

Drug-related Medical Events

The investigator assessed the relationship between each ME and the use of study drug. MEs considered drug-related were reported for slightly more patients in the 3-day treatment group (27/261) 10.3% than in the 7-day treatment group (18/273) 6.6%. Table 19.

With the exception of the body as a whole, the incidence of drug-related events affecting each body system was balanced between the two treatment groups (Table 18). The most frequent drug-related MEs were those affecting the urogenital system and the body as a whole, occurring in 5.4% (14/261) and 3.4% (9/261), respectively, of patients in the 3-day treatment group, and in 5.1% (14/273) and 0.7% (2/273), respectively, of patients in the 7-day treatment group.

Drug-related MEs are presented by body system and COSTART description in Table 19. With the exception of moniliasis (within the body as a whole, rather than vaginal), there were few differences between the treatment groups with regard to the frequency of drug-related MEs. The greatest difference between treatment groups in frequency of events considered drug related was seen for moniliasis; reports of moniliasis were classified as drug related more often for the 3-day group, even though moniliasis was reported more frequently overall in the 7-day group. Moniliasis was considered drug-related for 7 (2.7%) of 261 patients in the CVC 3-day treatment group and 1 (0.4%) of 273 patients in the CVC 7-day treatment group. The distinction between moniliasis and vaginal moniliasis is an artifact of COSTART coding, since some events described by investigators as "candidiasis" or "moniliasis" (likely to be vaginal in this patient population) are included under the COSTART description of moniliasis within the body as a whole. The combined incidence of drug-related events classified as moniliasis and vaginal moniliasis was 5.0% for CVC 3-day patients and 3.7% for CVC 7-day patients, with one patient in the 7-day group experiencing both types of event. The difference between the two treatment groups is unlikely to be clinically relevant.

The majority of MEs that occurred in this study were not considered drug-related (195/243) 80.2%. Of the 48 drug-related events, 46 (95.8%) were of mild or moderate intensity and two (4.2%) were reported as severe in intensity (Table 20). Both severe drug-related MEs were experienced by patients treated with CVC for 3 days: Patient number 259, who had a vulvovaginal disorder (vaginal pruritus); and Patient number 558, who had moniliasis.

Table 18
Drug-Related Medical Events By Body System
Patients who Receive at Least one Dose of Medication

BODY SYSTEM	CVC 3-DAY		CVC 7-DAY		TOTAL	
	N	%	N	%	N	%
BODY	9	3.4	2	0.7	11	2.1
DIGESTIVE	3	1.1	2	0.7	5	0.9
SKIN	2	0.8	1	0.4	3	0.6
UROGENITAL	14	5.4	14	5.1	28	5.2
NUMBER OF PATIENTS ON WHICH % IS BASED	261		273		534	

TABLE 19
DRUG-RELATED MEDICAL EVENTS BY BODY SYSTEM AND COSTART DESCRIPTION (MET)

BODY SYSTEM	COSTART DESCRIPTION (MET)	CVC 3-DAY		CVC 7-DAY		TOTAL	
		N	%	N	%	N	%
PATIENTS WITH NO MEDICAL EVENTS		234	89.7	255	93.4	489	91.6
PATIENTS WITH AT LEAST ONE MEDICAL EVENT		27	10.3	18	6.6	45	8.4
BODY	ABDOMINAL PAIN GENERALIZED	1	0.4			1	0.2
	ABDOMINAL PAIN LOCALIZED	1	0.4			1	0.2
	MICROBIOLOGICAL TEST ABNORMAL NOS			1	0.4	1	0.2
	MONILIASIS	7	2.7	1	0.4	8	1.5
DIGESTIVE	DIARRHEA	1	0.4	2	0.7	3	0.6
	NAUSEA	2	0.8			2	0.4
	ERYTHEMA			1	0.4	1	0.2
SKIN	MONILIASIS SKIN	1	0.4			1	0.2
	PRURITUS NON-APPLICATION SITE	1	0.4			1	0.2
	DISORDER VULVOVAGINAL	8	3.1	6	2.2	14	2.6
UROGENITAL	MONILIASIS VAGINAL	6	2.3	9	3.3	15	2.6
	TOTAL NUMBER OF MEDICAL EVENTS	28		20		48	
NUMBER OF PATIENTS ON WHICH % IS BASED		261		273		534	

TABLE 20
Drug Related Medical Events By Body System
COSTART Description and Maximum Intensity

BODY SYSTEM	COSTART DESCRIPTION (MET)	CVC 3-DAY			CVC 7-DAY		TOTAL			
		MILD	MOD	SEV	MILD	MOD	MILD	MOD	SEV	TOT
BODY	ABDOMINAL PAIN GENERALIZED	1					1			1
	ABDOMINAL PAIN LOCALIZED	1					1			1
	MICRO TEST ABNORMAL NOS				1		1			1
	MONILIASIS	3	3	1		1	3	4	1	8
DIGESTIVE	DIARRHEA	1			2		3			3
	NAUSEA	1	1				1	1		2
	ERYTHEMA				1		1			1
SKIN	MONILIASIS SKIN		1					1		1
	PRURITUS NON-APPLICATION SITE	1					1			1
	DISORDER VULVOVAGINAL	5	2	1	3	3	8	5	1	14
UROGENITAL	MONILIASIS VAGINAL	4	2		5	4	9	6		15
TOTAL NUMBER OF MEDICAL EVENTS		17	9	2	12	8	29	17	2	48

Dropouts Due to Medical Events

A listing of patients who dropped out of the study due to MEs is shown in Table 21. Fifteen patients dropped out due to MEs, 10 in the 3-day treatment group and 5 in the 7-day treatment group. None of the MEs that led to a patient dropping out of the study met the protocol definition of a serious ME. Eight patients dropped out of the study due to drug-related MEs, 6 in the 3-day group and 2 in the 7-day group.

Table 21

Patients Who Dropped Out Due to Medical Events

PATIENT NUMBER	INVESTIGATOR	EVENT(INVESTIGATOR DESCRIPTION)	MAXIMUM INTENSITY	STUDY DAY	DRUG RELATED*
CLINDAMYCIN VAGINAL CREAM 3-DAY TREATMENT					
55	SIK	CANDIDIASIS	MODERATE	13	YES
255	BORNSTEIN	VAGINAL DISCHARGE	MODERATE	48	NO
259	BORNSTEIN	VAGINAL PRURITUS	SEVERE	1	YES
354	DAMM	BLEEDING	MILD	3	NO
547	PRILEPSKAYA	CANDIDIASIS	MILD	7	YES
560	PRILEPSKAYA	CANDIDIASIS	MODERATE	37	YES
602	NEL	CANDIDIASIS	MILD	10	YES
831	PETERSON	PREGNANCE	MILD	11	NO
878	LARKIO-MIETTINEN	1. URINARY INFECTION 2. MONILIASIS	1. MILD 2. MILD	1. 1 2. 1	1. NO 2. YES
924	AHMED	URINARY TRACT INFECTION	MILD	9	NO
CLINDAMYCIN VAGINAL CREAM 7-DAY TREATMENT					
208	PAPP	VAGINAL DISCHARGE/ CANDIDIASIS	MILD	4	NO
257	BORNSTEIN	<i>E. COLI</i> IN URINE CULTURE	MILD	20	NO
348	DAMM	VAGINAL CANDIDA	MILD	6	YES
594	NEL	VAGINAL CANDIDIASIS	MODERATE	10	YES
762	SCHAETZING	TRICHOMONIASIS	MILD	11	NO

*INVESTIGATOR'S OPINION

Narratives

3-Day Treatment Group

Patient # 55

This 46-year-old, 80-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on August 30, 1996. Her medical history included a previous episode of BV and spondylolisthesis of the fourth and fifth lumbar vertebrae for which she was receiving analgesia. She had also been receiving treatment for hypertension since 1994. After successful completion of study treatment, candidiasis was reported as a non-serious ME on September 11, 1996 and led to the patient's withdrawal from the study. The event was of moderate severity and resolved without sequelae on September 20, 1996, following treatment with clotrimazole.

Patient # 255

This 40-year-old, 52-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 31 October 1996. Her medical history included previous actual and suspected episodes of BV. Vaginal discharge was documented on pelvic examination at baseline. On 15 November 1996, pelvic examination was normal, but the patient underwent voluntary termination of a pregnancy, which had been

undetected at the time of entry into the study. Vaginal discharge of moderate intensity was reported as a ME on 17 December 1996, associated with the presence of *Candida* on KOH smear. The patient was discontinued from the study. The *Candida* infection resolved without sequelae, though at the time of follow-up the patient was still experiencing vaginal discharge. Both events were considered non-serious and unrelated to study medication.

Patient #259

This 28-year-old, 50-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 28 November 1996. Her medical history included previous actual and suspected episodes of BV, with vaginal discharge documented on pelvic examination at baseline. She experienced vaginal pruritus on Day 1 of treatment and discontinued from the study. The event was severe, but resolved without treatment after 4 days. This episode of pruritus was considered by the investigator to be related to study medication.

Patient #354

This 26-year-old, 62-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 3 May 1996. She had a past medical history of endometriosis in 1992, but no other abnormality was noted. Two days after the start of study treatment she experienced mild bleeding, which was non-serious and not considered related to study medication. She was withdrawn from the study and bleeding resolved without treatment after 8 days. On 8 May 1996 she also experienced a mild headache for which she received paracetamol 500 mg qds.

Patient # 547

This 21-year-old, 46-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 15 May 1996. Her past medical history included rubella in 1976 and pneumonia in 1984. At the 10 day follow-up, pelvic examination revealed vaginal pruritus and discharge and a ME of candidiasis was reported as commencing on 21 May 1996. The event was mild in intensity and non-serious. However, it was considered by the investigator to be related to study medication and led to the patient being discontinued from the study having completed study medication. She received vaginal natamycin cream 100 mg qds for 3 days, and symptoms resolved after 1 week.

Patient # 560

This 32-year-old, 65-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 27 August 1996. Pelvic examination revealed an extorcion of the cervix. At the 30-day follow-up visit, the patient had a vaginal discharge and hyperemia. Candidiasis was reported as a non-serious ME of moderate intensity, commencing on 2 October 1996. It was deemed by the investigator to be related to study medication and resulted in the patient refusing to continue in the study. She received vaginal natamycin cream 100 mg qds for 6 days, and symptoms resolved on 9 October 1996.

Patient # 602

This 50-year-old, 59 kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 6 March 1996. She had been receiving treatment for mild essential hypertension and hypothyroidism since 1985 and had undergone a hysterectomy in 1990. Following completion of study medication, a *Candida* infection was reported as a non-serious ME of mild severity, commencing on 15 March 1996. The event was considered related to study medication and the patient was discontinued from

the study. She received vaginal clotrimazole 50 mg nocte for 8 days, and the event was resolved on 29 March 1996.

Patient #831

This 18-year-old, 53-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 14 October 1996. She had a history of gastritis in April 1995, and a baseline pregnancy test was negative. At the Day 10 follow-up, BV was improved and no MEs were recorded. At the Day 30 follow-up on 27 November 1996, BV was cured. However, the patient had a confirmed pregnancy (last monthly period 24 October 1996, expected date of delivery 5 August 1997) and had been suffering from hyperemesis of moderate intensity since 26 November 1996. She was hospitalized from 26 to 29 November 1996 for the treatment of the hyperemesis, which was considered by the investigator to be related to the pregnancy. While in hospital, a non-serious ME of cystitis was also reported, for which the patient received amoxicillin. At the time of the last follow-up, the pregnancy was ongoing.

Patient #878

This 38-year-old, 52-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 1 October 1996. She had no relevant medical history or concomitant illness. On Day 1 of treatment, MEs of urinary infection and moniliasis were recorded. Both were non-serious and mild in intensity. The *Monilia* infection resolved within 1 day without treatment and was considered related to study medication. The urinary infection was not considered drug-related and cleared within 6 days after treatment with oral cinoxacin 500 mg qds for 8 days. Both MEs were documented as the reason the patient discontinued from the study.

Patient #924

This 32-year-old, 52-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 23 October 1996. She had a history of BV and had suffered a ruptured ovarian cyst in 1994. On pelvic examination at baseline she was found to have a vulval wart. After completion of study medication, the patient suffered a urinary tract infection which was treated with oral trimethoprim 200 mg bd from 7 November 1996. The ME was mild in severity, non-serious, and considered not related to study medication. However, the patient was discontinued from the study.

7-day Treatment Group

This 26-year-old, 57-kg white woman had a diagnosis of BV and started study medication (7-day treatment) 26 September 1996. Her medical history was unremarkable with only previous suspected episodes of BV noted. Vaginal discharge/candidiasis was reported as a non-serious medical event starting on 29 September 1996, confirmed by pelvic examination on 3 October 1996. The event was of mild intensity and considered unrelated to study medication. The patient was discontinued from the study at the Day 10 visit. She was treated for 3 days with vaginal econazole, and the candidiasis resolved without sequelae on 6 October 1996.

Patient #257

This 32-year-old, 60 kg white woman had a diagnosis of BV and started study medication (7-day treatment) on 21 November 1996. Her medical history included previous actual and suspected episodes of BV, with vaginal discharge documented on pelvic examination at baseline. She completed study medication, and on 5 December 1996 pelvic examination was normal. However, *E. coli* was cultured in urine, and this was reported as a ME commencing on 10 December 1996. The event was mild and considered not related to study medication. At the Day 30 follow-up visit on 19 December 1996, vaginal discharge was noted on pelvic examination and the patient discontinued from the study as a result of both the *E. coli* infection and vaginal discharge.

Patient #348

This 26-year-old, 48-kg white woman had a diagnosis of BV and started study medication (7-day treatment) on 21 March 1996. In addition to BV, she had perineal itching, possibly due to eczema, and fibromyalgia at baseline, but was not receiving any treatment. Topical hydrocortisone butyrate 0.1% was started on 21 March 1996 for the treatment of eczema. The patient reported two MEs, first a mild urine infection beginning on 23 March 1996, which resolved on treatment with oral norfloxacin 200 mg bd from 24 March to 3 April 1996. This event was considered non-serious and not related to study medication. From 26 to 28 March 1996, she also experienced a mild *Candida* infection, which resulted in her being discontinued from the study. This was treated on 27 March 1996 with oral fluconazole 150 mg qds and resolved without sequelae. The infection was considered by the investigator to be related to study medication.

Patient #594

This 35-year-old, 76-kg white woman had a diagnosis of BV and started study medication (7-day treatment) on 13 August 1996. She had a recent history of sinusitis and insomnia and had been taking oral zopiclone 7.5 mg nocte since 1 April 1996. At the Day 10 follow-up visit, the patient had a yellow vaginal discharge and candidiasis of moderate severity was reported as a ME, commencing on 22 August 1996. The event was considered non-serious, and the patient discontinued from the study. She received vaginal clotrimazole 5 g nocte for 7 days from 27 August 1996, and the event was resolved on 3 September 1996.

Patient #762

This 40-year-old, 71-kg black woman had a diagnosis of BV and started study medication ((7-day treatment) on 13 October 1996. A *Trichomonas* infection was reported as a non-serious ME of mild severity, on 23 October 1996, after completion of study medication. This resulted in the patient discontinuing from study, though the event was considered unrelated to study medication. At the last follow-up visit, the event was continuing.

Deaths and Serious Medical Events

There were no patient deaths during the study.

Four patients, three in the 3-day treatment group and one in the 7-day treatment group, had serious MEs during the study. None of these events were considered related to study medication, and none led to the patient dropping out of the study. For two patients (No. 345 and No. 369), the serious MEs were of severe intensity. Details of all serious MEs are given in the following narrative summaries:

Patient # 345

Serious Medical Event: Operation - Thyroid Resection

This 46-year-old, 58-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 27 February 1996. At baseline, it was noted that she was awaiting surgery for a euthyroid goiter, and examination revealed an enlarged thyroid. At the Day 10 follow-up on 5 March 1996, BV was cured and no MEs were recorded. At the Day 30 follow-up, her condition was classified as improved, and a non-serious ME of influenza, treated with paracetamol, was documented. One week prior to the final study visit, she was hospitalized for a thyroid resection. Although this was a preexisting condition, the event was classified as serious by definition due to the hospitalization, and was reported as severe. The patient remained in hospital for 2 days and received various anesthetic and analgesic medications during that time. She subsequently recovered and completed the Day 90 follow-up visit.

Patient #823

Serious Medical Event: Bartholinitis

This 43-year-old, 59-kg white woman had a diagnosis of BV and started study medication (3-day treatment) on 31 May 1996. Her past medical history included hepatitis A and migraine, and she had undergone laparoscopic sterilization in 1991. On the day of the baseline visit, she commenced oral cimicifuga 1 mg bd for the treatment of climacteric symptoms. At the Day 10 follow-up on 7 June 1996, BV was cured and no MEs were recorded. At the Day 320 follow-up, BV remained cured, but the patient experienced a non-serious vaginal *Candida* infection from 10 June to 11 July 1996. This event was of mild severity and considered not to be related to study medication. The patient was treated with vaginal clotrimazole 20 mg. At the Day 90 visit, the patient remained cured, but two further MEs were reported. Bartholinitis of moderate severity was recorded from 23 July 1996, and was considered unrelated to study medication. On examination, the patient was found to have an acute left Bartholin's abscess and was hospitalized for removal and marsupialization. On 26 August 1996, a non-serious ME of mastitis was recorded. This was considered unrelated to study medication and, despite treatment, was ongoing at the time of the final evaluation.

Patient #831

Serious Medical Event: Hyperemesis

This 18-year-old, 53-kg white woman had a diagnosis of BV and started study medication (e-day treatment) on 14 October 1996. She had a history of gastritis in April 1995, and a baseline pregnancy test was negative. At the Day 10 follow-up, BV was improved and no MEs were recorded. At the Day 30 follow-up on 27 November 1996, BV was cured. However, the patient had a confirmed pregnancy (last monthly period 24 October 1996, expected date of delivery 5 August 1997) and had been suffering from hyperemesis of moderate intensity since 26 November 1996. She was hospitalized from 26 to 29 November 1996 for the treatment of the hyperemesis, which was considered by the investigator to be related to the pregnancy. While in hospital, a non-serious ME of cystitis was also reported, for which the patient received amoxicillin. At the time of the last follow-up, the pregnancy was ongoing.

Patient #369

Serious Medical Event: Endometriosis

This 37-year-old, 72-kg white woman had a diagnosis of BV and started study medication (7-day treatment) on 5 March 1996. She was documented as having completed treatment. Physical findings at the baseline visit confirmed the presence of a growth on the left ovary. Pelvic examination also demonstrated p[probable endometriosis and a possible left ovarian cyst. She was admitted to the hospital with acute pain on 8 March 1996 and underwent a laparoscopy. Severe ovarian endometriosis was diagnosed and a laparoscopic ovarian resection performed. The patient received a number of anesthetic and analgesic medications during the period of hospitalization, but study medication was uninterrupted, and the patient attended the Day 10 follow-up on 14 March 1996, where her condition was classified as improved.

**APPEARS THIS WAY
ON ORIGINAL**

Summary of Supplement

Efficacy

The Applicant submitted this amendment to Supplement 002 of NDA 50-680 for the purpose of obtaining approval for the use of clindamycin vaginal cream 2% once daily for three (3) days in treating patients with bacterial vaginosis (BV). The Applicant feels that a shorter duration of therapy than the approved 7-day will improve compliance and add convenience to the consumer thereby improving efficacy and decreasing the likelihood of adverse effects associated with systemic clindamycin administration.

Supplemental NDA 50-680 was initially submitted to the FDA on May 4, 1995 to support a labeling change from 7 day to a "3 to 7" consecutive day dosage regimen. Safety and efficacy of clindamycin in a 3 day regimen was evaluated in two placebo controlled studies and one active controlled study comparing the 3-day clindamycin regimen with the approved 7-day regimen. These data indicate, based on the overall treatment outcome with cure defined as absence of clue cells and odor, that clindamycin once daily for 3 days is statistically more effective than placebo and inferior in efficacy to the 7-day clindamycin regimen for the treatment of BV. See page 4 of this review. Based on the results obtain in study 0020, the FDA was not able to determine if the 3-day course of treatment with clindamycin is as effective as the currently approved 7-day course of treatment.

In order to obtain approval for the use of clindamycin for 3 days in the treatment of BV, the Applicant agreed to conduct a second active controlled study. The study was designed essentially the same as study 0020 and compared the efficacy and safety of the once daily dose regimen for 3 days to that of the 7-day regimen. The exception was that this study conducted in Europe rather than the US.

The primary efficacy of the treatment regimens was based on the success rate at the 30 day follow-up visit. There were two analyses performed by the Applicant and the Medical Officer on evaluable patients in each treatment group. In the first analysis, assessment of treatment outcome was based on the four diagnostic criteria (increased vaginal discharge, vaginal fluid pH, "fishy" amine odor and clue cells). At the recommendation of the FDA, a second analysis was done on the evaluable patients with treatment outcome based on two diagnostic criteria only (amine odor and clue cells).

In the Applicant's data analyses, the number of patients found to be cured based on the four diagnostic criteria was 136/202 (67%) and 145/218 (67%), respectively for the 3 and 7-day regimens.

Patients were considered by the applicant as being a success (cure + improved) in 168/202 (83%) and 190/218 (87%) respectively for the 3 and 7-day regimens.

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

When clinical outcome was based on amine odor and clue cells only, 161/199 (81%) of patients in the 3-day treatment group and 181/216 (84%) in the 7-day treatment group were determined as cures in the Applicant's analyses compared to 189/219 (86%) in the 3-day treatment group and 205/232 (88%) in the Medical Officer's analyses.

For both treatment groups, there appeared to be no statistical significant differences in the proportion of patients who were classified as cures at Day 30, by either the analyses of

the Applicant or the Medical Officer whether all four diagnostic criteria were used or only amine odor and clue cells.

TABLE 22
PATIENTS CURED AT DAY 30

	BASED ON 4 DIAGNOSTIC CRITERIA PATIENTS CURED			BASED ON AMINE ODOR AND CLUE CELLS PATIENTS CURED		
	CVC 3-DAY	CVC 7-DAY	95%CI	CVC-3-DAY	CVC 7-DAY	95% CI
APPLICANT CURED	67% (136/202)*	67% (145/218)*	-9, 10	80% (161/202)	83% (181/218)	-11, 5
CURED/ IMPRO	83% (168/202)	87% (190/218)	-11, 3	-	-	
MED OFF CURED	74% (162/219)	73% (170/232)	-8, 9	86% (189/219)	88% (205/232)	-8, 5

*Note: In the above data analyses there is small difference in the number of evaluable patients reported by the Applicant to those that were considered as evaluable by the Reviewing Medical Officer. The applicant reported 199 evaluable patients in the 3-day treatment group and 216 evaluable patients in the 7-day treatment group. However, this difference in the number of evaluable patients has no impact on the clinical cure rates of either treatment group.

SAFETY

The incidence of MEs was similar for the two treatment groups, with 30.7% of patients treated for 3 days and 32.6% of patients treated for 7 days experiencing one or more MEs. The most common MEs were those affecting the urogenital system, namely vaginal moniliasis, moniliasis, vulvovaginal disorder, and BV. More than 95% of all MEs were mild or moderate in intensity, with severe MEs reported by four patients in the 3-day group and three patients in the 7-day group. The incidence of drug-related MEs was higher for the CVC 3-day treatment group (10.3%) than for the 7-day group (6.6%), with reports of drug-related moniliasis (classified by COSTART within the body as a whole, as opposed to vaginal moniliasis) accounting for much of the difference. The combined incidence of drug related events classified as moniliasis and vaginal moniliasis was 5.0% for CVC 3-day patients and 3.7% for CVC 7-day patients.

Ten patients treated for 3 days dropped out of the study due to MEs, compared to five patients from the 7-day group. For six patients in the 3-day group and two in the 7-day group, the event leading to withdrawal was considered by the investigator to be drug-related. Serious MEs were experienced by four patients, but none were drug-related and none led to withdrawal from the study.

Conclusion

In this clinical study, Clindamycin Vaginal Cream 2% administered as a 5-gram dose once daily for three consecutive days, appear to be therapeutically equivalent to 5 grams of clindamycin vaginal cream administered once daily for 7 consecutive days in treating patients with bacterial vaginosis. Both regimens appear to be safe; in this study there was no clinically-significant difference in the incidence of adverse events between the two regimens although drug-related medical events were reported more frequently among patients treated for 3 days.

The results of this study suggest that a 3-day regimen of clindamycin is an appropriate therapy for the treatment of bacterial vaginosis however it does not offer an advantage to the consumer in either efficacy or safety when compared to the approved 7-day regimen.

Recommendation: The Applicant requests approval for the use of clindamycin vaginal cream for 3 or 7 days in treating non-pregnant patients with bacterial vaginosis. Based on the results of this clinical study and the results obtained in the US study that was submitted and analyzed previously, I recommend approval of this supplement to NDA 50-680 provided the labeling appropriately reflect the results obtained in both clinical studies.

/S/

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

cc: NDA 50-680
HFD-340
HFD-590
HFD-590-Dep/Dir/RAIbrecht
HFD-590/MO/JKWinfield
HFD-590 MO/DDavis
HFD-725/Stat/Dixon
HFD-590-/TmLdr/BLeissa /S/ 7/2/92
HFD-590/CS./CH:

Concurrence Only:
HFD-590/Div/Dir/MGoldberge

/S/

MAK

References:

1. L.; Dukes, C.D. Hemophilus Vaginalis Vaginitis: A Newly Defined Specific Infection Previously Classified "Nonspecific Vaginitis. American Journal of Obstetrics and Gynecology 1955; 69:962-976.
2. Mc Cue JD, et al.; Strategies for Diagnosing Vaginitis. J. Family Practice 1979; 9:395-402.
3. Rosene K, et al.: Polymicrobial Early Postpartum Endometritis with Facultative and Anaerobic Bacteria, Genital Mycoplasmas, and *Chlamydia trachomatis*, Treatment with Pepiracillin or Cefoxitin, J Infec Dis 1986; 153; 1028-1037
4. Gravett MG, et al.: Preterm Labor Associated with Subclinical Amniotic Fluid Infection and with Bacterial Vaginosis. Obstet Gynecol 1988; 67: 229-237.
5. Faro, S. Bacterial vaginitis. Clinical Obstetrics and Gynecology 1991; 34:582-586.
6. Amsel, R.; Totten, P.A.; Spiegel, C.A.; Chen, K.C.S.; Eschenbach, D.A.; Holmes, K.K. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. American Journal of Medicine 1983; 74:14-22.
7. Eschenbach, D.A.; Hillier, S.L.; Critchlow, C.W.; Stevens, C.; DeRouen, T.; Holmes, K.K. Diagnosis and clinical manifestations of bacterial vaginosis. American Journal of Obstetrics and Gynecology 1988; 158:819-828.
8. Thomason, J.L.; Gelbart, S.M.; Anderson, R.J.; Walt, A.K.; Osypowski, P.J.; Broekhuizen, F.F. Statistical evaluation of diagnostic criteria for bacterial vaginosis. American Journal of Obstetrics and Gynecology 1990; 162:155-160.
9. Krohn, M.A.; Hillier, S.L.; Eschenbach, D.A. Comparison of methods for diagnosing bacterial vaginosis among pregnant women. Journal of Clinical Microbiology 1989; 27:1266-1271.
10. Hillier, S.L.; Holmes, K.K. Bacterial vaginosis. In: Holmes, K.K.; Mardh, P-A; Sparling, P.F.; Wiesner, P.J. eds. Sexually transmitted diseases. 2nd ed. New York: McGraw Hill Information Services Co., 1990:547-559.
11. Bump, R.C.; Zuspan, F.P.; Buesching, W.J.; Ayers, L.W.; Stephens, T.J. The prevalence, six-month persistence, and predictive values of laboratory indicators of bacterial vaginosis (nonspecific vaginitis) in asymptomatic women. American Journal of Obstetrics and Gynecology 1984; 150: 917-924.
12. Livengood, C. H. et al.; Bacterial vaginosis: Diagnostic criteria and pathogenic findings during topical clindamycin therapy. Am J Obstet and Gynecology 1990; 163 (2) : 515-520. 1990

13. Hammill H.A. et al.: Development of Topical Clindamycin Cream for Treatment of Bacterial Vaginosis. Drug Intell Clin Pharm 1986; 20(6):450..
14. Hillier S, et al.: Microscopic effect of Intravaginal Clindamycin Cream for the Treatment of Bacterial Vaginosis. Obstet and Gynaecol 1990; 76(1): 407-413.
15. Albert DB, Timm JA, Hearnon MS, Powley GW. Efficacy of clindamycin vaginal cream vs oral metronidazole in the treatment of bacterial vaginosis (Protocol M/1115/0017). Upjohn Technical Report 9156-91-013. 11 June 1991.
16. Noah ML, Le VH, Gerard GC, Hearnon MS; Efficacy of clindamycin vaginal cream vs oral metronidazole in the treatment of bacterial vaginosis. Upjohn Technical Report 9156-91-011, June 10, 990.

APPEARS THIS WAY
ON ORIGINAL

MAY 7 1996

NDA 50-680/S-002

Chi
520

DATE SUBMITTED: May 4, 1995
DATE RECEIVED: May 8, 1995
DATE COMPLETED: May 1, 1996

MEDICAL OFFICER'S REVIEW OF NDA 50-680/S-002

Applicant: The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Drug: Cleocin (clindamycin phosphate 2%) Vaginal Cream

Drug Category: Antimicrobial

Dosage Form: Vaginal Cream

Dosage: One applicatorful (5 grams) of 2% Cleocin Vaginal Cream inserted intravaginally once daily for three consecutive days.

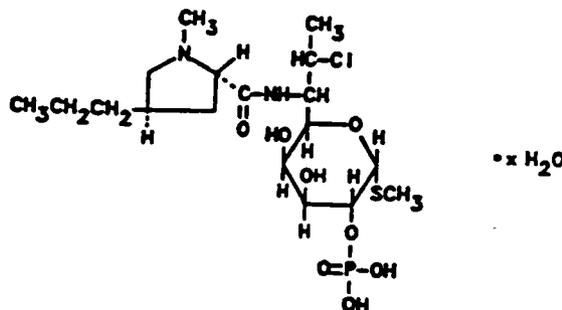
Related Submissions: IND
NDA 50-680

Chemical Name: L-threo- α -D-galacto-octopyranoside, methyl-7-chloro-6,7,8-trideoxy-6-[[[(1-methyl-4-propyl-2-pyrrolidinyl) carbonyl]amino]-1-thio,2-(dihydrogen Phosphate), 2S-trans)-.

Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$

Molecular Weight: 504.96

Structural Formula: The structural formula is represented below:



Background-Rationale

Bacterial Vaginosis (BV) continues to be the most common type of vaginal disorder seen in the physician's office today. It represents approximately 40% of all vaginitis, surpassing both vaginal candidiasis and vaginal trichomoniasis. The etiology of bacterial vaginosis (BV) is thought to be the result of a replacement of the normal lacto-bacillus dominant vaginal flora with several other organisms including *Gardnerella vaginalis*, *Mobiluncus mulieris*, *Mobiluncus curtissi*, *Mycoplasma hominis* and anaerobes (*Peptostreptococcus* spp, and *Bacteroides* spp).

Clindamycin has demonstrated good anti-bacterial activity against both anaerobic (gram-positive and gram-negative) and aerobic (gram-positive) organisms and has been available since the early 1970's for the treatment of serious anaerobic infections.

In vitro susceptibility of several bacterial vaginosis organisms to clindamycin suggested that clindamycin would be an effective treatment for this condition. The development of clindamycin as an intravaginal preparation was prompted by an investigator in the 1980s who was searching for an effective topical therapy for the treatment of bacterial vaginosis and treated 10 women with a 1% clindamycin cream administered twice daily. There was marked improvement or cure in all 10 patients. In 1988, another study reported that oral clindamycin hydrochloride 300 mg twice daily for 7 days was effective in the treatment of bacterial vaginosis.

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

NDA 50-680 provided the results of four Phase III efficacy and safety clinical trials which was the basis for approval of the 2%

Clindamycin Vaginal Cream once-a-day dosage for the 7 day treatment for bacterial vaginosis (BV) and was approved in August 1992. Supplement 001 to NDA 50-680 presented data from clinical trials that used the 2% Clindamycin Vaginal Cream once daily for seven days in second trimester pregnant patients. This supplement was approved October, 1995.

The Applicant feels that a once-a-day, three day treatment using 2% clindamycin vaginal cream will "potentially improve compliance and decrease the adverse events associated with the seven day treatment."

To support these hypotheses, The Applicant conducted three Phase III clinical trials. Two of these, (Protocol 0021 and 0027), were placebo-controlled, prospective, randomized, double-blind clinical trials that were conducted in the United Kingdom. The third, (Protocol 0020), conducted in the United States, was an observer-blind, active-controlled, multicenter, prospective study in which patients were randomized to receive either three day or seven day regimens of clindamycin vaginal cream.

Data from the three studies submitted by the Applicant will be analyzed and discussed by the medical officer in this review.

Microbiology: See review dated 1/7/93

Pharmacology: See review dated 10/9/91

Chemistry: See review dated 5/29/92

Objective: The objective of this NDA Supplement is to provide data which will demonstrate that "Cleocin (clindamycin phosphate) 2% Vaginal Cream used once daily for three consecutive days is safe and effective for use in the treatment of bacterial vaginosis and that it is equivalent in efficacy to Cleocin (clindamycin phosphate) 2% Vaginal Cream when used once daily for seven days."

Overview of Clinical Studies

Bacterial Vaginosis (BV) is a common disease among women especially in the reproductive age group and accounts for approximately 40% of all cases of vaginal infections. A diagnosis of BV is based on clinical findings which include the presence of a vaginal discharge that (1) gives off a fishy-amine odor when mixed with 10% potassium hydroxide (KOH), (2) has a pH greater than 4.5 and (3) contains clue cells on microscopic examination. Bacteriological culture is not reliable in making a diagnosis since so many different organisms may be present. Gram stain of the vaginal fluid has been used to determine if the vaginal discharge is consistent with a diagnosis of BV. A scoring system was utilized by the Applicant to categorize the gram stain as normal, intermediate or bacterial vaginosis.

The following bacterial morphotypes were quantitated under oil immersion (x 1,000):

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

Quantitation

0	morphotype/oif	=	0
<1	morphotype/oif	=	1+
1-5	morphotype/oif	=	2+
6-30	morphotype/oif	=	3+
>30	morphotype/oif	=	4+

**APPEARS THIS WAY
ON ORIGINAL**

Scoring

<u>Morphotype</u>	<u>Quantity</u>	<u>Points</u>
Lactobacillus	4+	0
Lactobacillus	3+	1
Lactobacillus	2+	2
Lactobacillus	1+	3
Lactobacillus	0	4
<i>G. vaginalis/Bacteriodes</i>	0	0
<i>G. vaginalis/Bacteriodes</i>	1+	1
<i>G. vaginalis/Bacteriodes</i>	2+	2
<i>G. Vaginalis/Bacteriodes</i>	3+	3
<i>G. Vaginalis/Bacteriodes</i>	4+	4
<i>Mobiluncus</i>	0	0
<i>Mobiluncus</i>	1+ or 2+	1
<i>Mobiluncus</i>	3+ or 4+	2

Interpretation of Score

Points	
0-3	Normal
4-6	Intermediate
7-10	Bacterial Vaginosis

The efficacy of the three day regimen of clindamycin vaginal cream was evaluated by the Applicant in two placebo-controlled studies, (Protocols 0027 and 0021), and in one active controlled study, (Protocol 0020), in which the three day regimen was compared to the approved seven day regimen.

All studies were prospective, randomized, parallel-group studies. The two placebo-controlled studies were double-blind and the active controlled study was investigator-blind. All patients were treated once daily with either 5 grams of 2% clindamycin vaginal cream or with a matching placebo cream for 3 or 7 days. In the placebo-controlled studies, two follow-up visits were scheduled approximately one week and one month after the end of

therapy. In the active-controlled study, only one follow-up visit was scheduled, 21 to 35 days after the completion of therapy.

In all three studies, a clinical diagnosis of BV was based on a vaginal discharge that had: (1) a pH greater than 4.5, (2) the presence of clue cells and (3) the presence of an amine (fishy) odor after adding 10% potassium hydroxide (KOH). Additionally, a gram stain score of the vaginal fluid smear was done to confirm the presence of BV.

Inclusion Criteria: To be included in the studies, women were required to have a clinical diagnosis of BV and be at least 18 years of age and premenopausal in the placebo-controlled studies and 16 to 60 years old in the active-controlled study.

Exclusion criteria: Patients were excluded from the study for any of the following reasons: known allergy to clindamycin; pregnant or breast feeding; presence of intrauterine contraceptive device; not taking adequate contraceptive measures if of child-bearing potential; systemic or vaginal antimicrobial therapy within the previous two weeks; history of antibiotic-associated colitis, inflammatory bowel disease or frequent periodic diarrhea; atrophic vaginitis; clinical evidence of genital herpes, cervical or vaginal vault warts, or symptoms suggestive of pelvic inflammatory disease; previous enrollment in this study, current participation in any other clinical trials, or any other investigational medication within the previous 3 months; previous hysterectomy; and any other serious or uncontrolled disease. Women who were menstruating at baseline or expected to menstruate in the next 7 days were also excluded.

Efficacy Analyses: In the Applicant's analyses in all three studies, the primary efficacy endpoint was the cure/improvement rate at the final follow-up visit. Efficacy results by the Applicant were classified in the following manner:

First Follow-up Visit:

- **Cure:** a return to normal of all three diagnostic criteria (vaginal fluid pH, odor, and clue cell findings).

- Improvement: a return to normal of two of the three diagnostic criteria
- Failure: a return to normal of one or none of the three diagnostic criteria.
- ME Failure: the patient was unable to complete the protocol therapy due to drug-related adverse medical events."

"Second Follow-up Visit:

- Cure: all three diagnostic criteria (vaginal fluid pH, odor, and clue cell findings) remained within normal range or became normal since the first follow-up visit.
- Improvement: two of the three diagnostic criteria were normal.
- Failure: one or none of the three diagnostic criteria were normal."

In the Medical Officer's analyses of the studies, efficacy analyses differed somewhat in the definitions used. In the placebo-controlled studies in which there were two return visits, a patient was considered a cure, an improvement or a failure at the first return visit based on the presence or absence of clue cells and odor in the vaginal discharge without the pH returning to < 4.5. At the second visit the improvement category was eliminated, therefore, the patient was considered either a cure or a failure based on the presence or absence of an odor and clue cells in the vaginal discharge. In most cases the pH had returned to < 4.5 for a cure but was not critical. In the active-controlled study (0020), only one return visit occurred. Therefore, the subject was either a cure or a failure based on the above clinical findings at that return visit.

Safety Evaluation: all patients who entered a study and received any medication were evaluated for safety.

APPEARS THIS WAY
ON ORIGINAL

Study 0021 (Pilot Study)

Title: Treatment of Bacterial Vaginosis (BV) with a Three Day Course of 2% Clindamycin Vaginal Cream: a pilot study.

Investigator: This was a single center, double-blind, placebo-controlled, parallel group study in which a single investigator in the United Kingdom enrolled a total of 55 patients.

Objective: To evaluate the efficacy and safety of a 3-day course of 2% clindamycin cream in the treatment of bacterial vaginosis.

Study Design: This was a prospective, randomized, double-blind, placebo-controlled study. Patients were randomized to receive either clindamycin cream 2% or matching placebo cream for a period of three days. Twenty-seven (27) patients were randomized into the clindamycin vaginal cream 2% group and 28 patients into the placebo group. Each patient was instructed to insert 5 grams of 2% clindamycin cream or 5 grams of matching placebo cream high into the vagina at bedtime daily for three consecutive days.

Unused cream was to be returned at the next clinic visit. The patients were assessed at approximately 7 to 9 days (return visit 1) and 28-35 days (return visit 2) after the start of therapy.

Inclusion Criteria: Patients were included in the study if they were women 18 years of age and over that presented to the clinic complaining of symptoms consistent with Bacterial Vaginosis which was confirmed as defined on page 6.

Exclusion Criteria:

Patients were excluded from the study if they presented with or gave a history of any of the criteria listed under the exclusion criteria on page 6. The investigator excluded from the second return visit any patients who had failed at the first return visit. These patients were carried forward in the Medical Officer's Review and counted as failures at the second visit. This explains the significant difference in the number of

evaluable patients by the Medical Officer listed in Table 1 compared to the number of evaluable patients by the investigator.

In the Applicant's analyses, to be evaluable for efficacy patients must have:

- 1) completed the protocol therapy, and attended the first follow-up visit.
- 2) had no menses within 72 hours of the last application Of protocol therapy.
- 3) not have taken other antibiotics for other indications during the four week study period.

At day 7 (first follow-up evaluation, the following endpoints were defined by the Investigator:

"1. Success: Bacterial vaginosis was not present based on:

The absence of all symptoms attributable to bacterial vaginosis.

The gram stain was not compatible with a diagnosis of bacterial vaginosis.

An absence of clue cells in the vaginal fluid on microscopic examination.

and all of the following were true

Normal vaginal fluid

Vaginal fluid pH \leq 4.5

Negative amine odor test with KOH.

2. Improved: Bacterial vaginosis was no present based on:

The absence of symptoms attributable to bacterial vaginosis

The gram stain was not compatible with a diagnosis of bacterial vaginosis.

An absence of clue cells in the vaginal fluid on

microscopic examination.

But two or less of the following criteria were true:

- normal vaginal fluid
- vaginal fluid pH ≤ 4.5
- a negative amine odor test with KOH

3. Failure Bacterial vaginosis was present based on the admission criteria

4. Medical Event Failure: Unable to complete protocol treatment due to a medical event.

At Day 28 (final follow-up evaluation). The following therapeutic endpoints were defined by the Investigator:

1. Success: Bacterial vaginosis was not present based on:

The gram stain was not compatible with a diagnosis of bacterial vaginosis.

An absence of clue cells in the vaginal fluid on microscopic examination.

and all of the following were true

Normal vaginal fluid

Vaginal fluid pH ≤ 4.5

Negative amine odor test with KOH.

2. Improved: Bacterial vaginosis was no present based on:

The gram stain was not compatible with a diagnosis of bacterial vaginosis.

An absence of clue cells in the vaginal fluid on microscopic examination.

But two or less of the following criteria were true:

- normal vaginal fluid
- vaginal fluid pH ≤ 4.5

- a negative amine odor test with KOH

3. Failure Bacterial vaginosis was present both at the first follow-visit and at the final visit.
4. Recurrence Following either success or improvement at the first follow-up evaluation (as defined above) BV had recurred as per the criteria above.

In the Medical Officer's analyses only two categories were defined in the final visit:

Cure: Bacterial Vaginosis was not present based on the absence of clue cells in the vaginal fluid and a negative amine (fishy) odor with the addition of KOH to the vaginal fluid with a pH equal to or less than 4.8. The gram stain was not considered in the Medical Officer's analyses.

Failure: Bacterial Vaginosis was present based on the presence of either clue cells or an amine odor with the addition of 10% KOH to the vaginal discharge (all failures at visit one were carried forward as failures at visit two).

Results

APPEARS THIS WAY
ON ORIGINAL

Study Population: A total of 55 female patients with a clinical diagnosis of bacterial vaginosis were enrolled in the study, 27 in the clindamycin group and 28 in the placebo group. All patients who received any study medication were evaluated for safety and all evaluable patients were included in the efficacy evaluations. The investigator, his geographical location and the number of patients enrolled and evaluable for efficacy as determined by the investigator and the medical officer is shown in Table 1.

APPEARS THIS WAY
ON ORIGINAL

Table 1
Patients Valid* for Efficacy

Investigator	Treatment Group	Number Enrolled	# EVALUABLE By Applicant		# EVALUABLE By MED OFFICER	
			RV-1	RV-2	RV-1	RV-2
Arya, O. M.D. Liverpool, UK	Clindamycin	27	24	18	18	18
	Placebo	28	21	9*	20	20

* All patients who were non-evaluable were due to failure to return to follow-up visits. The Applicant failed to include failures from visit 1 in the return visit 2 placebo patients.

Demographics

There were no statistically-significant differences at baseline in terms of age, weight or other reported demographic data between the two treatment groups as shown in Table 2.

Table 2
Demographics and Baseline Data
(0021)

	Clindamycin	Placebo
<u>Total Number of Patients</u>	27	28
<u>Age</u>		
Mean	27.0	25.7
Range		
<u>Weight (KG)</u>		
Mean	59.9	59.9
<u>Gravidity (%)</u>		
0	40.7%	53.6%
>1	55.6%	46.4%
NOT REPORTED	3.7%	-
<u>Previous BV Infection</u>		
Yes	33.3%	32.1%
No	29.6%	32.1%
Unknown	37.0%	35.7%

Table 3
Efficacy Analyses of Evaluable Patients
(By Applicant)

<u>OUTCOME</u>	<u>CLINDAMYCIN</u>	<u>PLACEBO</u>
CURE	13/18 (72%)	2/9 (22%)
IMPROVEMENT	2/18 (11%)	-
FAILURE	3/18 (17%)	7/9 (78%)

Table 4
Efficacy Analyses of Evaluable Patients
(By Medical Officer)

<u>OUTCOME</u>	<u>CLINDAMYCIN</u>	<u>PLACEBO</u>
CURE	12/18 (67%)	0/20 (0%)
FAILURE	6/18 (33%)	20/20 (100%)

SAFETY

The Medical Events experienced during the study are listed in Table 5. Five subjects from the clindamycin group reported untoward events. Subject #15 complained of moderate diarrhea and abdominal cramps thought to be associated with the use of clindamycin cream (no signs of bleeding/occult blood per rectum). There was thought to be no association between clindamycin cream and the vulval warts reported by Subject #35, or acute tonsillitis and candidiasis reported by Subject #39. Vaginitis was reported for Subjects #10 and #25 and was considered to be related to treatment with clindamycin.

Treatment associated mild diarrhea and vaginitis were recorded for Subject #52 in the placebo group, while Subject #55 (also in the placebo group) complained of lightheadedness, dizzy spells and sickness, thought by the investigator to possible be related

to excess alcohol. Vaginitis was reported for Subject #16 and was considered to be related to treatment with placebo.

Table 5
Medical Events

Medical Event	2%CVC N=27		PLACEBO N=28	
	n	%	n	%
Number of Patients Reporting Medical Events	5	18.5	3	10.7
Vaginitis/cervicitis	2	7.4	2	7.1
Diarrhea	1	3.7	1	3.6
Candidal vulvovaginitis	1	3.7	--	--
Warts (vulvar)	1	3.7	--	--
Acute tonsillitis	1	3.7	--	--
Lightheadedness			1	3.6
Dizziness	--	--	1	3.6
Nausea	--	--	1	3.6

Conclusion: This was a pilot study with relatively few evaluable subjects and a single investigator which showed that 5 grams of 2% clindamycin vaginal cream applied daily for 3 consecutive days was superior to placebo in the treatment of patients with bacterial vaginosis.

**APPEARS THIS WAY
ON ORIGINAL**