 (24.6)	124 (37.9)	157 (46.8)	90 (44.3)	76 (38.8)
Protocol-defined window	22 (37.3)	15 (26.3)	134 (40.9)	165 (49.2)	98 (48.3)	86 (43.7)†
FDA-recommended window	19 (32.2)	14 (24.6)	128 (39.1)	164 (48.9)	93 (45.8)	80 (40.6)†

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
MET – metronidazole, 7-day treatment
Windows for second follow-up visit, as defined on page eight
† Including 1 nonevaluable patient whose data were unavailable for the study report analysis; percentage based on N=197.

In study 0283, the most common primary reason for nonevaluability was failure to observe required windows for follow-up visits, reported for 8.6% (10/116) of total patients based on the study report window. The most common primary reason for nonevaluability in studies 0001 and 0002 was failure to meet inclusion criteria post-enrollment, reported for 13.9% (92/662) of total patients in study 0001 and 18.8% (75/399) of total patients in study 0002. In each study, the percentage of patients considered nonevaluable for each primary reason was similar for the two treatment groups. The nonevaluability rate in study 0283 was consistently lower than that of studies 0001 and 0002, possibly because of a smaller proportion of patients who did not meet inclusion criteria post-enrollment. Relative to the protocol-defined windows, the widened follow-up windows for evaluability provided sufficient increases in the numbers of evaluable patients to enhance the statistical reliability of the corresponding analyses.

Overall Clinical Outcome for Evaluable Patients

Analyses of overall clinical outcome were performed based on 2 or 3 diagnostic criteria for BV (amine odor, clue cells, and pH). To be assessed as cured overall based on 3 diagnostic criteria, a patient was required to have been cured at the first follow-up visit (requiring resolution of at least 2 of 3 criteria) and at the second visit (requiring resolution of all 3 criteria). Assessment of overall cure based on 2 diagnostic criteria required resolution of amine odor and clue cells at both follow-up visits. All other outcomes were considered overall failures or, if data were unavailable, were considered non-assessable.

A summary of the overall clinical outcome for patients evaluable by the study report windows for the second visit is shown in Table 52 using 3 criteria and Table 53 using 2 criteria.

Table 52. Overall Clinical Outcome Based on 3 Diagnostic Criteria—Evaluable Patients (FDA-Recommended, Protocol-Defined, and Study Report Windows)

Window	Outcome/ Parameter	No. of Patients (% of Assessable Patients)					
		Study 0283		Study 0001		Study 0002	
		CVO	Placebo	CVO	CVC	CVO	MET
Study Report	Cure*	22 (52.4)	6 (14.0)	109 (53.7)	85 (47.8)	57 (50.4)	70 (58.3)
	Failure	20 (47.6)	37 (86.0)	94 (46.3)	93 (52.2)	56 (49.6)	50 (41.7)
	Total assessable	42	43	203	178	113	120
	95% CI for Difference‡	20.1, 56.7		-4.1, 16.0		-20.7, 4.9	
Protocol-Defined	Cure*	17 (45.9)	5 (11.9)	99 (51.3)	77 (45.3)	49 (46.7)	61 (55.0)
	Failure	20 (54.1)	37 (88.1)	94 (48.7)	93 (54.7)	56 (53.3)	50 (45.0)
	Total assessable	37	42	193	170	105	111
	95% CI for Difference‡	15.2, 52.9		-4.3, 16.3		-21.6, 5.0	
FDA-rec	Cure*	20 (50.0)	6 (14.0)	105 (52.8)	78 (45.6)	54 (49.1)	67 (57.3)
	Failure	20 (50.0)	37 (86.0)	94 (47.2)	93 (54.4)	56 (50.9)	50 (42.7)
	Total assessable	40	43	199	171	110	117
	95% CI for Difference‡	17.4, 54.7		-3.0, 17.3		-21.1, 4.8	

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
MET – metronidazole, 7-day treatment
* Cured at both follow-up visits
‡ 2-sided 95% confidence interval for difference between cure rates

Table 53. Overall Clinical Outcome Based on 2 Diagnostic Criteria—Evaluable Patients (FDA-Recommended, Protocol-Defined, and Study Report Windows)

Window	Outcome/ Parameter	No. of Patients (% of Assessable Patients)					
		Study 0283		Study 0001		Study 0002	
		CVO	Placebo	CVO	CVC	CVO	MET
Study Report	Cure*	26 (61.9)	8 (18.6)	134 (66.0)	106 (59.6)	77 (68.1)	80 (66.7)
	Failure	16 (38.1)	35 (81.4)	69 (34.0)	72 (40.4)	36 (31.9)	40 (33.3)
	Total assessable	42	43	203	178	113	120
	95% CI for Difference‡	24.7, 62.0		-3.4 to 15.2		-10.6 to 13.4	
Protocol-Defined	Cure*	21 (56.8)	7 (16.7)	124 (64.2)	98 (57.6)	70 (66.7)	71 (64.0)
	Failure	16 (43.2)	35 (83.3)	69 (35.8)	72 (42.4)	35 (33.3)	40 (36.0)
	Total assessable	37	42	193	170	105	111
	95% CI for Difference‡	20.6, 59.6		-3.4,,16.7		-10.0 to 15.4	
FDA-rec.	Cure*	24 (60.0)	8 (18.6)	131 (65.8)	99 (57.9)	75 (68.2)	77 (65.8)
	Failure	16 (40.0)	35 (81.4)	68 (34.2)	72 (42.1)	35 (31.8)	40 (34.2)
	Total assessable	40	43	199	171	110	117
	95% CI for Difference‡	22.3, 60.5		-2.0 to 17.8		-9.9 to 14.6	

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
MET – metronidazole, 7-day treatment
* Cured at both follow-up visits
‡ 2-sided 95% confidence interval for difference between cure rates

In study 0283, 52.4% (22/42) of the evaluable patients in the clindamycin VO group were cured based on 3 criteria and 61.9% (26/42) were cured based on 2 criteria; in both cases, the cure rates were significantly greater than the cure rates for the placebo group (14.0% [6/43] and 18.6% [8/43], respectively).

In study 0001, 53.7% (109/203) of evaluable patients in the clindamycin VO group were cured based on 3 diagnostic criteria compared with 47.8% (85/178) of patients in the clindamycin VC group; this difference was not statistically significant. The cure rates based on 2 diagnostic criteria were 66.0% (134/203) of patients in the clindamycin VO group and 59.6% (106/178) of patients in the clindamycin VC group; this difference was not statistically significant. The 95% confidence interval was calculated using investigator-adjusted confidence limits. For both analyses, the 95% confidence intervals for the difference in cure rates between treatment groups (-4.1% to 16.0% by 3 criteria, and -3.4% to 15.2% by 2 criteria) were also consistent with equivalence.

In study 0002, 57 (50.4%) of the 113 evaluable patients in the clindamycin VO group were cured based on 3 criteria compared with 70 (58.3%) of the 120 patients in the metronidazole group; this difference was not statistically significant. The lower bound of the 95% confidence interval for the difference between cure rates based on 3 criteria (-20.7) is slightly over the generally accepted limit (-20%) for an interval consistent with equivalence. However, the cure rates based on 2 diagnostic criteria were 68.1% (77/113) of patients in the clindamycin VO group and 66.7% (80/120) of patients in the

metronidazole group; this difference was not statistically significant, and the 95% CI for the difference (-10.6% to 13.4%) was consistent with equivalence. No statistically significant investigator-by-treatment interaction was found for either analysis.

Analyses of overall outcome based on 3 diagnostic criteria were also performed for patients evaluable by the FDA-recommended and protocol-defined windows For each evaluable window, cure rates and statistical relationships between cure rates of treatment groups within each study were similar to those observed for patients evaluable by the study report windows.

Within each study, cure rates for both treatment groups by 2 criteria were similar for the 3 evaluable populations defined by the FDA-recommended, protocol-defined, and study report windows.

Secondary Efficacy Results

Overall Clinical Outcome for ITT Patients

Table 54 summarizes overall clinical outcome based on 3 and 2 diagnostic criteria for the ITT population in all three studies.

Table 54. Overall Clinical Outcome—ITT Patients

Analysis	Outcome/ Parameter	No. of Patients (% of Assessable Patients)					
		Study 0283		Study 0001		Study 0002	
		CVO (N = 59)	Placebo (N = 57)	CVO (N = 327)	CVC (N = 335)	CVO (N = 203)	MET (N = 196)
3 criteria	Cure*	27 (55.1)	7 (14.3)	134 (56.3)	113 (50.4)	90 (57.7)	93 (60.0)
	Failure	22 (44.9)	42 (85.7)	104 (43.7)	111 (49.6)	66 (42.3)	62 (40.0)
	Nonassessable	10	8	89	111	47	41
	95% CI for Difference‡	23.8, 57.8		-3.2 to 14.9		-13.2 to 8.6	
2 criteria	Cure*	31 (63.3)	9 (18.0)	164 (68.3)	142 (62.3)	114 (73.1)	107 (68.6)
	Failure	18 (36.7)	41 (82.0)	76 (31.7)	86 (37.7)	42 (26.9)	49 (31.4)
	Nonassessable	10	7	87	107	47	40
	P-value†	<0.0001		0.1689		0.3833	
	95% CI for Difference‡	28.1, 62.5		-2.6 to 14.7		-5.6 to 14.6	

CVO - clindamycin vaginal ovule, 3-day treatment
CVC - clindamycin vaginal cream, 7-day treatment
MET - metronidazole, 7-day treatment
* Cured at both follow-up visits
‡ 2-sided 95% confidence interval for difference between cure rates

Within each study and treatment group, cure rates based on 3 or 2 criteria for the assessable ITT patients were similar to those observed for evaluable patients. In study 0283, the clindamycin VO cure rates for ITT patients were statistically significantly greater than those of the placebo group. For ITT patients in studies 0001 and 0002, there were no statistically significant differences in cure rates between treatment groups, and the 95% confidence intervals for the differences were consistent with equivalence. There was no statistically significant investigator-by-treatment interaction in the analysis of overall clinical outcome for ITT patients in any study.

Gram Stain Results

Analysis of Gram stain results by clinical status at each visit (based on 3 diagnostic criteria) in both studies indicates that the Gram stain scoring method used, which is based on a subjective assessment of the presence or absence of abnormal bacterial colonization and the presence or absence of lactobacilli, is not fully compatible with a clinical diagnosis of cure utilizing the standard criteria. For patients evaluable by the study report windows, the rate of concordance of the Gram stain score with the clinical definition of cure (i.e., the percentage of cured patients with normal Gram stain results) at a given visit was as follows: in study 0001, ≤76.1% in the clindamycin VO group and ≤80.4% in the clindamycin VC group; in study 0002, ≤77.2% in the clindamycin VO group and ≤93.1% in the metronidazole group. When this analysis was performed with the ITT patient populations, similar rates of concordance were observed: in study 0001, ≤76.1% in the clindamycin VO group and ≤81.3% in the clindamycin VC group; in study 0002, ≤80.7% for clindamycin VO and ≤92.6% for metronidazole. The differences in concordance between treatment groups in study 0002 may reflect the difference between the two treatments in their effect on vaginal lactobacilli.

Summary of Results of All Controlled Studies

The results of all efficacy analyses for overall clinical outcome demonstrate that a 3-day course of clindamycin vaginal ovules is superior to placebo and equally effective as 7-day courses of clindamycin vaginal cream or oral metronidazole in the treatment of bacterial vaginosis (BV). Analysis of overall outcome by 3 diagnostic criteria (clue cells, odor, and pH) in patients evaluable by the study report windows, which was the primary efficacy parameter in all the studies, showed the following cure rates: In study 0283, clindamycin VO 52.4%, placebo 14.0%; in study 0001, clindamycin VO 53.7%, clindamycin VC 47.8%; in study 0002, clindamycin VO 50.4%, metronidazole 58.3%. Similar overall cure rates by 3 criteria for the ITT populations were observed: In study 0283, clindamycin VO 55.1%, placebo 14.3%; in study 0001, clindamycin VO 56.3%, clindamycin VC 50.4%; in study 0002, clindamycin VO 57.7%, metronidazole 60.0%. The cure rates based on 2 diagnostic criteria (clue cells and odor) were higher than those based on 3 diagnostic criteria, as expected. Cure rates based on 2 criteria for patients evaluable by the study report windows were as follows: In study 0283, clindamycin VO 61.9%, placebo 18.6%; in study 0001, clindamycin VO 66.0%, clindamycin VC 59.6%; in study 0002, clindamycin VO 68.1%, metronidazole 66.7%. Comparable cure rates based on 2 criteria were observed for the ITT population: In study 0283, clindamycin VO 63.3%, placebo 18.0% in study 0001, clindamycin VO 68.3%, clindamycin VC 62.3%; in study 0002, clindamycin VO 73.1%, metronidazole 68.6%.

There were no statistically significant differences in overall cure rates between treatment groups in studies 0001 and 0002, and the 95% confidence intervals for the differences were consistent with equivalence in every analysis except overall outcome based on 3 criteria for evaluable patients in study 0002, in which the lower bound of the confidence interval (-20.7%) was slightly outside accepted limits for equivalence.

Additional analyses of the efficacy data were performed based on windows for patient evaluability (defining allowable time intervals for the second follow-up visit) designated by the FDA and windows defined in the study protocols. The overall cure rates based on 2 criteria for evaluable patients were similar for the treatment groups within all three studies irrespective of the evaluability windows applied; this was also the case for overall cure rates based on 3 criteria. Results observed for secondary efficacy parameters were generally consistent with the findings from analysis of overall clinical outcome, i.e., superiority of clindamycin VO treatment relative to placebo and equivalence with the comparator treatments studied.

SAFETY

Methods & PROCEDURES

All patients except those documented as not having received study medication in the studies listed above are included in the integrated summary of safety information. Demographic, exposure, adverse event, and in utero exposure data are displayed for two groups of studies: clinical safety/efficacy studies with clindamycin vaginal ovule in nonpregnant patients with BV, and a Phase I pharmacokinetic study in healthy subjects. Additionally, adverse event data pertaining specifically to vaginitis and moniliasis are presented for clinical safety/efficacy studies.

All adverse events that were spontaneously reported by the patient or directly observed by the investigator during the study are included in this review regardless of whether the events were considered to be related to treatment with the study medication. Also, any events that the investigator judged to be related to treatment with the study medication and that occurred subsequent to the study period were to be reported.

Demographic Data

Age and race data were integrated for the three ovule studies and displayed by treatment group for the intent-to-treat population. Table 55 shows that the four treatment groups in the three clinical safety/efficacy studies were well matched with regard to age (mean and range); the majority of the patients ranged from 21 to 40 years of age. Some differences are seen with regard to race due to the geographic location of the study centers; i.e., a greater proportion of other races were treated in the CVC group (22%) than in the other treatment groups (12%, 2%, and 5%), a greater proportion of whites were treated in the metronidazole group (90%) than in the other treatment groups (52%, 33%, and 19%), and a greater proportion of blacks were included in the placebo ovule group (75%) than in the other treatment groups (35%, 44%, and 8%). The differences resulted primarily from higher percentages of blacks enrolled in US study sites and higher percentages of whites enrolled in European and Canadian study sites. These differences, however, had no obvious effects on the safety evaluation of the clindamycin vaginal ovule.

Table 55. Demographic Characteristics

Demographic Variable	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Age: years	*			
Mean ± SD	30.7 ± 9.4	29.5 ± 8.0	33.6 ± 10.7	27.8 ± 8.4
Range				
Age: No. (%)	*			
16-20 yrs	68 (11.6%)	34 (10.1%)	16 (8.2%)	12 (21.1%)
21-30 yrs	258 (43.9%)	170 (50.7%)	76 (38.7%)	27 (47.4%)
31-40 yrs	165 (28.1%)	93 (27.8%)	50 (25.5%)	12 (21.1%)
41-50 yrs	78 (13.3%)	34 (10.1%)	36 (18.4%)	5 (8.8%)
>50 yrs	19 (3.2%)	4 (1.2%)	18 (9.2%)	1 (1.8%)
Race: No. (%)				
White	308 (52.3%)	112 (33.4%)	178 (90.8%)	11 (19.3%)
Black	208 (35.3%)	149 (44.5%)	14 (7.2%)	43 (75.4%)
Other	73 (12.4%)	74 (22.1%)	4 (2.0%)	3 (5.3%)

Abbreviations CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Oral Metronidazole, PBO-VO = Placebo vaginal ovule
*Age-related data in the CVO group are based on 588 patients reporting

Drug Exposure

Table 56 shows that a total of 1177 patients with a diagnosis of BV were included in the intent-to-treat (ITT) population for the three clinical safety/efficacy studies with clindamycin vaginal ovule, and that 589 of the 1177 patients were enrolled in the clindamycin ovule 3-day treatment group.

Table 56. Numbers of Patients Exposed to Clindamycin or Its Comparators During Studies with Clindamycin Vaginal Ovule

Protocol No.	CVO (3-Day)	CVC (7-Day)	MET (7-Day)	PBO-VO (3-Day)	Total
0001	327	335	--	--	662
0002	203	-	196	-	399
0283	59	-	-	57	116
All Protocols	589	335	196	57	1177

Abbreviations: CVC = clindamycin vaginal cream, CVO = clindamycin vaginal ovule, MET = metronidazole, PBO = placebo

Overall Summary of Adverse Events Data

Adverse event data for the three clindamycin vaginal ovule studies were integrated and are displayed for the intent-to-treat population. Several tabulations are provided for adverse events:

- Total number of adverse events and the number of patients with at least one adverse event

- Number and percent of patients with at least one adverse event in a given COSTART body system category (patients with more than one event in a given system were counted only once for that body system)

- Number and percent of patients with specific events (patients with multiple reports of the same event – i.e., the same COSTART medically equivalent term – were counted only once for that event).

Table 57 shows an overall summary of adverse events in the three safety and efficacy studies (Protocols 0001, 0002, and 0283) with clindamycin vaginal ovules in nonpregnant women with BV. No clinically important differences were observed among the four treatment groups with regard to the frequencies of adverse events, discontinuations of treatment due to adverse events, and serious adverse events. The frequency of treatment-related adverse events, however, was at least 60% higher in the metronidazole group than in the other treatment groups.

Table 57. Overall Summary of Adverse Events with 3-Day Clindamycin Vaginal Ovules and Comparators

Patients (Number & %) with	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=87
No adverse events	397 (67.4%)	228 (68.1%)	130 (66.3%)	41 (71.9%)
At least 1 adverse event	192 (32.6%)	107 (31.9%)	67 (34.2%)	16 (28.1%)
Number of Events* Reported	310	171	112	17
Adverse event(s) leading to discontinuation of treatment	4 (0.7%)	6 (1.8%)	6 (3.1%)	0 (0%)
Number of Events* Reported	7	10	13	0
Treatment-related adverse event(s)	62 (10.5%)	31 (9.3%)	33 (16.8%)	2 (3.5%)
Number of Events* Reported	83	43	54	2
Serious adverse event(s)†	1 (0.2%)	4 (1.2%)	1 (0.5%)	0 (0.0%)
Number of Events* Reported	1	8	1	0

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Oral Metronidazole, PBO-VO = Placebo vaginal ovule

*For each patient, multiple occurrences of the same event were counted only once.

† No patient deaths occurred during any of the studies.

All Reported Events

Table 58 shows the number and percent of patients for whom adverse events were reported by body system. It also shows the frequency of individual events that were reported by 1% or more of the patients within any treatment group. No unexpected differences were noted among the treatment groups.

The body system for which adverse events were most frequently reported in all four treatment groups was the body as a whole, with headache generally being the most frequently reported event. Urogenital complaints were also frequently reported for patients in the three active treatment groups (i.e., clindamycin ovule, clindamycin cream, and metronidazole tablets), with vulvovaginal disorders as the most frequent events (5.1%, 8.4%, and 6.1%, respectively). The vast majority of events coded as vulvovaginal

disorder were described by the investigators as vaginal itching or vaginal irritation. Vulvovaginal disorders were not reported for patients in the placebo ovule group. Digestive signs and symptoms (primarily nausea) were frequently reported for patients in the oral metronidazole group, but not in the other treatment groups.

Table 58. Number & Percent of Patients with Adverse Events by Body System and Frequently Reported Events

COSTART Body System* COSTART Term (≥1%)†	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Body as a Whole	**94 (16.0)**	**56 (16.7)**	**23 (11.7)**	**8 (14.0)**
Abdominal Cramp	7 (1.2)	6 (1.8)	-	-
Abdominal Pain, generalized	2 (0.3)	6 (1.8)	1 (0.5)	-
Abdominal Pain, localized	6 (1.0)	2 (0.6)	2 (1.0)	-
Flu Syndrome	6 (1.0)	9 (2.7)	2 (1.0)	-
Headache	29 (4.9)	12 (3.6)	3 (1.5)	5 (8.8)
Infection, Bacterial (NOS)	4 (0.7)	1 (0.3)	2 (1.0)	-
Infection, Fungal (NOS)	6 (1.0)	4 (1.2)	-	-
Infection (NEC)	2 (0.3)	-	2 (1.0)	-
Infection, Parasitic (NOS)	-	-	-	1 (1.8)
Microbiologic Test Abnormal (NOS)	3 (0.5)	1 (0.3)	3 (1.5)	-
Moniliasis	6 (1.0)	1 (0.3)	4 (2.0)	-
Trauma	7 (1.2)	1 (0.3)	-	-
Upper Respiratory Infection	8 (1.4)	3 (0.9)	3 (1.5)	2 (3.5)
Urogenital	**91 (15.4)**	**59 (17.6)**	**25 (12.7)**	**5 (8.8)**
Bacterial Vaginosis	5 (0.8)	-	3 (1.5)	-
Disorder, Vulvovaginal	30 (5.1)	28 (8.4)	12 (6.1)	-
Dysmenorrhea	6 (1.0)	4 (1.2)	1 (0.5)	-
Dysuria	4 (0.7)	3 (0.9)	2 (1.0)	-
Infection, Urinary Tract	14 (2.4)	8 (2.4)	2 (1.0)	1 (1.8)
Metrorrhagia	1 (0.2)	5 (1.5)	-	-
Moniliasis, Vaginal	15 (2.5)	3 (0.9)	6 (3.0)	-
Pregnancy, Unintended	3 (0.5)	4 (1.2)	-	2 (3.5)
Vaginal Pain	12 (2.0)	3 (0.9)	1 (0.5)	1 (1.8)
Vaginitis, Trichomonal	-	-	-	1 (1.8)
Digestive	**30 (5.1)**	**10 (3.0)**	**25 (12.7)**	**2 (3.5)**
Diarrhea	9 (1.5)	3 (0.9)	4 (2.0)	1 (1.8)
Gastritis	1 (0.2)	2 (0.6)	-	1 (1.8)
Increased Thirst	-	-	2 (1.0)	-
Nausea	8 (1.4)	4 (1.2)	14 (7.1)	-
Vomiting	5 (0.8)	1 (0.3)	2 (1.0)	-
Skin	**20 (3.4)**	**4 (1.2)**	**7 (3.6)**	**1 (1.8)**
Herpes Simplex, Derm	1 (0.2)	1 (0.3)	2 (1.0)	1 (1.8)
Pruritus, Nonapplication Site	8 (1.4)	1 (0.3)	2 (1.0)	-
Respiratory	**18 (3.1)**	**10 (3.0)**	**4 (2.0)**	**0 (0.0)**
Bronchitis	2 (0.3)	2 (0.6)	2 (1.0)	-
Sinusitis	5 (0.8)	5 (1.5)	1 (0.5)	-
Nervous	**5 (0.8)**	**3 (0.9)**	**5 (2.5)**	**1 (1.8)**
Dizziness	-	-	2 (1.0)	1 (1.8)
Special Senses	**4 (0.7)**	**0 (0.0)**	**7 (3.6)**	**0 (0.0)**
Taste Perversion	-	-	7 (3.6)	-
Cardiovascular‡	**2 (0.3)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**
Endocrine‡	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Hemic/Lymphatic‡	**1 (0.2)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**
Metabolic/Nutritional‡	**1 (0.2)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**
Musculoskeletal‡	**1 (0.2)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Oral Metronidazole, NEC = Not elsewhere classified, NOS = Not otherwise specified, PBO-VO = Placebo vaginal ovule

*Patients with one or more events in a given body system were counted only once for that system.

†Patients who experienced more than one occurrence of the same event were counted once for that event.

‡Events reported in this body system occurred at a frequency less than 1%.

Vaginitis and Moniliasis

The verbatim descriptions provided by the investigators at different sites to report vaginitis and moniliasis were varied, and the descriptions coded to several COSTART medically equivalent terms. In order to determine a more precise incidence of vaginitis and moniliasis in the patients enrolled in the clinical safety/efficacy studies, the COSTART terms were collapsed to the following composite terms.

- Vaginitis:
  One or more of the following – bacterial vaginosis, vulvovaginal disorder, leukorrhea, vaginal discharge (NOS), trichomonal vaginitis, or vaginitis/vaginal infection.

- Moniliasis:
  One or more of the following – fungal infection (NOS), moniliasis, or vaginal moniliasis.

Table 59 summarizes the overall frequency of these conditions in the studies with clindamycin vaginal ovules. There were no clinically significant differences among the active treatment groups with regard to the percent of patients with either or both these composite events.

Table 59. Number and Percent of BV Patients with Vaginitis or Moniliasis Reported During Studies with Clindamycin Vaginal Ovule

Event	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Vaginitis*	39 (6.6)	28 (8.4)	15 (7.6)	1 (1.8)
Moniliasis†	27 (4.6)	8 (2.4)	10 (5.1)	0 (0.0)
Vaginitis/Moniliasis‡	63 (10.7)	35 (10.4)	23 (11.7)	1 (1.8)

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Metronidazole oral PBO-VO = Placebo vaginal ovule

*Vaginitis – one or more of the following COSTART terms: bacterial vaginosis, vulvovaginal disorder, leukorrhea, vaginal discharge (NOS), trichomonal vaginitis, or vaginitis/vaginal infection

†Moniliasis - one or more of the following COSTART terms: fungal infection (NOS), moniliasis, or vaginal moniliasis

‡Either vaginitis or moniliasis, as defined above

All Adverse Events: Stratified by Maximum Intensity

Tabulation of the maximum intensity of each adverse event showed that the majority of the events reported for the 3-day clindamycin vaginal ovule group was mild to moderate in intensity. Eleven events reported for the clindamycin vaginal ovule group were severe, compared to 19 for the 7-day clindamycin vaginal cream group, 3 for the 7-day oral metronidazole group, and 1 for the 3-day placebo ovule group.

Of the 11 severe events reported for 8 patients in the clindamycin vaginal ovule group, 3 events (flank pain, diarrhea, and vulvovaginal disorder) in 3 patients were nonserious and were considered by the investigator to be related to treatment with the study

medication, and one event (pyelonephritis) met the criteria for a serious event and was considered by the investigator (but not the medical monitor) to be related to treatment. A narrative summary for the patient (Protocol 0001, Patient 2605) with pyelonephritis is provided in (Narrative Summaries for Patients with Serious Adverse Events). The remaining 7 severe events were nonserious and not considered related to treatment with the study medication.

Of the 19 severe events reported for 12 patients in the clindamycin 7-day cream group, 8 events in 4 patients were considered by the investigator to related to treatment with the study medication: back pain and dysuria in one patient; burning sensation in a second patient; abdominal cramps in a third patient; and abdominal cramps, abdominal distension, nausea, and diarrhea in a fourth patient. One patient in this treatment group (Protocol 0001, Patient 1199) had two severe events, both of which were serious and considered unrelated to treatment with the study medication: chest pain and shortness of breath. A narrative summary for this patient is also provided in (Narrative Summaries for Patients with Serious Adverse Events). The remaining 9 severe events were nonserious and considered unrelated to treatment with the study medication.

Each of the 3 severe events reported for 3 patients in the oral metronidazole group were considered by the investigator to be related to treatment with the study medication. These events – localized abdominal pain, emotional lability, and vulvovaginal disorder (i.e., vulvovaginal blistering, itching, and swelling) – were not serious.

Only one event (unintended pregnancy) was categorized as a severe event in the placebo ovule group.

Treatment-Related Adverse Events

The discussion of treatment-related events (i.e., events judged by the investigator to have a reasonable possibility of having been caused by the study medication) is divided into two sections: all treatment-related events, and treatment-related vaginitis and moniliasis.

All Treatment-Related Adverse Events

For each patient who was reported by the investigator to have had a treatment-related adverse event. Table 60 shows by both body system and event the number and percent of patients for whom treatment-related adverse events were reported. Similar incidences of treatment-related events involving the urogenital system and the body as a whole were reported for the three active treatment groups. Higher incidences of treatment-related events involving the digestive, special senses, and nervous systems were reported for the oral metronidazole group than for the clindamycin (ovule/7-day cream) and placebo ovule groups.

Table 60. Number & Percent of Patients with Treatment-Related Adverse Events (by Body System and Event)

COSTART Body System* COSTART TERM†	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Urogenital	**39 (6.6)**	**22 (6.6)**	**12 (6.1)**	**1 (1.8)**
Disorder, Menstrual (NEC)	2 (0.3)	-	-	-
Disorder, Vulvovaginal	20 (3.4)	16 (4.8)	7 (3.6)	-
Dyspareunia	-	-	1 (0.5)	-
Dysuria	1 (0.2)	2 (0.6)	2 (1.0)	-
Leukorrhea	-	-	1 (0.5)	-
Metrorrhagia	-	1 (0.3)	-	-
Moniliasis, Vaginal	9 (1.5)	2 (0.6)	4 (2.0)	-
Pyelonephritis	1 (0.2)	-	-	-
Vaginal Discharge (NOS)	2 (0.3)	-	1 (0.5)	-
Vaginal Pain	11 (1.9)	2 (0.6)	-	1 (1.8)
Vaginitis, Vaginal Infection	1 (0.2)	-	1 (0.5)	-
Body as a Whole	**15 (2.5)**	**12 (3.6)**	**6 (3.0)**	**0 (0.0)**
Abdominal Cramp	3 (0.5)	3 (0.9)	-	-
Abdominal Distension	-	1 (0.3)	-	-
Abdominal Pain, Generalized	-	1 (0.3)	1 (0.5)	-
Abdominal Pain, Localized	1 (0.2)	-	1 (0.5)	-
Asthenia	-	-	1 (0.5)	-
Back Pain	-	1 (0.3)	-	-
Fever	1 (0.2)	-	-	-
Flank Pain	1 (0.2)	-	-	-
Generalized Pain	1 (0.2)	1 (0.3)	-	-
Headache	2 (0.3)	1 (0.3)	1 (0.5)	-
Infection, Fungal (NOS)	6 (1.0)	2 (0.6)	-	-
Localized Edema	1 (0.2)	-	-	-
Moniliasis	1 (0.2)	1 (0.3)	2 (1.0)	-
Pelvic Pain	-	2 (0.6)	-	-
Reaction Unevaluable	-	1 (0.3)	-	-
Skin	**10 (1.7)**	**1 (0.3)**	**1 (0.5)**	**0 (0.0)**
Pruritus, Nonapplication Site	5 (0.8)	1 (0.3)	1 (0.5)	-
Rash	3 (0.5)	-	-	-
Topical Application Site Pain	1 (0.2)	-	-	-
Topical Application Site Pruritus	1 (0.2)	-	-	-
Digestive	**9 (1.5)**	**3 (0.9)**	**19 (9.6)**	**1 (1.8)**
Diarrhea	5 (0.8)	2 (0.6)	3 (1.5)	1 (1.8)
Disorder, Gastrointestinal	-	-	1 (0.5)	-
Disorder Tongue	-	-	1 (0.5)	-
Flatulence	-	-	1 (0.5)	-
Increased Thirst	-	-	2 (1.0)	-
Nausea	3 (0.5)	3 (0.9)	11 (5.6)	-
Vomiting	1 (0.2)	-	1 (0.5)	-
Special Senses	**0 (0.0)**	**0 (0.0)**	**6 (3.0)**	**0 (0.0)**
Taste Perversion	-	-	6 (3.0)	-
Nervous	**0 (0.0)**	**0 (0.0)**	**4 (2.0)**	**0 (0.0)**
Dizziness	-	-	2 (1.0)	-
Emotional Lability	-	-	1 (0.5)	-
Hallucination	-	-	1 (0.5)	-

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Oral Metronidazole, NEC = Not elsewhere classified, NOS = Not otherwise specified, PBO-VO = Placebo vaginal ovule

*Patients with more than one treatment-related event in a given body system were counted only once for that system.

†Patients who experienced more than one occurrence of the same treatment-related event were counted once for that event.

Treatment-Related Vaginitis and Moniliasis

Table 61 shows the number and percent of patients with vaginitis or moniliasis (using collapsed COSTART medically equivalent terms) that was considered by the investigators to be related to treatment with the study medication. There were no clinically significant differences among the active treatment groups with regard to the percent of patients with either or both these composite events.

Table 61. Number and Percent of Patients with Treatment-Related Vaginitis or Moniliasis

Treatment-Related* Event	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Vaginitis†	21 (3.6)	16 (4.8)	8 (4.1)	-
Moniliasis‡	16 (2.7)	5 (1.5)	6 (3.1)	-
Vaginitis/Moniliasis§	34 (5.8)	21 (6.3)	13 (6.6)	-

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Metronidazole oral, PBO-VO = Placebo vaginal ovule

*Events considered by the investigator to be related to treatment with the study medication

†Vaginitis: one or more of the following COSTART terms: bacterial vaginosis, vulvovaginal disorder, leukorrhea, vaginal discharge (NOS), trichomonal vaginitis, or vaginitis/vaginal infection

‡Moniliasis: one or more of the following COSTART terms: fungal infection (NOS), moniliasis, or vaginal moniliasis.

§Either vaginitis or moniliasis, as defined above

Premature Treatment Discontinuation Because of Adverse Events

Table 62 summarizes information regarding the numbers of patients in each treatment group who had adverse events that led to discontinuation or interruption of treatment; Table 63 shows by treatment group, body system, and event the number and percent of patients who discontinued or interrupted treatment because of adverse events. Table 64 lists the patients who prematurely discontinued treatment and the events responsible for this action.* Narrative descriptions of the individual patients follow the three in-text tables.

Few patients discontinued treatment in any group because of an adverse event. For the clindamycin groups, urogenital events were the most common cause for discontinuation, while digestive complaints were the most common in the metronidazole group. None of the events experienced by these patients were considered serious; most, however, were considered to be related to treatment with the study medication.

*These numbers are different from those cited in the individual study reports; i.e., the patients cited here are those who stopped dosing early (according to study medication use records) and who experienced one or more adverse events during the dosing period for which the action taken was interruption or discontinuation of treatment. The patients cited in the study reports for Protocols 0002 and 0283 are those for whom "Discontinued due to medical event" was checked on the CRF final report; the numbers cited in the study reports thus reflect all patients who discontinued the study at any time but who did not necessarily discontinue treatment.

Table 62. Patients Who Discontinued or Interrupted Treatment Because of Adverse Events

Treatment Group	N	No. Pts (%)	No. Events*	No. Events Related to Treatment†	No. Events Recovered/ Continued‡
CVO (3-Day)	589	4 (0.7)	7	6	7/0
CVC (7-Day)	335	6 (1.8)	10	9	8/2
MET-PO (7-Day)	196	6 (3.1)	15	12	15/0
PBO-VO (7-Day)	57	0 (0.0)	-	-	-
All Groups	1177	16 (1.4)	32	27	30/2

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Metronidazole oral PBO-VO = Placebo vaginal ovule
*Events associated with discontinuation or interruption of treatment
†Investigator's opinion
‡Referring to reported event outcomes of recovered without residual effects or continuing

Table 63. Number & Percent of Patients Who Discontinued or Interrupted Treatment Because of an Adverse Event (by Body System and Event)

COSTART Body System* COSTART TERM	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Urogenital	**3 (0.5)**	**5 (1.5)**	**2 (1.0)**	**0 (0.0)**
Disorder, Menstrual (NEC)	1 (0.2)	-	-	-
Disorder, Vulvovaginal	2 (0.3)	2 (0.6)	1 (0.5)	-
Dysuria	-	2 (0.6)	1 (0.5)	-
Infection, Urinary Tract	-	1 (0.3)	-	-
Vaginal Discharge (NOS)	1 (0.2)	-	-	-
Body as a Whole	**2 (0.3)**	**2 (0.6)**	**1 (0.5)**	**0 (0.0)**
Abdominal Cramp	-	1 (0.3)	-	-
Abdominal Pain, Generalized	-	1 (0.3)	-	-
Abdominal Pain, Localized	-	-	1 (0.5)	-
Back Pain	-	1 (0.3)	-	-
Infection, Fungal (NOS)	1 (0.2)	-	-	-
Infection, Viral (NOS)	1 (0.2)	-	-	-
Skin	**1 (0.2)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**
Pruritus, Nonapplication Site	-	-	1 (0.5)	-
Rash	1 (0.2)	--	--	-
Digestive	**0 (0.0)**	**1 (0.3)**	**5 (2.5)**	**0 (0.0)**
Diarrhea	-	1 (0.3)	-	-
Nausea	-	1 (0.3)	4 (2.0)	-
Vomiting	-	-	2 (1.0)	-
Nervous	**0 (0.0)**	**0 (0.0)**	**2 (1.0)**	**0 (0.0)**
Dizziness	-	-	1 (0.5)	-
Hallucination	-	-	1 (0.5)	-
Special Senses	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**
Taste Perversion	-	-	1 (0.5)	-

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET-PO = Oral Metronidazole, NOS = Not otherwise specified, PBO-VO = Placebo vaginal ovule
*Patients with more than one event (that led to discontinuation of treatment) within a given body system were counted only once for that system.

Table 64. Listing of Adverse Events That Led to Discontinuation/Interruption of Treatment (By Treatment Group, Protocol, and Patient No.)

Treatment Group	Protocol/Pt No. Investigator	Investigator's Verbatim Description Term	Drug Related?*	Outcome
CVO (3-Day)	0002/408 Moi	Mononucleosis (Infection, viral, NOS)	No	RWRE
	0002/767 Ahmed-Jushuf	Menstrual bleed started early (Disorder, menstrual NEC)	Yes	RWRE
	0002/1105 Radcliffe	Internal vaginal itching (Disorder vulvovaginal)	Yes	RWRE
		Vaginal discharge (Vaginal discharge, NOS)	Yes	RWRE
		Vulvovaginal irritation (Disorder, vulvovaginal)	No	RWRE
	0283/141 Livengood	Red rash on stomach and forearms (Rash)	Yes	RWRE
		Vaginal itching Disorder, vulvovaginal)	Yes	RWRE
		Yeast infection (Infection. fungal, NOS)	Yes	RWRE
CVC (7-Day)	0001/71 Livengood	Abdominal pain (Abdominal pain, generalized)	Yes	RWRE
	0001/164 Lesser	Burning & itching affecting labia (Disorder vulvovaginal)	Yes	RWRE
	0001/1150 Peipert	Urinary tract infection (Infection, urinary tract)	No	Continues
	0001/1161 Reed	Abdominal pain/cramping (Abdominal cramp)	Yes	RWRE
		Back pain (Back pain)	Yes	RWRE
		Pain with urination (Dysuria)	Yes	RWRE
	0001/2604 Peipert	Burning on urination (Dysuria)	Yes	RWRE
		Pelvic pain (Pelvic pain)	Yes	RWRE
	0001/2663 Gall	Diarrhea (Diarrhea)	Yes	RWRE
		External vaginal irritation (Disorder vulvovaginal)	Yes	Continues
		Nausea (Nausea)	Yes	RWRE
MET-PO (7-Day)	0002/4 Paavonen	Blistering of vulva (Disorder vulvovaginal)	Yes	RWRE
		Itching of vulva (Disorder vulvovaginal)	Yes	RWRE
		Swelling of vulva (Disorder vulvovaginal)	Yes	RWRE
	0002/106 Ahmed-Jushuf	Dizziness (Dizziness)	Yes	RWRE
		Nausea (Nausea)	Yes	RWRE
	0002/706 Capetta	Nausea (Nausea)	No	RWRE
	0002/754 Radcliffe	Nausea (Nausea)	No	RWRE
		Vomiting (Vomiting)	No	RWRE
	0002/759 Radcliffe	Dry/Itchy skin (Pruritus, nonapplication site)	Yes	RWRE
		Dysuria (Dysuria)	Yes	RWRE
		Metallic taste in mouth (Taste perversion)	Yes	RWRE
		Nausea (Nausea)	Yes	RWRE
		Severe right-sided abdominal pain (Abdominal pain, localized)	Yes	RWRE
		Slight [sic] hallucinations (Hallucination)	Yes	RWRE
	0002/770 Ahmed-Jushuf	Vomiting (Vomiting)	Yes	RWRE

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET -PO = Metronidazole oral, RWRE = Recovered without residual effects

*Investigator's opinion of whether the event was possibly caused by the study medication

Narrative descriptions (ordered by treatment group) are provided below for the patients who, while enrolled in the clindamycin vaginal ovule studies, experienced adverse events that led to discontinuation or interruption of treatment with the study medication.

Narrative Descriptions of Patients who Discontinued Treatment Because of Adverse Events

Clindamycin Vaginal Ovule: 1x (hs)/Day for 3 Days)

Protocol 0002: Patient 408 (Investigator Moi; Norway)
Reason for Discontinuing Treatment: Mononucleosis
This 18-year-old patient with a diagnosis of BV was enrolled in the study on October 24, 1995 and assigned to treatment with clindamycin vaginal ovule. The patient used one ovule on the day of enrollment only. On the following day, October 25, the patient was found to have mononucleosis and was dropped from the study. The event was not considered by the investigator to be related to treatment with the study medication.

Protocol 0002: Patient 767 (Investigator Ahmed; UK)
Reason for Discontinuing Treatment: Menstrual bleed started early
This 28-year-old patient with a diagnosis of BV was enrolled in the study on September 11, 1995 and assigned to treatment with clindamycin vaginal ovule. On September 13, her menstrual period started earlier than expected. Study medication was reportedly interrupted; yet, the Study Medication Use Record reveals that the only dose not taken was the third ovule. The investigator considered this event related to treatment with the study medication.

Protocol 0002: Patient 1105 (Investigator Radcliffe; UK)
Reasons for Discontinuing Treatment: Internal vaginal itching, vaginal discharge, vulvovaginal irritation
This 21-year-old patient with a diagnosis of BV was enrolled in the study on May 23, 1995 and assigned to treatment with clindamycin vaginal ovule. The ovule was not used on the third day of treatment, May 25, due to internal vaginal itching and vaginal discharge which began on May 23 and May 24, respectively. Both events, which were considered by the investigator to be related to study medication, resolved without residual effects on May 25, 1995.

Protocol 0283: Patient 141 (Investigator Livengood; US)
Reason for Discontinuing Treatment: Red rash on stomach & forearms, vaginal itching, yeast infection
This 30-year-old patient with a diagnosis of BV was enrolled in the study on November 15, 1993 and assigned to treatment with clindamycin vaginal ovule. On November 17, 1993 the patient developed vaginal itching and a rash on her abdomen; no clue cells were found, but yeast was found on the screening examination. The investigator believed that the red rash on the stomach may have been an allergic reaction to the study medication, of which the patient took only one dose. The patient was dropped from the study because of the adverse events. The investigator considered all of the events to be related to treatment with the study medication.

Clindamycin Vaginal Cream: 1x (hs)/Day for 7 Days)

Protocol 0001: Patient 71 (Investigator Livengood; US)
Reason for Discontinuing Treatment: Abdominal pain
This 23-year-old patient with a diagnosis of BV was enrolled in the study on January 6, 1995 and assigned to treatment with clindamycin vaginal cream. She complained of moderate abdominal pain each time she applied the cream. The last day she used study medication was January 8, 1995. At follow-up, her tests for BV were negative, and she reported no further pain. The investigator noted that the patient's abdominal pain was possibly related to treatment with the study medication.

Protocol 0001: Patient 164 (Investigator Lesser; US)
Reason for Discontinuing Treatment: Burning and itching affecting labia
This 28-year-old patient with a diagnosis of BV was enrolled in the study on February 2, 1995 and assigned to treatment with clindamycin vaginal cream. On the second day of treatment (February 3, 1995), she complained of mild labial burning and itching. After treatment for another 2 days, the study medication was discontinued on February 5, 1995. The adverse event resolved the following day without any treatment (as reported). This event was considered by the investigator to be related to treatment with the study medication.

Protocol 0001: Patient 1150 (Investigator Peipert; US)
Reason for Discontinuing Treatment: Urinary tract infection
This 25-year-old patient with a diagnosis of BV was enrolled in the study on September 9, 1995 and assigned to treatment with clindamycin vaginal cream. At the first follow-up visit (October 4, 1995), an antibiotic was prescribed for a urinary tract infection that was reported to have started on September 30, 1995. A stop date for the study medication was not provided, but it was reported that the medication was discontinued due to the adverse event. The investigator considered the adverse event to be unrelated to treatment with the study medication.

Protocol 0001: Patient 1161 (Investigator Reed; US)
Reason for Discontinuing Treatments: Abdominal pain/cramping, back pain, pain with urination
This 23-year-old patient with a diagnosis of BV was enrolled in the study on August 16, 1995 and assigned to treatment with clindamycin vaginal cream. The patient reported moderate abdominal pain/cramping, severe back pain, and severe pain with

urination after the second day of treatment. The medication was discontinued a day later (August 18, 1995). The adverse events resolved the following day without treatment. The investigator could not rule out the study medication as the cause of the adverse events.

Protocol 0001: Patient 2604 (Investigator Peipert; US)
Reason for Discontinuing Treatment: Burning on urination
This 25-year-old patient with a diagnosis of BV was enrolled in the study on July 8, 1997 and assigned to treatment with clindamycin vaginal cream. She reported that she noticed mild intermittent burning on urination after the first dose and so did not take the medication as directed, using it irregularly over a span of 11 days. The investigator reported that the burning on urination was related to treatment with the study medication.

Protocol 0001: Patient 2663 (Investigator Gall; US)
Reason for Discontinuing Treatment: Diarrhea, external vaginal irritation, nausea
This 33-year-old patient with a diagnosis of BV was enrolled in the study on August 7, 1997 and was assigned to treatment with clindamycin vaginal cream . On the second day of treatment (August 8, 1997), she began experiencing nausea, diarrhea, and external vaginal irritation, all of moderate intensity. After 4 doses, medication was discontinued on August 10, 1997. The following day the nausea and diarrhea had resolved without treatment. However, the vaginal irritation continued. The patient was unable to be contacted to obtain a date of resolution for the external vaginal irritation. The investigator noted that there was a reasonable possibility that these events were related to treatment with the study medication.

Metronidazole Oral: BID for 7 Days

Protocol 0002: Patient 4 (Investigator Paavonen ; Finland)
Reason for Discontinuing Treatment: Blistering/Itching/Swelling of vulva
This 39-year-old patient with a diagnosis of BV was enrolled in the study on May 30, 1995 and assigned to treatment with metronidazole tablets. Her medical history included bronchial asthma since 1992. She applied 1 placebo ovule and took 4 capsules. On May 31, 1995 she reported swelling, itching, and blistering of the vulva. She discontinued medication and fully recovered within 3 weeks without sequelae. The event was considered nonserious and related to medication.

Protocol 0002: Patient 106 (Investigator Ahmed; UK)
Reasons for Discontinuing Treatment: Nausea, dizziness
This 16-year-old patient with a diagnosis of BV was enrolled in the study on June 26, 1995 and assigned to treatment with metronidazole tablets. On June 28 she began experiencing nausea and dizziness and consequently discontinued the study medication. She recovered without residual effects on June 29. The investigator considered the events related to treatment with the study medication.

Protocol 0002: Patient 706 (Investigator Capetta; Italy)
Reason for Discontinuing Treatment: Nausea
This 31-year-old patient with a diagnosis of BV was enrolled in the study on November 9, 1995 and was assigned to treatment with metronidazole tablets. Her medical history did not mention any disorders. She discontinued on her own request after taking 2 full days of medication; during these 2 days she complained of nausea of moderate intensity. The investigator did not consider the event related to study medication.

Protocol 0002: Patient 754 (Investigator Radcliffe; UK)
Reasons for Discontinuing Treatment: Nausea, vomiting
This 21-year-old patient with a diagnosis of BV was enrolled in the study on August 9, 1995 and assigned to treatment with metronidazole tablets. On the same day, she was given another antibiotic for a diagnosis of tonsillitis. On the third day of treatment (August 11, 1995), the patient reported nausea and vomiting. The study medication was stopped after the first dose on August 12. The nausea and vomiting were not considered related to treatment with the study medication and resolved without residual effects August 12, 1995.

Protocol 0002: Patient 759 (Investigator Radcliffe; UK)
Reasons for Discontinuing Treatment: Severe right-sided abdominal pain, dry/itchy skin, nausea, metallic taste in mouth, dysuria, slight hallucinations
This 41-year-old patient with a diagnosis of BV was enrolled in the study on October 17, 1995 and assigned to treatment with metronidazole tablets. On October 18, the second day of treatment, she reported a metallic taste in her mouth. On October 21 she reported dry/itchy skin and dysuria. The next day, October 22, she reported severe right-sided abdominal pain, nausea, and slight hallucinations. Study medication was discontinued at that time. All events resolved without residual effects by October 24, 1995. The investigator considered all of the events to be related to treatment with the study medication

Protocol 0002: Patient 770 (Investigator Ahmed; UK)
Reasons for Discontinuing Treatment: Vomiting
This 26-year-old patient with a diagnosis of BV was enrolled in the study on September 28, 1995 and assigned to treatment with metronidazole tablets. On October 3, the seventh day of treatment, she experienced mild vomiting and discontinued study medication. She recovered without residual effects the same day. The investigator considered the event to be related to treatment with the study medication.

Serious Adverse Events

Six patients who were enrolled in the studies with clindamycin vaginal ovules experienced serious adverse events (1 in the clindamycin ovule group, 4 in the clindamycin 7-day cream group, and 1 in the oral metronidazole group). Table 65 shows (by treatment group, body system, and event) the number and percent of patients who experienced serious events during study participation.

Table 65. Number and Percent of Patients with Serious Adverse Events Reported During Studies with Clindamycin Vaginal Ovule

COSTART Body System* / COSTART Term†	CVO 3-Day N=589	CVC 7-Day N=335	MET-PO 7-Day N=196	PBO-VO 3-Day N=57
Body as a Whole	**0 (0.0)**	**3 (0.9)**	**0 (0.0)**	**0 (0.0)**
Abdominal Pain	-	1 (0.3)	-	-
Chest Pain	-	1 (0.3)	-	-
Fever	-	1 (0.3)	-	-
Flu Syndrome	-	1 (0.3)	-	-
Overdose	-	1 (0.3)	-	-
Respiratory	**0 (0.0)**	**2 (0.6)**	**0 (0.0)**	**0 (0.0)**
Bronchitis	-	1 (0.3)	-	-
Dyspnea	-	1 (0.3)	-	-
Urogenital	**1 (0.2)**	**1 (0.3)**	**1 (0.5)**	**0 (0.0)**
Carcinoma, Cervix	-	-	1 (0.5)	-
Hemorrhage, Vaginal	-	1 (0.3)	-	-
Pyelonephritis	1 (0.2)	-	-	-

Abbreviations: CVC = Clindamycin vaginal cream, CVO = Clindamycin vaginal ovule, MET = Medically Equivalent term, MET-PO = Metronidazole oral, PBO-VO = Placebo vaginal ovule

*Patients with more than one serious event in a given body system were counted only once for that system.

†Patients who experienced more than one occurrence of the same serious event were counted once for that event

Table 66 lists the patients who experienced a serious adverse event while enrolled in study with clindamycin vaginal ovules. All of these patients recovered without residual effects.

Table 66 Listing of Patients Who Experienced a Serious Adverse Event*

Treatment Group	Protocol No	Patient No.	Event	Treatment-Related†
CVO (3-Day)	0001	2605	Pyelonephritis	Yes‡
CVC (7-Day)	0001	1145	Acetaminophen overdose	No
		1199	Chest pain	No
			Shortness of breath	No
		1249	Bronchitis/Asthma	No
		2665	Fever	No
			Heavy vaginal bleeding	No
			Lower abdominal cramping	No
			Viral episode (flu)	No
MET-PO (7-Day)	0002	1302	Microinvasive cervical cancer	No

*All patients recovered without residual effects.
†Investigator's opinion
‡Per the medical monitor, this event is most likely unrelated to treatment with the study medication (See narrative below).

Narrative descriptions (ordered by treatment group) are provided below for the six patients who experienced serious adverse events while enrolled in the clindamycin vaginal ovule studies.

Narrative Summaries for Patients with Serious Adverse Events

Clindamycin Vaginal Ovule: 1x (hs)/Day for 3 Days)

Protocol 0001: ***Patient 2605 (Investigator Peipert; US)***
Serious Adverse Event: Pyelonephritis
This 21-year-old patient with a diagnosis of BV and a pretreatment history of pyelonephritis and urinary tract infections was enrolled in the study on July 14, 1997 and assigned to treatment with clindamycin vaginal ovule. Three days after treatment completion, severe pyelonephritis accompanied by right-flank pain, dysuria, nausea, vomiting, abdominal cramps, and fever was diagnosed. Treatment consisted of intramuscular gentamicin, acetaminophen, codeine, and [redacted]. She recovered 5 days later without residual effects. The investigator considered the pyelonephritis related to treatment with the study medication. However, the P&U monitor noted that although theoretically possible, the study medication was an unlikely cause.

Clindamycin Vaginal Cream: 1x (hs)/Day for 7 Days)

Protocol 0001: Patient 1145 (Investigator Peipert; US)
Serious Adverse Event: Overdose of acetaminophen
This 23-year-old patient with a diagnosis of BV was enrolled in the study on July 14, 1995 and assigned to treatment with clindamycin vaginal cream. Five days after treatment was completed, she took an overdose of acetaminophen and went to a local hospital, where her stomach was pumped and she received a referral for counseling. She recovered without residual effects. The investigator considered the adverse event to be unrelated to treatment with the study medication.

Protocol 0001: Patient 1199 (Investigator Sobel)
Serious Adverse Event: Chest pain, shortness of breath
This 47-year-old patient with a diagnosis of BV was enrolled in the study on October 13, 1995 and assigned to treatment with clindamycin vaginal cream. Fourteen days after treatment completion, she was hospitalized with chest pain and shortness of breath, both of severe intensity. EKG and stress tests were normal. The patient received a diagnosis of esophageal reflux/gastritis, which was treated with propranolol hydrochloride and omeprazole. The patient recovered 8 days later without residual effects. The investigator considered these adverse events to be unrelated to treatment with the study medication.

Protocol 0001: Patient 1249 (Investigator Watson)
Serious Adverse Event: Bronchitis/asthma
This 26-year-old patient with a diagnosis of BV and a history of asthma was enrolled in the study on September 14, 1995 and assigned to treatment with clindamycin vaginal cream. Five days after completion of treatment, a diagnosis of bronchitis/asthma was made. The entry in the MEF indicated that the study medication was interrupted; however, the days of use recorded on the Study Medication Use Record indicated that the treatment was completed 5 days prior to the onset of the adverse event. She was treated with erythromycin, triamcinolone acetonide, and albuterol, and recovered 4 days later without residual effects. The investigator considered the adverse event to be unrelated to treatment with the study medication.

Protocol 0001: Patient 2665 (Investigator Gall; US)
Serious Adverse Events: Fever, heavy vaginal bleeding, lower abdominal cramping, viral episode (flu)
This 22-year-old patient with a diagnosis of BV was enrolled in the study on September 3, 1997 and assigned to treatment with clindamycin vaginal cream. Subsequent to study entry, she was found to be ineligible for study participation because of a positive test for *Chlamydia* and a Gram stain score of '3' at pretreatment. Relevant medical history included a therapeutic abortion 3 weeks prior to treatment and a Depo-Provera injection on the day prior to treatment. On the second day of treatment, she reported episodic lower abdominal cramping of moderate intensity. Four days after treatment, she was hospitalized with a viral episode, heavy vaginal bleeding, and abdominal pain. She developed a fever the next day, was treated with IV antibiotics, and recovered on September 16, 1997 without residual effects. The investigator considered these adverse events to be unrelated to treatment with the study medication.

Metronidazole Oral: BID for 7 Days

Protocol 0002: Patient 1302 (Investigator Wilson; UK)
Serious Adverse Event: Microinvasive Carcinoma of the Cervix
This 31-year-old patient was enrolled in the study on September 6, 1995 and assigned to treatment with metronidazole tablets. No relevant abnormalities were noted during the review of the patient's medical history at baseline. The patient completed the 7-day metronidazole regimen on September 13, 1995. She reported no symptoms at her first follow-up visit (September 19, 1995); but she complained of vulvitis – which was thought to be due to candidal infection – at the second follow-up visit (October 6, 1995). At this visit, a colposcopy revealed a microinvasive carcinoma of the cervix. The patient underwent cone biopsy of the cervix on October 24, 1995, at which time the lesion was fully excised. The investigator noted that there was not a reasonable possibility that the event was caused by the study medication.

In Utero Exposure

Nine patients are known to have become pregnant while enrolled in the three clinical safety/efficacy studies with clindamycin vaginal ovule. Table 67 provides details of the outcomes of the pregnancies. Three of the 9 patients had either spontaneous or therapeutic abortions, one was lost to follow-up, and 5 had live births with no abnormalities noted.

Table 67. Pregnancy Outcomes of Patients with Possible In Utero Exposure to Study Medication

Treatment Group	Pt No. (Protocol) Investigator	Pregnancy Outcome
Clindamycin Vaginal Ovule (3-Day)	1504 (0001) Martel	Normal vaginal delivery. Live birth. No abnormalities observed.
	2696 (0001) Peipert	Live birth. No abnormalities observed.
	320 (0002) Thoren	Live birth. No abnormalities observed.
Clindamycin Vaginal Cream (7-Day)	66 (0001) Livengood	Therapeutic/Elective abortion
	91 (0001) Gordon	Live birth. No abnormalities observed.
	281 (0001) Chatwani	Spontaneous (missed) abortion approximately 7 weeks after the last dose of study medication followed by a D&C with evacuation of a 7-week fetus. The investigator considered the spontaneous abortion to be unrelated to study medication.
	1159 (0001) Peipert	Live birth. No abnormalities observed.
Placebo Vaginal Ovule (3-Day)	49 (0283) Adams	Elective abortion
	92 (0283) Adams	Patient was lost to follow-up

Five-Day Maximum Exposure to Clindamycin Vaginal Ovule

Fourteen patients enrolled in Protocol 0283 were randomized to 5 days of treatment; 8 patients were randomized to treatment with clindamycin vaginal ovule and 6 to placebo vaginal ovule. One patient randomized to the clindamycin vaginal ovule group was reported to have used no study medication and was, therefore, excluded from the intent-to-treat (ITT) population.

Demographic Data

The mean age for the clindamycin group (N=7) was 23.4 ± 7.9 years; and for the placebo group (N=6), 20.8 ± 4.3 years. All 13 of the patients in the 5-day treatment arms were black.

All Reported Adverse Events

Table 68 shows the number and percent of the 13 patients treated in the 5-day treatment arms of Protocol 0283 who experienced adverse events during the study.

Table 68. Number and Percent of Patients in the 5-Day Arms of Protocol 0283 Who Experienced Adverse Events

Body System	Adverse Event (COSTART TERM)	CVO (5-Day) N=7	PBO-VO (5-Day) N=6
Body (As a Whole)	Headache	1 (14.3)	0 (0.0)
	Upper respiratory infection	0 (0.0)	1 (16.7)
Digestive	Nausea	0 (0.0)	1 (16.7)
Skin	Herpes simplex derm	0 (0.0)	1 (16.7)
Urogenital	Hemorrhage uterine	1 (14.3)	0 (0.0)
	Infection urinary tract	1 (14.3)	0 (0.0)
Patients with at least one adverse event reported		3 (42.9)	2 (33.3)
Total number of adverse events reported*		3	3

No event was reported by more than one patient in either treatment group. None of the reported events were considered by the investigator to be related to treatment with the study medication. All reported events were rated as mild in intensity.

Deaths, Other Serious Adverse Events, and Dropouts Due to Adverse Events

There were no deaths or serious adverse events reported for patients who received 5 days of treatment. Two patients dropped out of the study because of nonserious adverse events; these patients, however, completed their course of treatment before dropping out. The events that led to discontinuation, neither of which was considered related to treatment with the study medication, are summarized in Table 69 and are described in the following two narrative summaries.

Table 69. Listing of Patients in the 5-Day Arm of Protocol 0283 Who Dropped Out Due to Adverse Events

Treatment	Patient No. Investigator	Event (CI's Description)	Intensity	Study Day*	Related to Treatment†
CVO (5-Day)	1013 Adams	Urinary tract infection	Mild	+3	No
PBO-VO (5-Day)	1011 Adams	HSV II flare-up	Mild	+3	No

Protocol 0283: Patient 1011 (Investigator Adams; US)
Reason for Dropout: Herpetic flare-up
This 19-year-old patient with a diagnosis of BV was enrolled in the study on October 26, 1993 and assigned to treatment with placebo vaginal ovule. At the first follow-up visit (November 9, 1993), the patient was found to have continuing symptoms of bacterial vaginitis, as well as a herpetic eruption on the labia majora. The patient received Flagyl and Zovirax as treatment for these conditions. The patient was dropped from the study secondarily to the herpetic flare-up. The investigator did not consider this event to be related to treatment with the study medication.

Protocol 0283 Patient 1013 (Investigator Adams; US)
Reason for Dropout: Urinary tract infection
This 21-year- patient with a diagnosis of BV was enrolled in the study on November 5, 1993. At the first follow-up visit (November 12, 1993), the patient was found to have a urinary tract infection for which she received treatment with Keflex. The patient was dropped from the study because of the use of the systemic antibiotic. The patient continued to have symptoms of a urinary tract infection symptoms and on November 29, 1993, she was started on ciprofloxacin therapy. The investigator did not consider this event to be related to treatment with the study medication.

Safety Summary and Conclusions:

Safety of 3-Day Clindamycin Vaginal Ovule

A total of 1177 patients were treated in three studies (excluding patients in the 5-day arms of Protocol 0283) to evaluate the safety and efficacy of clindamycin vaginal ovules administered once daily in women with BV. Of the 1177 patients, 589 were randomized to treatment with clindamycin vaginal ovules for 3 days and the remainder randomized to treatment with either placebo vaginal ovules for 3 days, clindamycin vaginal cream for 7 days, or metronidazole oral tablets for 7 days. There were no clinically significant differences among treatment groups with regard to the percentages of patients who experienced adverse events, who discontinued treatment because of an adverse event, or who experienced serious adverse events.

The majority of the events reported during the three ovule studies were mild to moderate in intensity. Eleven events reported for patients in the ovule group were classified as severe, but none was considered by both the investigator and the monitor to be related to treatment with the study medication.

The percentage of patients who experienced treatment-related adverse events was highest in the metronidazole group and lowest in the placebo group. The body systems with the highest frequencies of events were the body as a whole for all four treatment groups (primarily headache), urogenital for all the active comparators (primarily vulvovaginal disorder; which was generally described by the investigators as vaginal itching or vaginal irritation), and digestive for the metronidazole group (primarily nausea).

Selected COSTART terms were collapsed in order too more precisely determine the frequency at which patients reported vaginitis and moniliasis. No clinically significant differences were noted among the active treatment groups – clindamycin vaginal ovule, clindamycin vaginal cream, and metronidazole tablets – with regard to the percentage of patients with one or both of these conditions (10.7%, 10.4%, and 11.7%, respectively). Similar proportions of patients in these treatment groups were considered by the investigator to have had treatment-related vaginitis and/or moniliasis (5.8%, 6.3%, and 6.6%, respectively).

Few patients discontinued or interrupted treatment because of adverse events. The incidence of premature treatment discontinuation was highest in the metronidazole group (3.1%: 6/196) compared to the 3-day clindamycin vaginal ovule group (0.7%: 4/589) and the 7-day clindamycin vaginal cream group (1.8%: 6/335). The shorter treatment period with the ovule may have been a factor in the low discontinuation rate in this treatment group. Of the clindamycin-treated patients, 3 of the 4 who discontinued treatment with the ovule and 5 of the 6 who discontinued treatment with clindamycin cream did so because of urogenital disorders (e.g., vulvovaginal disorder), while 5 of the 6 who discontinued treatment with metronidazole did so primarily because of gastrointestinal complaints (e.g., nausea and vomiting). None of the patients in the placebo ovule group discontinued or interrupted treatment due to adverse events.

Six patients (1 in the ovule group, 4 in the cream group, and 1 in the metronidazole group) experienced a serious adverse event. The events experienced by 5 of the 6 patients were considered unrelated to treatment with the study medication. The serious event – pyelonephritis – experienced by the sixth patient (3-day ovule group) was considered by the investigator but not the medical monitor to be related to treatment with the study medication. All patients recovered without residual effects.

No studies were done to evaluate the safety of clindamycin vaginal ovule in pregnant women. However, 9 patients are known to have become pregnant while enrolled in the ovule studies. Of the 3 in the clindamycin vaginal ovule group, all had normal live births; of the 4 in the clindamycin 7-day cream group, 2 had normal live births and 2 aborted (1 spontaneously and 1 electively); of the 2 in the placebo ovule group, 1 had an elective abortion and the other was lost to follow-up.

In conclusion, the safety profile of clindamycin vaginal ovule administered for 3 days in women with BV is not unlike that of clindamycin vaginal cream administered for 7 days. No new or unexpected events were reported during the studies integrated for this

Safety of 5-Day Clindamycin Vaginal Ovule

The adverse event profiles of the seven patients treated for 5 days with clindamycin vaginal ovule in Protocol 0283 appeared to be consistent with those of the patients treated for 3 days. No definitive comparisons (e.g., dose-response analyses of the 3- and 5-day results) can be made due to the small numbers of patients treated for 5 days.

Safety Information from Pharmacokinetics Study

Frequency of All Adverse Events and Treatment-Related Events

Table 70 shows all adverse events, including those considered by the investigator to be related to treatment with the study medication, that were reported by subjects in Protocol 0003 after administration of the specified cross-over treatment.

Table 70. Number of Subjects* Enrolled in Pharmacokinetic Study (Protocol 0003) Who Had Adverse Events

Body System	Event (COSTART TERM)	CVO† N=13	CVC‡ N=12	C-SS§ N=11
Body as a Whole	Abdominal pain, generalized	1 [1 R]	0	0
	Back pain	1	0	0
	Chills	1	0	0
	Exposure in Utero	1¶	0	0
	Headache	3	5	1 [1 R]
Cardiovascular	Vasodilation	1**	0	0
Digestive	Diarrhea	2 [1 R]	1 [1 R]	0
	Dyspepsia	0	1	0
	Flatulence	2 [2 R]	1 [1 R]	0
	Nausea	2 [2 R]	1 [1 R]	0
Nervous	Dizziness	2 [2 R]	0	0
Respiratory	Cough	2	0	0
	Pharyngitis	1	0	0
	Rhinitis	3	0	0
Skin	Eczema	1	0	0
	Herpes simplex derm	0	1	0
Urogenital	Disorder, vulvovaginal	2 [2 R]	0	0
	Dysuria	0	1	0
	Vaginal pain	3 [3 R]	0	0

Abbreviations: CVC = clindamycin vaginal cream, CVO = clindamycin vaginal ovule, C-SS = clindamycin sterile solution, R = related to treatment (appears after number of subjects with events judged by the investigator and monitor to be related to study medication)

*Subjects with multiple occurrences of the same event were counted only once for that particular event.

†One 100-mg clindamycin phosphate vaginal ovule administered intravaginally in the evening for 3 consecutive days

‡One 100-mg dose (one applicatorful [5 grams]) of clindamycin phosphate vaginal cream 2% administered intravaginally in the evening for 3 consecutive days

§One 100-mg dose (10 mL) of clindamycin phosphate 10 mg/mL sterile solution administered intravenously over 4 minutes

¶Outcome: pregnancy was terminated at 5 weeks (1 month after last dose of study medication) without complications

**Described by investigator as "hot flashes"

A total of 40 adverse events (none of which were serious) were reported by 11 of the 13 subjects enrolled in Protocol 0003. The greatest number of adverse events was reported following exposure to the vaginal ovule (28 events in 10 subjects) compared to the vaginal cream (11 events in 8 subjects) and the intravenous treatment (1 event in 1 subject). Headache, the most frequently reported event, occurred in 3 subjects during ovule treatment, in 5 subjects during vaginal cream treatment, and in 1 subject during intravenous treatment. The next most common event was flatulence, reported by 2 subjects in the ovule group and 1 subject in the vaginal cream group.

During treatment with the vaginal ovule, a sensation of vaginal burning (COSTART description: vaginal pain) was reported by 3 subjects, and vulvar or vaginal pruritus (COSTART description: disorder vulvovaginal) was reported by 2 subjects. These events were not reported by any subject during treatment with the vaginal cream or the intravenous infusion of clindamycin sterile solution.

The investigator and the medical monitor reviewed adverse events, and 17 of the total 40 adverse events were considered to be possibly related to treatment with the study medication. All of the reported events were considered to be mild in intensity, except for one headache (reported after vaginal cream dosing) rated as moderate.

Two patients were dropped from the study. Patient No. 5, who was treated with clindamycin vaginal ovule, had a positive urine drug screen prior to the second study period. Patient No. 9, who was treated with clindamycin vaginal cream and subsequently with clindamycin vaginal ovule, had a positive pregnancy test prior to the third study period. The latter patient had an elective abortion.

Conclusions

The frequently reported events (headache in both the clindamycin ovule and cream treatment groups and urogenital events in the ovule group) are qualitatively similar to those seen in the three clinical safety and efficacy studies. Consequently, the use of the vaginal ovule should not result in a higher incidence of adverse effects than that associated with the use of clindamycin cream.

Other Safety Information

Drug-Drug and Drug-Disease Interactions

No systemic drug interactions are known or anticipated with clindamycin vaginal ovules. Antagonism between clindamycin and erythromycin has been demonstrated in vitro. One patient (No. 1228; Protocol 0002) treated with clindamycin vaginal ovules received concomitant treatment with azithromycin, an antibiotic structurally related to erythromycin; no adverse events, however, were reported for this patient.

No information is available on the concomitant use of clindamycin vaginal ovules and other intravaginal medications. In all three clindamycin vaginal ovule studies, the use of other intravaginal medication was not permitted under protocol requirements. Adverse event data for patients who deviated from this requirement were not analyzed separately to identify potential drug-drug interactions.

Adverse event profiles of patient subgroups defined by concomitant medications or by pre-existing diseases were not analyzed to identify potential drug-drug or drug-disease interactions. Consequently, no safety concerns could be identified with regard to such interactions.

Long-Term Safety Information and Withdrawal Effects

The safety of clindamycin vaginal ovules was not studied beyond the 3- and 5-day treatment periods and the follow-up visits specified in the study protocols. Data from studies of a 7-day regimen of clindamycin vaginal cream (summarized in previous regulatory submissions) do not indicate increased risk with longer exposure. Withdrawal effects are not generally attributed to antibiotics.

Antibiotic-Associated Colitis

Clindamycin, like most other antibiotics, has the potential to cause antibiotic-associated colitis (AAC). This condition appears to develop as a result of suppression of bowel flora by the antibiotic, allowing overgrowth of *Clostridium difficile* and the potential for initiation of the disease process. Although clindamycin has been the most historically implicated cause of AAC, recent studies show that broad-spectrum penicillins and cephalosporins are most often implicated in current practice. Other antibiotics, such as erythromycin, metronidazole, neomycin, [redacted] tetracycline, and vancomycin are also under scrutiny. Non-antibiotic risk factors for *C difficile*-associated diarrhea include gastrointestinal stimulants, enemas, stool softeners, antacids, laxatives, severity of underlying disease, age, etc.

Several studies done in the last decade report a low incidence of diarrhea and no cases of AAC with clindamycin. The wide variance in the reported incidence of AAC possibly reflects differences in the definitions of pseudomembranous and colitis, study methods used, and differences in the severity of illness encountered in the study populations.

Reports of antibiotic-associated colitis or pseudomembranous colitis in association with topical clindamycin phosphate (which has been marketed since 1980 as a 1% solution for the treatment of acne vulgaris) have been extremely uncommon. P&U have received few voluntary reports of AAC or related adverse events associated with clindamycin vaginal cream, which has been marketed since 1992. Because of the low systemic absorption of clindamycin from the vagina, the likelihood of intravaginal clindamycin precipitating AAC would seem remote.

In all clinical studies with clindamycin, investigators were asked to follow up, as clinically indicated, any cases of significant diarrhea. Of the 589 patients enrolled in the clindamycin vaginal ovule treatment arms of the three clinical safety and efficacy studies included in this submission, one (No. 828, Protocol 0002) reported severe episodic diarrhea that lasted 6 days. This event was considered by the investigator to be related to treatment with the study medication but it did not meet the criteria for a serious event. The patient recovered without residual effects.

Conclusions

Although systemic absorption of clindamycin in healthy subjects is approximately seven-fold higher following intravaginal administration of the ovule formulation than that following administration of the cream formulation, the exposure following administration of the vaginal ovule is still considerably less than that from a therapeutic oral or intravenous dose of clindamycin. Comparison of the safety profile of 589 patients treated in controlled clinical trials for 3 days with clindamycin phosphate vaginal ovule with that of the previously established safety profile in patients treated for 7 days with clindamycin phosphate vaginal cream, moreover, does not reveal an indication of an increased incidence of systemic side effects with the ovule.

The most commonly reported adverse events for patients treated with the ovule for 3 days and those treated with the active comparators were vulvovaginal disorder (primarily vaginal itching and vaginal irritation) and events that were collapsed programmatically to

either vaginal moniliasis or vaginitis. There were no clinically important differences among the active treatment groups with regard to the number and percent of patients who experienced these events.

The adverse events most frequently considered by the investigators to be possibly caused by the study medication are the same as those described above. With the exception of pyelonephritis, all of the events judged by the investigators to be related to treatment with the study medication were nonserious, and nearly all treatment-related events resolved with no residual effects. The one serious event (pyelonephritis) considered by the investigator to be possibly related to treatment occurred in one patient in the clindamycin ovule group, but was not considered by the medical monitor to be related to treatment; this event resolved with no residual effects.

In conclusion, the treatment-related events reported in patients treated with clindamycin vaginal ovule did not present substantial risk to the patients and would not be likely to deter clinical usage of the clindamycin ovule formulation.

16. Recommendation: From a clinical prospective, I recommend approval of this NDA which will provide for Clindamycin vaginal ovules, containing 100 mg of clindamycin phosphate per ovule, for the 3-day treatment of bacterial vaginosis. The proposed labeling dated September 22, 1998 and submitted with the NDA should be revised to reflect the changes suggested in the Review of Labeling dated July 26, 1999.

/S/

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

CC:NDA 50-767
HFD-590/DepDir/RAlbrecht
HFD-590/MO/Winfield
HFD-590/Bio-Pharm/
HFD-590/Pharm Tox/McMaster
HFD-590/Chem/Matecka
HFD-590/Stat/LShen
HFD-590/PMS/CChi
HFD-590/TL/BLeissa 8/1/99

Concurrence Only:
HFD-590/DivDir/MGoldberger

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DATE SUBMITTED BY SPONSOR: OCTOBER 13, 1998
DATE RECEIVED BY CDER: OCTOBER 14, 1998
DATE RECEIVED BY REVIEWER: OCTOBER 28, 1998
DATE REVIEW STARTED: MAY 22,, 1999
DATE REVIEW COMPLETED: JULY 26, 1999

MEDICAL OFFICER'S REVIEW OF LABELING OF NDA 50-767

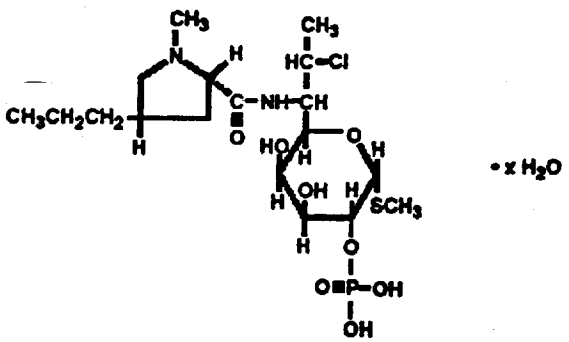
APPLICANT: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

GENERIC NAME: Clindamycin phosphate vaginal suppository

TRADE NAME: CLEOCIN® Vaginal Ovule

CHEMICAL NAME: 7-(S)-chloro-7-deoxylincomycin-2-phosphate

CHEMICAL STRUCTURE:



MOLECULAR FORMULA: $C_{18}H_{34}ClN_2O_8PS$

MOLECULAR WEIGHT: 504.96

PHARMACOLOGIC CATEGORY : Anti-bacterial

DOSAGE FORM: Vaginal suppository (ovule)

STRENGTH: 100 mg

ROUTE OF ADMINISTRATION: Intravaginal

PROPOSED INDICATION AND USAGE: Cleocin Vaginal Ovule is indicated for the 3-day treatment of bacterial vaginosis.

PROPOSED DOSAGE AND ROUTE OF ADMINISTRATION: The recommended dose is one Cleocin Vaginal Ovule (clindamycin phosphate equivalent to 100 mg

clindamycin per 2.5-g suppository) intravaginally, preferably at bedtime, for 3 consecutive days.

The proposed labeling for the package insert submitted by the sponsor has been reviewed and found to be satisfactory except for the following:

In the INDICATIONS AND USAGE section, insert "in non pregnant women." after "vaginosis", and delete "(formerly referred to as *Haemophilus vaginitis*, *Gardnerella vaginitis*, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis)." The second sentence should read: "There are no adequate well-controlled studies in pregnant women."

In the **WARNINGS** section; In the last sentence, delete: "clindamycin, even when administered by the vaginal route" and insert "Cleocin Vaginal Ovule, because ..."

In the **Precautions** section:, revise the **General** paragraph as follows:

General
The use of Cleocin Vaginal Ovules may result in the overgrowth of non-susceptible organisms in the vagina. In clinical studies 589 vaginal or non-vaginal moniliasis and fungal infection. Vaginitis includes the terms: vulvovaginal disorder, vaginal discharge, and vaginitis/vaginal infection

In the **Pregnancy: Teratogenic effect** section; delete, "This drug should be used during pregnancy only if clearly needed

In the **Directions For Use** section; item number 6 should precede item number 5. The section referring to the Insertion without an applicator should be deleted.

These changes and the changes recommended by the other reviewing disciplines should be communicated to the Applicant.

/S/

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

CC:NDA 50-767
HFD-590/DepDir/RAlbrecht
HFD-590/MO/Winfield
HFD-590/Bio-Pharm/
HFD-590/Pharmtox/McMaster
HFD-590/Chem/Matecka
HFD-590/Stat/
HFD-590/PMS/CChi
HFD-590/TL/BLeissa bc 8/1/99

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