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*APPLICATION NUMBER:*  
**50-793**

**MEDICAL REVIEW**

## CLINICAL REVIEW

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Established Name Clindamycin phosphate  
(Proposed) Trade Name Clindesse™  
Therapeutic Class Antibacterial  
Applicant KV Pharmaceutical Company

Priority Designation S

Formulation Vaginal cream  
Dosing Regimen Single invtravaginal application  
Indication Bacterial vaginosis  
Intended Population Non-pregnant females

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

The evidence presented in this NDA supports the approval of Clindesse™ as a single-dose regimen for the treatment of bacterial vaginosis (BV). In the pivotal clinical studies submitted for this NDA, Clindesse™ was shown to be superior to placebo, and non-inferior to Cleocin® vaginal cream 2%, which was previously approved for treatment of BV. No significant safety concerns with Clindesse™ were identified in this review. The most common adverse event associated with Clindesse™ treatment was vulvovaginal candidiasis. The safety profile of Clindesse™ was similar to that of Cleocin® vaginal cream and placebo.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

Not applicable

#### 1.2.2 Required Phase 4 Commitments

None

#### 1.2.3 Other Phase 4 Requests

None

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

Bacterial vaginosis (BV) is a clinical syndrome resulting from replacement of normal vaginal microflora, particularly the lactobacilli, with *Gardnerella vaginalis*, *Mycoplasma hominis*, and anaerobic bacteria, including *Prevotella sp.* and *Mobiluncus sp.* BV is a common vaginal infection in sexually active adolescents and adult females. A thin, malodorous, homogeneous vaginal discharge associated with minimal pruritis is the hallmark of BV, however many women with BV may be asymptomatic. BV has been associated with adverse pregnancy outcomes,

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including premature rupture of membranes, preterm birth, chorioamnionitis, and postpartum endometritis. Additionally, BV has been associated with endometritis, pelvic inflammatory disease and vaginal cuff cellulitis after certain invasive gynecologic surgical procedures (Hillier and Holmes, 1999).

Clindesse™ is an intravaginal antibacterial preparation developed by KV Pharmaceutical Company for the treatment of bacterial vaginosis. Clindesse™ contains clindamycin phosphate, 2%, contained in a patented drug delivery system called VagiSite™, a semisolid configuration of KV Pharmaceutical's SITE RELEASE® technology developed for intravaginal administration. FDA-approved products containing clindamycin for intravaginal use include Cleocin® vaginal cream (clindamycin phosphate, 2% vaginal cream NDA 50-680), and Cleocin® vaginal ovules (NDA 50-767). The SITE RELEASE® drug delivery system is currently a component of the FDA-approved intravaginal preparation, Gynazole-1®, which contains butaconazole nitrate, 2%, for treatment of vulvovaginal candidiasis (NDA 19-881). As per Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, this NDA is submitted for Clindesse™, a new formulation containing the same active pharmaceutical ingredient (clindamycin phosphate) as the approved product, Cleocin® vaginal cream (NDA 50-680).

In support of this NDA, two adequate, well-controlled studies were submitted: study 02-005, a placebo-controlled (superiority) study, comparing Clindesse™ to placebo; and 01-025, an active-controlled (non-inferiority) study, comparing Clindesse™ to Cleocin® vaginal cream. In addition, study KVP-214, which compared the relative bioavailability of Clindesse™ to Cleocin® vaginal cream, and a pilot bioavailability study, 01-012, were submitted in support of the application.

A total of 802 female patients with bacterial vaginosis were enrolled in the two pivotal clinical studies, protocols 02-005 and 01-025. In addition, 20 female patients with BV were enrolled in the pilot bioavailability study, protocol 01-012; and 20 normal healthy female subjects were enrolled in the relative bioavailability study, protocol KVP-214. Other than the 4 clinical studies submitted with this NDA, no other pertinent clinical data sources were provided for review.

### 1.3.2 Efficacy

The efficacy of Clindesse™ in the treatment of bacterial vaginosis was assessed in two phase 3 clinical trials. Study 02-005 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, comparing a single dose of Clindesse™ ~~metronidazole vaginal cream to placebo.~~

~~\_\_\_\_\_~~ but were provided for review at the Agency's request. Study 01-025 was a multicenter, randomized, single-blind, parallel-group study, comparing a single dose of Clindesse™ to 7 daily doses of Cleocin® vaginal cream.

The primary and secondary efficacy variables used in both pivotal clinical studies were those recommended in the 1998 FDA draft Guidance for Industry, "Bacterial Vaginosis- Developing Antimicrobial Drugs for Treatment". The primary endpoint was "therapeutic outcome", a

composite endpoint which required both “clinical cure” and “Nugent score cure” for therapeutic cure. Clinical cure required resolution of all Amsel criteria (Amsel, et al. 1983) used in diagnosis of BV. The Nugent scoring system is based on quantification of bacterial morphotypes seen on Gram’s stained smears of vaginal secretions (Nugent et al. 1991). A Nugent score of 0-3 (normal) was required for Nugent score cure. The secondary endpoints were clinical outcome, Nugent score outcome, and investigator outcome. The latter was based on the investigator’s assessment of whether the patient required further treatment for BV.

No problems were identified with the pivotal studies regarding choice of endpoints or controls, adequacy of blinding, or conduct of the studies. However, it should be noted that the use of the composite primary endpoint, therapeutic cure, in these studies resulted in lower than expected cure rates when compared to the studies used for approval of Cleocin® vaginal cream for this indication. Notably, when BV cure was based on only 2 clinical criteria (the absence of clue cells, and a negative “whiff” test) cure rates were 84-86% for treatment with 7 days of Cleocin® vaginal cream and were 72-81% for 3 days treatment (Cleocin® vaginal cream 2%, NDA #50,680). Additionally, in this review we show that the Nugent score outcome does not correlate well with clinical outcome, and inclusion of this surrogate marker in the primary endpoint results in lower rates of cure than would be obtained using clinical criteria alone.

The following conclusions can be made regarding the efficacy of Clindesse™ in the treatment of bacterial vaginosis:

- a. Study 02-005 showed that a single dose of Clindesse™ is superior to placebo for the treatment of BV for the primary endpoint, therapeutic cure, and for the secondary endpoints, clinical cure, Nugent score cure and investigator cure (Table 1).

Table 1. Efficacy of Clindesse™ in Treatment of BV in a Randomized, Double-blind, Placebo-Controlled Trial (Study 02-005)

Outcome	Clindesse™ N = 78	Placebo N= 66	Treatment Difference
	%	%	% [95% Confidence Interval]
Therapeutic Cure	29.5	3.0	26.5 [15.5, 37.4]
Clinical Cure	41.0	19.7	21.3 [6.8, 35.9]
Nugent Score Cure	44.9	6.1	38.8 [26.4, 51.3]
Investigator Cure	68.9	37.5	31.4 [15.5, 47.3]

N = number of patients in treatment group in modified intent-to-treat (MITT) analysis (note N=74 for Clindesse™ group and 64 for Cleocin® group for Investigator Cure Outcome)  
 % = percentage of patients cured in treatment group

- b. Study 01-025 showed that a single dose of Clindesse™ is non-inferior to Cleocin® vaginal cream, administered as 7 daily doses, for both the primary and secondary endpoints (Table 2).

Table 2. Efficacy of Clindesse™ in Treatment of BV in a Randomized, Investigator-blinded, Active-Controlled study with Cleocin® Vaginal Cream as Comparator (Study 01-025)

Outcome	Clindesse™ N=221	Cleocin® Vaginal Cream 2% N=211	Treatment Difference
	%	%	% [95% Confidence Interval]
Therapeutic Cure	33.0	37.0	-3.9 [-8.3, 7.3]
Clinical Cure	53.4	54.0	-0.6 [-10.0, 8.8]
Nugent Score Cure	45.7	49.3	-3.6 [-13.1, 5.8]
Investigator Cure	80.5	82.5	-2.0 [-9.3, 5.4]

N = number of patients in treatment group in MITT analysis

% = percentage of patients cured in treatment group

There are several limitations to these studies. Conclusions regarding the safety and efficacy of Clindesse™ in pregnant women cannot be made because of the limited numbers of pregnant women studied. Additionally, only a few patients older than 65 years were studied, so generalizations cannot be made regarding Clindesse™ use in this population. Women under the age of 18 were excluded from these studies, and BV is common in sexually-active adolescents. However, because the pathophysiology of BV is similar in post-menarchal females regardless of age, and because age-related differences in Clindesse™ safety and efficacy are not expected, we can extrapolate data from these studies to include all post-menarchal adolescents.

The dose of Clindesse™ used in the pivotal clinical studies (a single dose contained 100 mg clindamycin phosphate) was based on the approved Cleocin® dose for this indication (100 mg clindamycin phosphate daily for 3- or 7- days), and on the demonstration of efficacy in the pilot study, 01-012. However, the 3-7 day dosage regimen for Cleocin® vaginal cream results in a higher exposure to clindamycin with Cleocin® than with Clindesse™. Additionally, the relative bioavailability study (protocol KVP-214) showed that the systemic absorption of clindamycin from a single dose of Clindesse™ is approximately 12% less than that with a single dose of Cleocin® vaginal cream; while the systemic absorption of a single dose of Cleocin® vaginal cream (100 mg clindamycin phosphate) was approximately 5% of an oral clindamycin dose (NDA 50-680) Low systemic absorption of an antibiotic may be desirable for treatment of a superficial/mucosal infection such as bacterial vaginosis to minimize systemic adverse events. However, whether the use of systemic antibiotics for treatment of BV in pregnancy is necessary to prevent preterm birth and postpartum complications is not known.

Clindesse™ will be a useful addition to the existing treatment options for bacterial vaginosis. Currently FDA-approved drugs for treatment of BV include the following:

- Cleocin® (clindamycin phosphate) vaginal cream, 2% (3 day treatment for non-pregnant women, and 7 day treatment for pregnant women during the second and third trimester);

- Cleocin® (clindamycin phosphate) vaginal ovules (3 day treatment in non-pregnant women);
- Flagyl® ER (metronidazole extended release) 750 mg tablet (7 day treatment contraindicated during first trimester of pregnancy)
- MetroGel-Vaginal® (metronidazole vaginal gel, 0.75%) (5 day treatment).

### 1.3.3 Safety

The integrated safety data base included all patients in the intent-to-treat (ITT) populations for the two pivotal studies, 01-025 and 02-005, and in the pilot bioavailability study, 01-012. The safety data base included 803 patients, 368 of whom received a single dose of Clindesse™, 265 received up to 7 doses of Cleocin® vaginal cream, 85 received a single dose of ██████████ metronidazole vaginal cream, and 85 received placebo. The mean dose of clindamycin phosphate administered as Clindesse™ was 100 mg; while the mean dose of clindamycin phosphate administered as Cleocin® vaginal cream was 632.4 mg. The safety data from the relative bioavailability study, KVP-214, was not pooled with the other studies because of differences in study population and design. Adverse events that occurred in the 20 volunteers in study KVP-214 were compiled separately.

No deaths were reported in these studies. No serious adverse events were reported in patients who received Clindesse™. One serious adverse event, lower extremity cellulitis requiring hospitalization, was reported in a patient who received Cleocin® vaginal cream. This event was not considered to be drug-related, and resolved with treatment.

Adverse events were reported in 126 of the 368 patients (34.2%) who received Clindesse™ in comparison to 71 of the 265 patients (26.8%) who received Cleocin® vaginal cream, and 32 of 85 patients (37.6%) who received placebo. Adverse events were classified as “drug-related” in 39 (10.6%) of Clindesse™-treated, 21 (7.9%) of Cleocin® vaginal cream-treated, and 15 (17.6%) of placebo-treated patients. Study withdrawal due to adverse events occurred in 6 of 368 patients (1.6%) who received Clindesse™, 2 of 265 patients (0.8%) who received Cleocin® vaginal cream, and in no patients who received placebo.

The most common adverse events reported in these studies were vaginal fungal infections, which occurred in 14.1 % of patients who received Clindesse™, 10.2% of patients who received Cleocin® vaginal cream and 8.2% of patients who received placebo. The most common adverse events reported with Clindesse™ are shown in Table 3 below.

Table 3. Most Common Adverse Events\* Reported in Integrated Safety Database (Studies 01-025, 02-005, 01-012)

Adverse Event (Preferred Term)	Clindesse™ N=368	Cleocin® Vaginal Cream N=265	Placebo N=85
	n (%)	n (%)	n (%)
Vaginosis fungal NOS	52 (14.1)	27 (10.2)	7 (8.2)
Vulvovaginal pruritis	12 (3.3)	8 (3.0)	3 (3.5)
Headache NOS	10 (2.7)	4 (1.5)	2 (2.4)
Back pain	6 (1.6)	0 (0)	1 (1.2)
Nausea	5 (1.4)	0 (0)	3 (3.5)
Constipation	4 (1.1)	0 (0)	0 (0)
Nasopharyngitis	4 (1.1)	1 (0.4)	0 (0)
Urinary tract infection NOS	4 (1.1)	3 (1.1)	0 (0)
Vaginal discharge	4 (1.1)	3 (1.1)	2 (2.4)
Abdominal pain NOS	3 (0.8)	3 (1.1)	5 (5.9)
<i>Herpes simplex</i> infection	3 (0.8)	1 (0.4)	1 (1.2)
Vaginal burning sensation	3 (0.8)	1 (0.4)	1 (1.2)
Diarrhea NOS	2 (0.5)	2 (0.8)	2 (2.4)
Dysmenorrhea	2 (0.5)	1 (0.4)	2 (2.4)
Pelvic pain NOS	1 (0.3)	1 (0.4)	2 (2.4)
Vaginal irritation	1 (0.3)	1 (0.4)	2 (2.4)
Vaginal hemorrhage	0 (0)	3 (1.1)	0 (0)

Adverse events reported by MedDra Preferred Term, and reported in  $\geq 1\%$  patients in any treatment group

N= total number of patients in treatment group in pooled safety database

n= number of patients with reported adverse event

%= percentage of patients in treatment group with adverse event

NOS= not otherwise specified

Vaginal candidiasis was also the most common adverse event considered to be drug-related, occurring in 4.9% of Clindesse™-treated, 4.5% Cleocin® vaginal cream-treated and 2.4% of placebo-treated patients.

Information regarding overdosage with Clindesse™ is not available; and abuse potential is considered negligible with this topical antimicrobial agent. Insufficient numbers of pregnant women and patients older than 65 limit conclusions regarding safety in these populations.

Overall, Clindesse™ appears to be safe and effective for use as a single intravaginal dose for the treatment of BV in non-pregnant women. The safety profile for Clindesse™ is similar to that of the approved product, Cleocin® vaginal cream and to placebo. Vaginal candidiasis was the most common adverse event reported with Clindesse™, Cleocin® vaginal cream, and placebo in these studies.

#### 1.3.4 Dosing Regimen and Administration

The proposed dosage, one pre-filled applicator of Clindesse<sup>TM</sup>, containing 5 grams of 2% clindamycin phosphate (100 mg), administered as a single-day, single-dose regimen, is appropriate for treatment of BV in non-pregnant women.

#### 1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not performed. Significant systemic drug-drug- interactions would not be expected with intravaginal Clindesse<sup>TM</sup>, because of clindamycin's low systemic absorption. However, clindamycin is known to have neuromuscular blocking activity which may be increased with concomitant use of other neuromuscular blocking agents. Patients receiving other neuromuscular blocking agents were excluded from the clinical studies submitted for this NDA, so no conclusions can be drawn regarding concomitant use of intravaginal Clindesse<sup>TM</sup> with other neuromuscular blocking agents.

#### 1.3.6 Special Populations

Clindesse<sup>TM</sup> was not studied in patients with renal or hepatic insufficiency. Dose modification for these populations should not be necessary given the low systemic absorption of clindamycin from this intravaginal preparation. Clindesse<sup>TM</sup> was not studied in women under age 18; however, the data presented in these studies can be reasonably extrapolated to include all postmenarchal females because of the similar expected safety profile of the drug and similar pathophysiology of BV in younger women. Because Clindesse<sup>TM</sup> was studied only in limited numbers of pregnant women, conclusions cannot be drawn regarding the safety and efficacy of Clindesse<sup>TM</sup> for treatment of BV in pregnant women. Additionally, because of the limited number of patients  $\geq 65$  years old enrolled in the clinical studies submitted for this NDA, no conclusions can be drawn regarding the safety and efficacy of Clindesse<sup>TM</sup> in the geriatric population.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Clindesse™ is semi-solid, white cream, which contains 2% clindamycin phosphate, which is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic, lincomycin. The cream also contains edentate disodium, glycerol monoisostearate, lecithin, methylparaben, microcrystalline wax, mineral oil, polyglyceryl-3-oleate, propylparaben, purified water, silicon dioxide and sorbitol solution. Each pre-filled applicator of Clindesse™ contains 5 grams of vaginal cream with 100 mg clindamycin phosphate.

Clindesse™ contains clindamycin phosphate, which has been previously FDA-approved for use in treatment of BV as Cleocin® vaginal cream (NDA# 50,680), and Cleocin® vaginal ovules (NDA 50-767). The delivery vehicle for Clindesse™ differs from that used in Cleocin® vaginal cream. Clindesse™ contains clindamycin phosphate in KV Pharmaceutical Company's VagiSite™ vehicle, a semisolid form of the SITE RELEASE® technology used for single dose intravaginal administration. An intravaginal antifungal agent, butaconazole nitrate, 2%, contained in the SITE RELEASE vehicle, has been FDA-approved as Gynazole-1® (NDA 19-881) for the treatment of vulvovaginal candidiasis.

The proposed dosing regimen is a single intravaginal administration of Clindesse™ (each pre-filled applicator contains 100 mg clindamycin phosphate on one day for the treatment of BV in non-pregnant women.

### 2.2 Currently Available Treatment for Indications

A number of alternative regimens are available for treatment of bacterial vaginosis. The following regimens have been FDA-approved for BV treatment:

- Cleocin® (clindamycin phosphate) vaginal cream, 2% (3 day treatment for non-pregnant women, and 7 day treatment for pregnant women during the second and third trimester);
- Cleocin® (clindamycin phosphate) vaginal ovules (3 day treatment in non-pregnant women);
- Flagyl® ER (metronidazole extended release) 750 mg tablet (7 day treatment, contraindicated during first trimester of pregnancy)
- MetroGel-Vaginal® (metronidazole vaginal gel, 0.75%) (5 day treatment).

The following regimens are currently recommended by the Centers for Disease Control and Prevention (CDC) for treatment of BV in non-pregnant women (Workowski and Levine, 2002):

- Metronidazole 500 mg orally twice a day for 7 days; or

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- Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, once a day for 5 days; or
- Clindamycin cream 2%, one full applicator (5 grams) intravaginally at bedtime for 7 days.

Alternative regimens recommended by the CDC for BV treatment in non-pregnant women (Sexually Transmitted Diseases Treatment Guidelines, 2002) include the following:

- Metronidazole 2 grams orally in a single dose; or
- Clindamycin 300 mg orally twice a day for 7 days; or
- Clindamycin ovules 100 grams intravaginally once at bedtime for 3 days.

The CDC recommends the use of systemic antimicrobial therapy for BV in pregnancy, including either metronidazole 250 mg orally 3 times a day for 7 days; or clindamycin 300 mg orally twice daily for 7 days (Workowski and Levine, 2002).

### 2.3 Availability of Proposed Active Ingredient in the United States

Clindamycin for intravaginal use is currently available as Cleocin® (clindamycin phosphate) vaginal cream 2% or Cleocin® (clindamycin phosphate) vaginal ovules. Clindamycin is also available in this country in tablet form for oral administration (Cleocin HCl®), as an oral suspension of clindamycin palmitate hydrochloride for pediatric use (Cleocin Pediatric®), as a sterile solution for intramuscular and intravenous use (Cleocin phosphate®), and in a number of other preparations for other topical (dermal) use.

Clindamycin administered systemically in oral or parenteral preparations has been associated with pseudomembranous colitis, and clindamycin labels carry warnings about this adverse event. Clindamycin phosphate for injectable use also carries a warning regarding anaphylactoid reactions. In addition, the labels for injectable clindamycin phosphate and oral clindamycin formulations also carry a warning to inquire carefully regarding previous sensitivities to drugs and other allergens, and warn against the usage of clindamycin in meningitis, because clindamycin does not adequately diffuse into the cerebrospinal fluid.

### 2.4 Important Issues with Pharmacologically Related Products

Clindamycin and other antibiotics related to lincomycin, have known neuromuscular blocking activity. This is not expected to be an important issue with Clindesse™ because of the minimal systemic absorption of clindamycin with intravaginal use of this product.

## 2.5 Presubmission Regulatory Activity

This is a 505(b)(2) application based on the use of an FDA-approved product, Cleocin® vaginal cream, containing 2% clindamycin phosphate (NDA 50-680) in a vehicle approved for use in another approved product, Gynazole-1, (butaconazole nitrate 2% vaginal cream, NDA 19-881).

The 1998 FDA draft guidance document, "Bacterial Vaginosis- Developing Antimicrobial Agents for Treatment", was used by the Applicant as the basis for study design for this NDA submission, including patient inclusion and exclusion criteria, and study endpoints. The guidance document recommendation regarding bacterial vaginosis were discussed at an Anti-Infective Drugs Advisory Committee meeting held July 26, 1988.

Previous IND applications submitted for Clindesse™ for treatment of BV included: IND 62-397, for clindamycin phosphate vaginal cream, submitted on March 4, 2002. [REDACTED]

A pre-NDA meeting was held with the Applicant on September 23, 2003. At that time, results from the two pivotal clinical studies for the NDA submission were presented to the Division of Special Pathogens and Immunologic Drug Products. The applicant's proposal that Clindesse™ be labeled for use in pregnant women after the first trimester based on the Cleocin® vaginal cream 2% indication for BV in pregnancy was found unacceptable because an insufficient number of pregnant women were enrolled in the clinical studies with Clindesse™ submitted for this NDA.

Additionally, the Agency requested that the data from the metronidazole arm of the placebo-controlled study (02-005) [REDACTED] These data were provided by the applicant with this NDA submission.

## 2.6 Other Relevant Background Information

None

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

Please see Dr. D. Matecka's CMC review for full details. Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by 7(S)-chloro-substitution of the 7 (R)-hydroxyl group of the parent antibiotic, lincomycin. The drug product, clindamycin phosphate

Clinical Review  
Mary E. Singer, M.D., Ph.D.  
{NDA 50-793 N-000}  
Clindesse (clindamycin phosphate 2% vaginal cream)

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vaginal cream, 2%, is a soft, off-white, homogeneous cream formulated as an oil-external emulsion, which is intended to remain in contact with the vaginal mucosa with minimal systemic absorption.

Each gram of cream contains 20 mg of clindamycin base (provided by clindamycin phosphate), and a preservative system which consists of methylparaben \_\_\_\_\_ and propylparaben \_\_\_\_\_. Clindamycin phosphate vaginal cream, 2%, is not sterile; however, it meets the criteria of the US Pharmacopoeia (USP) Antimicrobial Preservative Effectiveness test. This submission was recommended for approval on the basis of product quality microbiology, as reviewed by the Office of Pharmaceutical Sciences Microbiology Team.

The drug is packaged in a \_\_\_\_\_ applicator which delivers a 5 gram dose of cream. The applicator is placed in a \_\_\_\_\_ tray for physical protection, and wrapped in a \_\_\_\_\_ pouch.

### **3.2 Animal Pharmacology/Toxicology**

Please refer to Dr. O. McMaster's Pharmacology review for full details. The applicant relied on literature review and a single animal study for the preclinical pharmacology/toxicology evaluation. A two-week rabbit study was performed to assess potential irritation and local tolerance of clindamycin and metronidazole vaginal creams. Rabbits treated with both Clindesse™ and Cleocin® vaginal cream had decreased weight gain and food consumption in comparison to animals which received placebo. Overall, Clindesse™ had no irritant effects on vaginal tissues; while placebo, Cleocin® and metronidazole had minimal irritant effects.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The clinical trials conducted by the Applicant are the sole sources of data used in this review.

### **4.2 Tables of Clinical Studies**

All clinical studies included in this NDA submission are listed in Table 4 below.

Table 4. Clinical Studies Submitted with NDA #50,793 for Treatment of Bacterial Vaginosis with Clindesse™

Clinical Study	Phase	Number of Patients enrolled	Purpose of Study	Comparator	Study Dates	Relevance for Review
02-005	3	262	Safety and Efficacy	Placebo	10/02-5/03	Pivotal study for safety and efficacy
01-025	3	540	Safety and Efficacy	Cleocin® Vaginal Cream, 2%	6/02-5/03	Pivotal study for safety and efficacy
01-012	1	20	Pilot bioavailability	None	1/02-7/02	Included in integrated safety review
KVP-214	1	20	Relative bioavailability	Cleocin® Vaginal Cream, 2%	3/03	Review of clinical pharmacology and descriptive safety data

### 4.3 Review Strategy

Data obtained from the written summaries of the clinical studies provided by the applicant was reviewed in conjunction with the raw data provided electronically for verification and further analyses as needed. For the efficacy analysis, only the pivotal studies, 02-005 and 01-025 were included in this review. For safety analysis, data from individual studies was reviewed; and data was pooled from studies 02-005, 01-025, and 01-012 for the integrated safety review. Safety data from the relative bioavailability study was not pooled with that from the other studies because of the different study population and study design, but was provided as descriptive data in tabular form.

The medical reviewer was responsible for the synthesis and documentation of overall conclusions for the applications. Reviews of clinical pharmacology, biostatistics, chemistry, and pharmacology/toxicology were completed by reviewers in those disciplines.

#### **4.4 Data Quality and Integrity**

No special audits were used to check the applicant's data or analysis. In this review, no significant disparities were found between treatment arms or investigative sites for patient discontinuation from the studies, or for outcome measures to necessitate a Division of Scientific Investigation inspection. Case report forms provided by the applicant for patients who had serious or unexpected adverse events were reviewed by the medical officer.

#### **4.5 Compliance with Good Clinical Practices**

No specific issues with informed consent, protocol violations, or any site-specific issues were identified in this review.

#### **4.6 Financial Disclosures**

Financial disclosures were provided for each investigator and subinvestigators for the two pivotal clinical studies, as well as for the pilot and bioavailability studies. There were no financial arrangements that would raise issues concerning data integrity.

### **5 CLINICAL PHARMACOLOGY**

#### **5.1 Pharmacokinetics**

Please refer to Dr. S. Jang's Clinical Pharmacology Review for full details. In brief, the applicant provided a literature review in addition to a bioavailability study in support of this NDA. The latter study showed that following a single intravaginal application of Clindesse™ cream to twenty healthy women, the mean  $AUC_{0-inf}$  estimate was 175 ng·hr/ml (range 38.6 to 541 ng·hr/ml); and the  $C_{max}$  estimate was 6.6 ng/ml (range 0.8 to 39 ng/ml). The mean  $C_{max}$  of clindamycin for Clindesse™ was approximately 0.3%, and 0.1% of that observed after administration of a 150 mg Cleocin® oral capsule (2.5 µg/ml) and a 600 mg Cleocin® intravenous injection (10.9 µg/ml), respectively. The peak serum concentration of clindamycin was attained approximately 20 hours post dosing for Clindesse™. The systemic exposure of clindamycin for Clindesse™ was approximately 12% of that observed with Cleocin® vaginal cream, 2%.

#### **5.2 Pharmacodynamics**

No pharmacodynamic studies were performed for this NDA submission.

### 5.3 Exposure-Response Relationships

No exposure-response studies were performed for this NDA submission.

## 6 INTEGRATED REVIEW OF EFFICACY

This section summarizes the results of the individual pivotal clinical studies in addition to presenting an integrated efficacy review. Detailed reviews of the two pivotal studies submitted for this NDA, studies 02-005 and 01-025, are included in the Appendix section 10.1.

### 6.1 Indication

The proposed indication for use of Clindesse™ is bacterial vaginosis (BV), a condition resulting in the alteration of normal vaginal microflora, replacing the normally predominant hydrogen peroxide-producing lactobacilli with organisms such as *Gardnerella vaginalis*, *Mycoplasma hominis*, *Mobiluncus spp.*, *Prevotella spp.* and other anaerobic bacteria.

#### 6.1.1 Methods

Data from studies 02-005 and 01-025 were obtained from both applicant's summaries and the electronic database to evaluate the efficacy of Clindesse™ for treatment of BV. Study 02-005 was a superiority study, comparing Clindesse™ to placebo; while study 01-025 was a non-inferiority study comparing Clindesse™ to Cleocin® vaginal cream for treatment of BV. Because both studies had similar study populations and study design, for the integrated analysis of efficacy, data from both studies was pooled to assess overall efficacy of Clindesse™ for treatment of BV. Both studies were of equal importance in evaluating the efficacy of Clindesse™ for this indication.

#### 6.1.2 General Discussion of Endpoints

The primary and secondary efficacy variables used in both pivotal clinical studies were those recommended in the 1998 FDA draft Guidance for Industry, "Bacterial Vaginosis- Developing Antimicrobial Drugs for Treatment". The primary endpoint was "therapeutic outcome", a composite endpoint which required both "clinical cure" and "Nugent score cure" for therapeutic cure. Clinical cure required resolution of all Amsel criteria used in the diagnosis of BV (Amsel, et al. 1983). The Nugent scoring system is based on quantification of bacterial morphotypes seen on Gram's stained smears of vaginal secretions (Nugent, et al. 1991). A Nugent score of 0-3 (normal) was required for Nugent score cure. The secondary endpoints were clinical outcome, Nugent score outcome, and investigator outcome. Investigator cure was based on the investigator's assessment as to whether the patient required further treatment for BV.

Previous NDAs for treatment of bacterial vaginosis with intravaginal clindamycin relied on clinical criteria alone for the primary study endpoints. Because the primary endpoint used for this application, therapeutic cure, is a composite outcome, requiring resolution of all clinical criteria used for BV diagnosis (vaginal discharge, pH, clue cells and “whiff” test), as well as a normal Nugent score, the cure rates would be expected to be lower in these studies than in earlier studies. Similarly, the outcomes of BV treatment reported in the literature are difficult to compare because of lack of standardization in choosing study endpoints.

We performed additional analyses using these data to evaluate the correlation of the Nugent score outcome with clinical outcome, investigator outcome, and subjective resolution of BV symptoms. These analyses are reported with the individual study reviews in the Appendix, section 10.1. We concluded that the Nugent score outcome does not correlate closely with clinical outcome, investigator outcome or symptom resolution. Nevertheless, the use of the composite primary endpoint in these studies did not change any conclusions regarding efficacy of Clindesse™ in comparison to placebo or to Cleocin® vaginal cream.

### 6.1.3 Study Design

Two adequate, well-controlled studies were submitted for this NDA. Study 02-005 was a randomized, double-blind, placebo-controlled, parallel group, Phase 3 study of 175 patients enrolled at 20 U.S. investigative sites, designed to show superiority of Clindesse™ (clindamycin phosphate vaginal cream, 2%), over placebo for the treatment of bacterial vaginosis. Study 01-025 was a randomized, single-blind, parallel group, active-controlled phase 3 study of 540 patients enrolled at 27 investigative U.S. sites, designed to show non-inferiority of Clindesse™ to Cleocin® vaginal cream, 2% for treatment of bacterial vaginosis.

The use of placebo as control group in study 02-005 was appropriate because BV is generally not considered a serious or life-threatening infection in non-pregnant women. The use of Cleocin® vaginal cream 2% as comparator in the 01-025 study was also appropriate for this 505 (b)(2) application, because Cleocin® vaginal cream has been previously approved for this indication, and it contains the same active ingredient (clindamycin) as Clindesse™.

The dose of clindamycin in Clindesse™ is identical to that in Cleocin® vaginal cream (100 mg clindamycin phosphate), however the proposed dosage regimen for Clindesse™ is a single applicator-full (100 mg clindamycin phosphate) compared to either 3 or 7 daily doses of Cleocin® vaginal cream. The differences in dosing regimen are related to the differences in the delivery vehicle for the two products. Clindesse™ is formulated in a vehicle referred to as the SITE RELEASE™ system, designed for sustained-release of the active ingredient; while Cleocin® is formulated in a standard cream. In addition, the pilot bioavailability study, 01-012, demonstrated the feasibility of using a single dose of Clindesse™ for treatment of BV (see Appendix, section 10.1 for individual study reviews)

Similar inclusion and exclusion criteria, study protocol, clinical assessments, data collection, and endpoints were used in both studies, with one exception. In study 01-025, pregnant women beyond the first trimester of pregnancy were not excluded. However, only 12 such patients were enrolled in that study. Both studies had similar methods for patient randomization to treatment. With regards to blinding, while study 02-005 was double-blinded, only the investigator was blinded to treatment in study 01-025 because of the difference in length of therapy for the two treatment arms (1 day for Clindesse™ and 7 consecutive days for Cleocin® vaginal cream). However, the study procedures utilized to minimize bias in the study were adequate.

In both pivotal clinical studies, the ITT population included all randomized patients who received at least one dose of study drug. The MITT population was a subset of the ITT population, including only patients with a baseline Nugent score  $\geq 4$ . The Per Protocol population was a subset of the MITT population, including only patients who completed the study without significant protocol violations.

#### 6.1.4 Efficacy Findings

##### Study 02-005: Efficacy of Clindesse™ vs. Placebo for Treatment of BV

For the full review of this study, including study protocol, patient demographics and evaluability, and additional analyses, including data for ~~metronidazole~~, see Appendix, section 10.1.1.

The primary endpoint for this study was therapeutic treatment outcome, a composite outcome which combines clinical criteria and Nugent score. The MITT population was pre-specified by the applicant for the primary assessment of outcome because only patients who received at least one dose of study medication and who had BV by both clinical criteria and Nugent score ( $\geq 4$ ) were included. Therapeutic treatment outcome was measured at the test-of-cure visit, which was 21-30 days after administration of study medication.

Table 5 shows therapeutic cure rates for the Clindesse™ and placebo treatment groups, for each analysis. Treatment with Clindesse™ resulted in a higher proportion of patients with therapeutic cure compared to placebo for treatment of BV in each analysis. The treatment difference for the Clindesse™ cure rate minus placebo cure rate was statistically significant.

Table 5. Therapeutic Treatment Outcome (Study 02-005)

Analysis Population	Clindesse™		Placebo		Treatment Difference % [95% Confidence Interval]
	N	n (%)	N	n (%)	
Intent-to-Treat	85	23 (27.1)	85	3 (3.5)	23.5 [13.3, 33.8]
Modified Intent-to-Treat	78	23 (29.5)	66	2 (3.0)	26.5 [15.5, 37.4]
Per-Protocol	52	20 (38.5)	42	0 (0.0)	38.5 [25.2, 51.7]

Treatment Difference= Clindesse™ cure rate – Placebo cure rate

N= number of patients evaluated

n=number patients with therapeutic cure

Secondary outcomes measured in this study included Nugent cure, clinical cure and Investigator cure, as defined above. For each of the secondary endpoints and for each analysis set, a higher proportion of patients were cured with Clindesse™ compared to placebo. These treatment differences were statistically significant. Please refer to the review of study 02-005 in the Appendix, section 10.1.1 for a full description of results.

*Medical Officer Comment: We can conclude from study 02-005, that for all outcomes, primary and secondary, and for all analyses, Clindesse™ was superior to placebo for treatment of BV.*

Study 01-025: Efficacy of Clindesse™ compared to Cleocin® vaginal cream for treatment of BV

For full review of this study, including study protocol, patient demographics and evaluability, and other analyses, see Appendix, section 10.1.2.

The primary efficacy variable for this study was therapeutic treatment outcome, a composite outcome, which combines clinical outcome and Nugent score outcome. Therapeutic cure required cure by both clinical and Nugent score criteria. Therapeutic outcome was assessed at the TOC visit, 21-30 days post initial dose of study medication. The Per Protocol population was used by the applicant for the primary efficacy analysis. Randomized patients with a baseline Nugent score of  $\geq 4$ , who completed the study without significant protocol violations were included in the per protocol analysis. Table 6 shows therapeutic outcome for all analyses. For the ITT and MITT analyses, defined in section 6.1.3, Clindesse™ was non-inferior to Cleocin® vaginal cream for treatment of bacterial vaginosis. In the Per Protocol analysis, the lower bound of the 95% confidence interval for the treatment difference exceeds the non-inferiority margin of  $\pm 15\%$  by a small margin.

Table 6. Therapeutic Treatment Outcome (All analyses) (Adapted from Applicant's Summary Tables W and X)

Analysis Population	Clindesse™			Cleocin® vaginal cream			Treatment difference %
	N	n	% cure	N	n	% cure	[95% Confidence Interval]
ITT	263	78	29.7	265	80	30.2	-0.5 [-8.3, 7.3]
MITT	221	73	33.0	211	78	37.0	-3.9 [-12.9, 5.1]
Per Protocol	126	53	42.1	125	57	45.6	-3.5 [-15.8, 8.7]

N is the number of evaluable patients in each group

n is number of patients cured for each group

Treatment Difference= Clindesse™ cure rate minus Cleocin® vaginal cream cure rate

**Medical Officer Comments:** For this analysis, the applicant proposed a non-inferiority margin of  $\pm 20\%$  for the treatment difference between Clindesse™ and Cleocin® vaginal cream. However, the pre-specified non-inferiority margin for this study was  $\pm 15\%$ , which should be used as the non-inferiority limit for analysis of this data. Non-inferiority of Clindesse™ to Cleocin® vaginal cream, within the  $\pm 15\%$  margin, was demonstrated in the ITT and MITT analyses. Although the lower bound of the 95% confidence interval for the treatment difference between Clindesse™ and Cleocin® vaginal cream in the per protocol analysis (-15.8, 8.7), lies outside the pre-specified limit, we can conclude that Clindesse™ is non-inferior to Cleocin® vaginal cream based on the ITT and MITT analyses.

### Secondary Outcome Measures

For each of the secondary outcome measures, clinical outcome, Nugent score outcome, and investigator outcome, Clindesse™ was shown to be non-inferior to Cleocin® vaginal cream for treatment of bacterial vaginosis (using the non-inferiority margin of  $\pm 15\%$ ), by ITT, MITT, and Per Protocol analyses. For a description of study results, please refer to the review of study 01-025 in the Appendix, section 10.1.2.

**Medical Officer Comments:** These data support the conclusions reached by analysis of the primary outcome measure, therapeutic treatment outcome, regarding non-inferiority of Clindesse™ in comparison to Cleocin® vaginal cream for treatment of BV.

Pooled Studies 01-025 and 02-005: Efficacy of Clindesse™ compared to Placebo and to Cleocin® vaginal cream for Treatment of BV

Populations Studied

A total of 802 patients were enrolled in the two pivotal studies, 262 in the placebo-control study (02-005), and 540 in the active-control study (01-025). A total of 348 patients were randomized to receive Clindesse™, 85 in the 02-005 study, and 263 in study 01-025. Eighty five patients were randomized to receive placebo (02-005), 265 to receive Cleocin® vaginal cream (01-025), and 85 to receive metronidazole cream (02-005).

Patient Evaluability

A summary of the patient evaluability for all analysis populations for studies 02-005 and 01-025 is shown in Table 7 below. Overall, 97.8% of patients randomized were eligible for ITT analysis, 81.0% by MITT analysis, and 49.5% by per protocol analysis. All three populations were analyzed for efficacy; however, the applicant pre-specified the MITT population as the primary analysis set for study 02-005, and the Per Protocol population as the primary analysis set for study 01-025. The ITT population was used for safety analysis for both studies.

Table 7. Patient Evaluability for Studies 01-025 and 02-005 (Adapted from Applicant's Table 2, section 5.3.5.3.1)

Analysis Population	Study 02-005			Study 01-025		Total Clindesse™	Overall
		Metronidazole	Placebo	Clindesse™	Cleocin® Vaginal cream		
	BV N=86	N=87	N=89	N=271	N=269		N=802
	n (%)	n (%)	n (%)	n (%)	n (%)		n (%)
ITT	85 (98.8)	85 (97.7)	85 (95.5)	263 (97.0)	265 (98.5)	348 (97.5)	783 (97.6)
MITT	78 (90.7)	72 (82.7)	66 (74.2)	221 (81.5)	211 (78.4)	299 (83.8)	648 (80.8)
Per Protocol*	53 (61.6)	48 (55.2)	42 (47.2)	128 (47.2)	125 (46.5)	181 (50.7)	396 (49.3)

N= Total number of patients randomized to treatment group

n = number of patients in analysis population for each treatment group(s)

%= percentage of randomized patients

\* Patients in the Per Protocol set included all MITT patients who completed the study with no major protocol violations.

*Medical Officer Comments: Approximately 50% of enrolled patients were considered evaluable for the per protocol analysis overall. No significant differences in patient evaluability and reasons for non-evaluability were observed between treatment groups.*

*The applicant designated different analysis sets for primary efficacy analysis for the two studies (MITT in the placebo-controlled study, and per protocol for the active-controlled study). However, the same conclusions can be drawn regarding efficacy of Clindesse™ for all 3 populations.*

### Patient Demographics

The patients in the two studies were generally similar. Most patients in each treatment group were of Caucasian or African American origin, and were 18-39 years old. A summary of patient characteristics for both studies is shown in Table 8.

Table 8. Comparison of Demographic Characteristics across Clinical Studies (ITT Analysis), Adapted from applicant's Table 2.7.3.3.1.2.

Characteristic	Study 02-005			Study 01-025	
	Clindesse™ N=85	Placebo N=85	Metronidazole N=85	Clindesse™ N=263	Cleocin® vaginal cream N=265
<b>Race</b>	n (%)	n (%)	n (%)	n (%)	n (%)
Asian	2 (2.4)	3 (4.5)	0 (0)	3 (1.1)	2 (0.8)
African American	32 (37.6)	25 (29.4)	32 (37.6)	91 (34.6)	95 (35.8)
Caucasian	39 (45.9)	48 (56.5)	37 (43.5)	137 (52.1)	136 (51.3)
Hispanic	11 (12.9)	9 (10.6)	16 (18.8)	27 (10.3)	25 (9.4)
Other	1 (1.2)	0 (0)	0 (0)	5 (1.9)	7 (2.6)
<b>Age (years)</b>					
18-39	56 (65.9)	53 (62.4)	66 (77.6)	186 (70.1)	195 (73.6)
40-64	29 (34.1)	32 (37.6)	19 (22.4)	74 (28.1)	68 (25.7)
65-75	0	0	0	2 (0.8)	2 (0.8)
> 75	0	0	0	1 (0.4)	0
Mean ± SD	34.5 ±10.7	35.8±11.3	32.47±8.78	34.6±10.7	33.9 ±10.8

N= total number of patients in treatment group

n= number of patients with designated characteristic

%= percentage of patients in treatment group.

SD= standard deviation

### Integrated Efficacy Outcome

The primary endpoint, therapeutic outcome, for the two pivotal studies, 01-025 and 02-005, is shown in Table 9 below. The overall therapeutic cure rate for Clindesse™ approximated 30% in the ITT and MITT analyses in both studies. Somewhat higher rates of therapeutic cure, approximately 39-42 %, were observed with Clindesse™ in the Per Protocol Analysis in the two

studies. — metronidazole data was not included in this analysis, because these data were withdrawn for consideration in this NDA by the applicant.

Table 9. Summary of Therapeutic Treatment Outcome for Placebo- (02-005) and Active-Controlled (01-025) Trials (All Populations) Adapted from Applicant's Table 5)

Analysis Population	Clindesse™ % cure	Cleocin® vaginal cream % cure	Placebo % cure	Treatment Difference* [95% Confidence Interval]
ITT (01-025)	29.7	30.2	NA	-0.5 [-8.3, 7.3]
ITT (02-005)	27.1	NA	3.5	23.5 [13.3, 33.8]
MITT (01-025)	33.0	37.0	NA	-3.9 [-12.9, 5.1]
MITT (02-005)	29.5	NA	3.0	26.5 [15.5, 37.4]
Per Protocol (01-025)	42.1	45.6	NA	-3.5 [-15.8, 8.7]
Per Protocol (02-005)	38.5	NA	0	38.5 [25.2, 51.7]

NA= not applicable

\*Treatment difference is point estimate of the percentage difference for Clindesse™ minus comparator.

*Medical Officer Comments: There was little inter-study variability when therapeutic treatment outcomes for Clindesse™ were compared across studies.*

Because patient characteristics were similar for the two studies, and because the study designs, including study entry criteria (except that study 01-025 did not exclude pregnant women in the second or third trimester), and study endpoints were virtually identical, data from the two pivotal studies was pooled to evaluate overall efficacy of Clindesse™ for treatment of BV.

*Medical Officer Comments: Only 12 pregnant patients were enrolled in the 01-025 study, so overall treatment outcome should not be affected by this variable.*

Primary and secondary efficacy outcomes for the ITT analyses are shown in Table 10 below for combined studies 01-025 and 02-005. For all outcome measures, the proportion of cured Clindesse™-treated patients exceeded the proportion of cured placebo-treated patients. In addition, the treatment difference between Clindesse™ and Cleocin® was not statistically significant and falls within the predetermined non-inferiority margin of ±15% for the ITT analysis.

Table 10. Primary and Secondary Treatment Outcome for Combined Studies 01-025 and 02-005 (ITT Analysis) (Reviewer's Analysis)

Treatment Outcome	Clindesse™ N=348*	Cleocin® vaginal cream N=265	Placebo N=85	Treatment Difference Clindesse™ minus Cleocin® [95% confidence interval]	Treatment Difference Clindesse™ minus Placebo [95% confidence interval]
	n (%)**	n (%)	n (%)	%	%
Therapeutic	101 (29.0)	80 (30.2)	3 (3.5)	-1.2 [-8.5, 6.1]	25.5 [19.3,31.7]
Clinical	162 (46.6)	126 (47.5)	14 (16.5)	-0.9 [-9.0,7.0]	30.1 [20.6, 39.6]
Nugent	160 (45.9)	112 (42.3)	5 (5.9)	3.6 [-4.2,11.6]	40.0 [32.9,47.3]
Investigator	265 (76.1)	215 (81.1)	26 (30.5)	-5.0 [-11.5,1.5]	45.6 [34.8, 56.3]

N= total number of patients in treatment group

\* Number of patients in Clindesse™ treatment group was obtained by adding patients from studies 01-025 and 02-005.

n = number of patients with "cure" by specified criteria

\*\* number and percentage of patients cured in Clindesse™ treatment group was obtained by adding the number of patients cured in the 01-025 and 02-005 studies, and calculating proportion based on 348 total patients from both studies.

**Medical Officer Comments:** *By combining the data from the two studies, the benefit of randomization may have been lost. Nevertheless, these combined data corroborate the conclusions drawn from the individual clinical studies. In the ITT analysis, for both primary and secondary outcome measures, Clindesse™ was superior to placebo, and was non-inferior to Cleocin® vaginal cream, for the treatment of BV.*

Primary and secondary treatment outcomes are shown for the MITT and per protocol analyses in Tables 11 and 12 below. The same conclusions can be drawn from these analyses as for the ITT analysis discussed above.

Table 11. Primary and Secondary Treatment Outcome for Combined Studies 01-025 and 02-005 (MITT Population) (Reviewer's Analysis)

Treatment Outcome	Clindesse™ N=299*	Cleocin® vaginal cream N=211	Placebo N=66	Treatment Difference Clindesse™ minus Cleocin® [95% confidence interval]	Treatment Difference Clindesse™ minus Placebo [95% confidence interval]
	n (%)**	n (%)	n (%)	%	%
Therapeutic	96 (32.1)	78 (37)	2 (3.0)	-4.9 [-13.3, 3.5]	29.1 [22.4, 35.8]
Clinical	150 (50.2)	114 (54)	13 (19.7)	-3.8 [-12.7, 4.9]	30.5 [19.3, 41.6]
Nugent Score	136 (45.5)	104 (49.3)	4 (6.1)	-3.8 [-12.6, 5.0]	39.4 [31.4, 47.5]
Investigator	229 (76.6)	170 (80.5)	24 (36.4)	-3.9 [-11.2, 3.2]	40.2 [27.7, 52.8]

\*Total number for Clindesse™ group was obtained by adding MITT patients from studies 01-025 and 02-005.

\*\*number and percentage of patients cured in the Clindesse™ groups from 01-025 and 02-005

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Table 12. Primary and Secondary Treatment Outcome for Combined Studies 01-025 and 02-005 (Per Protocol Population) (Reviewer's Analysis)

Treatment Outcome	Clindesse™ N=178*	Cleocin® vaginal cream N=125	Placebo N=42	Treatment Difference Clindesse™ minus Cleocin® [95% confidence interval]	Treatment Difference Clindesse™ minus Placebo [95% confidence interval]
	n (%)**	n (%)	n (%)	%	%
Therapeutic	73 (41)	57 (45.6)	0 (0)	-4.6 [-15.9, 6.7]	41.0 [33.8, 48.2]
Clinical	106 (59.5)	79 (63.2)	9 (21.4)	-3.7 [-14.8, 7.5]	38.1 [23.8, 52.5]
Nugent Score	99 (55.6)	71 (56.8)	1 (2.5)	-1.2 [-12.5, 10.2]	53.1 [44.6, 61.9]
Investigator	153 (86.0)	108 (86.4)	18 (42.9)	-0.4 [-8.3, 7.4]	43.1 [27.3, 58.9]

\*Total number for Clindesse™ group was obtained by adding Per Protocol patients from studies 01-025 and 02-005.

\*\*number and percentage of patients cured in the Clindesse™ groups from 01-025 and 02-005

**Medical Officer Comments:** In the MITT analysis of these data, the same conclusions can be drawn regarding efficacy of Clindesse™ as in the ITT analysis above. For therapeutic outcome in the Per Protocol analysis, the confidence interval around the treatment difference narrowly exceeds the non-inferiority margin of  $\pm 15\%$ . For this review, the denominator used to calculate proportion cured was the highest number of patients for all outcomes assessed. For example, if there were 125 patients in the per protocol population for Cleocin® for analysis of the therapeutic outcome, that number was used to calculate percentage cured for the secondary outcomes, even if the applicant used a smaller number as denominator when outcome data was missing. Consequently, missing data is counted as treatment failure for this analysis.

### Summary and Conclusions Regarding Efficacy

The results of the individual pivotal clinical studies and of the two combined studies show superiority of Clindesse™ to placebo, and non-inferiority to Cleocin® vaginal cream for the treatment of bacterial vaginosis in this population. The same conclusions can be drawn using either the primary or secondary endpoints for the ITT and MITT analyses. Study results were reproducible, with similar rates of therapeutic cure, 30-40%, obtained for Clindesse™ in both the placebo-controlled and active-controlled studies.

**Medical Officer Comment:** *In study 01-025, the lower boundary of the confidence interval for the treatment difference between Clindesse™ and Cleocin® vaginal cream in the Per Protocol analysis of therapeutic cure (-15.8%), marginally exceeded the predetermined noninferiority margin of -15%. Confidence intervals were not exceeded for the ITT or MITT analysis for therapeutic cure in this study. Because the ITT or MITT set is actually preferred for efficacy analysis, the conclusions regarding the non-inferiority of Clindesse™ to Cleocin® vaginal cream are valid.*

It should be noted that for Cleocin® vaginal cream, 2%, the clinical studies included in product labeling used a different, less stringent primary endpoint than that used in these studies. As included in the Cleocin® vaginal cream package insert, clinical cure was defined as the absence of clue cells on wet mount preparation and a negative “whiff” test. The clinical cure rates reported for BV in those studies ranged from 72% to 81% for 3-day treatment, and 84-86% for 7-day treatment with Cleocin® vaginal cream (NDA 50-680). Thus, because of the difference in primary endpoints, the studies presented for this NDA are not directly comparable to earlier studies used for licensing Cleocin® vaginal cream for this indication.

**Medical Officer Comment:** *Data from the clinical studies submitted with this NDA directly comparing Clindesse™ with Cleocin® vaginal cream will be incorporated into the Clindesse™ label.*

#### 6.1.5 Clinical Microbiology

Please refer to Dr. K. Suvarna’s Microbiology Review for full details. In summary, the applicant relied on microbiological studies in the published literature, and the approved label for Cleocin® vaginal cream, in support of this NDA. *In vitro*, clindamycin is active against most strains of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides sp.*, *Mobiluncus sp.*, and *Peptostreptococcus sp.*, which are associated with BV. Clindamycin exhibits some activity against *Lactobacillus sp. in vitro*. However, the effect of clindamycin on vaginal *Lactobacillus* colonization appears to be transient.

#### 6.1.6 Efficacy Conclusions

From these two pivotal clinical studies, we can conclude that Clindesse™ is superior to placebo, and is non-inferior to Cleocin® vaginal cream 2% for the treatment of BV in non-pregnant women.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Data sources used for the safety analysis included the printed summaries provided by the applicant, and safety information obtained directly from the electronic database. The ITT population (all randomized patients who received at least one dose of study drug) was used for the safety analysis which was based on 4 clinical studies:

- a. KVP-214, a randomized, single-dose, two-way crossover relative bioavailability study of Clindesse<sup>TM</sup> vs. Cleocin® in normal volunteers;
- b. 01-012, a pilot multicenter single-dose bioavailability screening study;
- c. 01-025, a randomized, single-blind, active-controlled, phase 3 study comparing single dose Clindesse<sup>TM</sup> to 7 days of Cleocin® vaginal cream; and
- d. 02-005, a randomized, double-blind, placebo-controlled, phase 3 study comparing Clindesse<sup>TM</sup> to placebo and to ~~—~~ metronidazole.

Because the study design differed and subjects were normal volunteers for study KVP-214, the safety evaluation was performed separately for that study; while an integrated safety analysis was performed on pooled data from studies 01-012, 01-025, and 02-005.

Overall, the adverse event profile of Clindesse<sup>TM</sup> was similar to that of both Cleocin® vaginal cream and placebo. There were no deaths in the studies, and there was only one serious adverse event, a lower extremity cellulitis which occurred in a patient who received Cleocin® vaginal cream. The most common adverse events reported in these studies were vulvovaginal candidiasis and pruritis.

#### 7.1.1 Deaths

No deaths were reported in any of these studies.

#### 7.1.2 Other Serious Adverse Events

One serious adverse event was reported among all the studies. This serious adverse event was a severe lower extremity cellulitis, requiring hospitalization, reported in a Cleocin®-treated patient, and considered unlikely related to study medication. This event has been described in detail in the review of study 01-025.

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

Patients who were discontinued early from the studies were evaluated at the early discontinuation visit and outcome assessed at that time was carried forward to the TOC visit. The reasons for study discontinuation for the combined studies are shown in Table 13 below. Most patients were discontinued from the studies early because of a baseline Nugent score <4.

Table 13. Reasons for Study Discontinuation (Pooled studies 01-025 and 02-005) (Reviewer's Analysis)

Reason for Discontinuation	Clindesse™ N=127	Cleocin® vaginal cream N=95	Placebo N=39
	n (%)	n (%)	n (%)
Nugent score <4	47 (37.0)	48 (50.5)	18(46.2)*
Lost to follow-up	27 (21.3)	14 (14.7)	4 (10.3)
Protocol violation	20 (15.7)	7 (7.4)	2 (5.1)
Other	12 (9.4)	9 (9.5)	3 (7.7)
Other antimicrobial for BV	8 (6.3)	5 (5.3)	11 (28.2)*
Other infection	6 (4.7)	3 (3.2)	1 (2.6)
Adverse event	4 (3.1)	2 (2.1)	0 (0)
Patient request	1 (0.8)	3 (3.2)	0 (0)
Study non-compliance	2 (1.6)	4 (4.2)	0 (0)

N= number of patients discontinued from study

\*p-value <0.05 for Clindesse™ vs. placebo

*Medical Officer Comments: In this analysis of the pooled study data, some differences between treatment groups are evident, including more discontinuations for baseline Nugent score <4, and for use of another antimicrobial agent for BV in the placebo grouping comparison to Clindesse™ group. The latter is not unexpected if patients continued to be symptomatic. Notably, only a few adverse events resulted in early study discontinuation.*

#### 7.1.3.2 Adverse events associated with dropouts

Eight patients were withdrawn from study participation due to adverse events, 6 of 368 patients in the Clindesse™ group, 2 of 265 patients in the Cleocin® group, and none of 85 patients in the placebo group. These adverse events are summarized in Table 14. Narrative reports on each of these cases can be found in the individual study reports.

Table 14. Adverse Events Leading to Early Discontinuation from Study (Adapted from Summary Table 33, volume 21).

Study/ Patient Number	Study Medication	Adverse Event Preferred Term	Severity	Relation to Study Drug	Action
01-012/ 001-011	Clindesse™	Papilloma virus infection NOS	Mild	Definitely not	Medication
	Clindesse™	Cervical dysplasia	Mild	Definitely not	None
01-012/ 003-031	Clindesse™	Dermatitis NOS	Mild	Possible	Medication
01-025/ 842294	Clindesse™	Drug hypersensitivi ty	Moderate	Definite	Other
01-025/ 512389	Clindesse™	Vaginosis fungal NOS	Moderate	Possible	Medication
01-025/ 602137	Clindesse™	Vaginosis fungal NOS	Mild	Definitely not	Medication
02-005/ 143122	Clindesse™	Dysfunctional uterine bleeding	Moderate	Remote/ unlikely	Medication
01-025/ 512390	Cleocin®	Vaginosis fungal NOS	Mild	Definitely not	Medication
01-025/ 742557	Cleocin®	Vaginosis fungal NOS	Moderate	Probably	Medication

NOS= not otherwise specified

*Medical Officer Comments: None of the adverse events resulting in premature study discontinuation was considered severe or serious. Notably, 2 patients in the Clindesse™ treatment arm and 2 in the Cleocin® treatment arm discontinued treatment due to vaginal candidiasis.*

#### 7.1.3.3 Other significant adverse events

A total of six pregnancies occurred during these studies, four in the active-controlled study (01-025), and 2 in the placebo-controlled study (02-005). In study 01-025, 3 of the 4 pregnancies occurred in Clindesse™-treated patients, and one in a Cleocin®-treated patient. Information regarding these pregnancies, including the pregnancy outcomes, is outlined in Table 15 below.

The 2 pregnancies that occurred in study 02-005 were in metronidazole-treated patients. None of the pregnancies were considered related to study medication. Narratives for each of these events can be found in the individual study reports (Appendix 10.1).

Table 15. Pregnancies that Occurred during Study 01-025

Patient Number	Study Medication	Date of Study Entry	Pregnancy Test on Study Entry	Contraceptive Method	Date of Positive Pregnancy Test	Pregnancy Outcome†
522250	Clindesse™	9/12/02	negative	barrier	(5 weeks pregnant on 10/11/02)	Normal delivery normal infant
602413	Clindesse™	11/6/02	negative	barrier; tubal ligation 11/02	11/02	Elective Abortion 11/02
622491	Cleocin® vaginal cream	11/21/02	negative	oral contraceptives	12/5/02	42 week delivery hematemesis in neonate*
812129	Clindesse™	8/27/02	negative	barrier	9/23/02	unknown

† Pregnancy outcome data provided in the 120-day safety update (7/23/04)

\* Neonate required 5 days in neonatal intensive care unit, but subsequently recovered.

*Medical Officer Comments: No conclusions can be drawn regarding safety of Clindesse™ in pregnancy because only 12 pregnant patients were enrolled in study 01-025, and only a few pregnancies occurred during the study.*

#### 7.1.4 Other Search Strategies

No additional search strategies were performed.

#### 7.1.5 Common Adverse Events

The ITT population for the combined studies was used to evaluate common adverse events. metronidazole safety data was not analyzed for this review.

##### 7.1.5.1 Eliciting adverse events data in the development program

Patients were assessed for adverse events at each study visit after administration of study medication, and at the time of interim telephone contact (study 02-005). Adverse events were also recorded in patient diaries in study 01-025.

*Medical Officer Comment: Adverse event monitoring in these studies seemed appropriate.*

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant used the MedDRA dictionary for classification of adverse events by system organ class (SOC) and preferred term (PT).

*Medical Officer Comment: Most adverse events seemed to be classified appropriately. However, the PT, "vaginosis fungal NOS", was classified under both SOC terms, "Infections and Infestations", and "Reproductive System and Breast Disorders". For this review, all events classified as "vaginosis fungal NOS" were combined regardless of SOC term to determine incidence of this adverse event.*

#### 7.1.5.3 Incidence of common adverse events

The number of patients with a reported adverse event was 126/368 (34.2%) for those who received Clindesse<sup>TM</sup>, 71/265 (26.8%) with Cleocin®, and 32/85 (37.6%) with placebo. Adverse events were considered drug-related in 39 (10.6%) of Clindesse<sup>TM</sup>-treated, in 21 (7.9%) of Cleocin®-treated, and in 15 (17.6%) of placebo-treated patients. Most adverse events reported in the pooled safety database were mild or moderate. Severe adverse events were reported in 8 patients (2.2%) treated with Clindesse<sup>TM</sup>, in 5 (1.9%) Cleocin®-treated patients, and in 3 (3.5%) patients who received placebo.

Table 16 summarizes the incidence of adverse events in the pooled safety database. No statistically significant differences were noted between treatment arms for overall incidence of adverse events.

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Table 16. Categories of Adverse Events in Pooled Safety Database (Studies 01-012, 01-025, 02-005) (Adapted from Applicant's Table 2.7.4.2.1.1, volume 2)

Adverse Events (AEs) Category	Clindesse™ N=368	Cleocin® N=265	Placebo N=85	Overall N=718
	n (%)	n (%)	n (%)	n (%)
Patients with AEs	126 (34.2)	71 (26.8)	32 (37.6)	229 (31.9)
Number of AEs	193	97	46	336
Patients with drug-related AEs	39 (10.6)	21 (7.9)	15 (17.6)	75 (10.4)
Number of drug-related AEs	41	22	19	82
Patients with AEs leading to early study discontinuation	6 (1.6)	2 (0.8)	0 (0)	8 (1.1)
Number of AEs leading to early study discontinuation	7	2	0	9
Patients with serious AEs	0 (0)	1 (0.4)	0 (0)	1 (0.1)
Number of serious AEs	0	1	0	1

N= total number of patients in treatment group

n= number of patients or adverse events in each category

%= percentage of patients in treatment group

#### 7.1.5.4 Common adverse event tables

The most common adverse events in the pooled database were “vaginosis fungal NOS”, reported in 52 (14.1%) Clindesse™-treated patients, 27 (10.2%) Cleocin®-treated patients, and 7 (8.2%) placebo-treated patients. The second most common adverse event was “vulvovaginal pruritis”, reported in 12 (3.3%) Clindesse™-treated patients, 8 (3.0%) Cleocin®-treated patients, and 3 (3.5%) placebo-treated patients. The most commonly reported adverse events in the pooled safety database, classified by Preferred Term (PT) are summarized in Table 17 below. The incidence of specific adverse events was comparable for all treatment groups, with no

statistically significant differences between treatment groups except for “abdominal pain NOS”, which was reported in 5 (5.9%) patients who received placebo, 2 (0.8%) patients who received Cleocin®, and 3 (0.8%) patients who received Clindesse™. The incidence of abdominal pain was higher in the placebo group than in the Clindesse™ group (p value = 0.007); but was not significantly different in the Clindesse™ vs. Cleocin® treatment groups (p value = 1.0).

Table 17. Most Common Adverse Events\* Reported in Integrated Safety Database (Studies 01-015, 02-005, 01-012) (Adapted from Applicant’s Table G, volume 21).

Adverse Event (Preferred Term)	Clindesse™ N=368	Cleocin® Vaginal Cream N=265	Placebo N=85
	n (%)	n (%)	n (%)
Vaginosis fungal NOS	52 (14.1)	27 (10.2)	7 (8.2)
Vulvovaginal pruritis	12 (3.3)	8 (3.0)	3 (3.5)
Headache NOS	10 (2.7)	4 (1.5)	2 (2.4)
Back pain	6 (1.6)	0 (0)	1 (1.2)
Nausea	5 (1.4)	0 (0)	3 (3.5)
Constipation	4 (1.1)	0 (0)	0 (0)
Nasopharyngitis	4 (1.1)	1 (0.4)	0 (0)
Urinary tract infection NOS	4 (1.1)	3 (1.1)	0 (0)
Vaginal discharge	4 (1.1)	3 (1.1)	2 (2.4)
Abdominal pain NOS	3 (0.8)	3 (1.1)	5 (5.9)
Herpes simplex	3 (0.8)	1 (0.4)	1 (1.2)
Vaginal burning sensation	3 (0.8)	1 (0.4)	1 (1.2)
Diarrhea NOS	2 (0.5)	2 (0.8)	2 (2.4)
Dysmenorrhea	2 (0.5)	1 (0.4)	2 (2.4)
Pelvic pain NOS	1 (0.3)	1 (0.4)	2 (2.4)
Vaginal irritation	1 (0.3)	1 (0.4)	2 (2.4)
Vaginal hemorrhage	0 (0)	3 (1.1)	0 (0)

Adverse events reported by Preferred Term, and reported in  $\geq 1\%$  patients in any treatment group  
 N= total number of patients in treatment group in pooled safety database

n= number of patients with reported adverse event

%= percentage of patients in treatment group with adverse event

NOS= not otherwise specified

**Medical Officer Comments:** *The number of cases reported for vaginal candidiasis (reported in the database as the PT vaginosis fungal NOS) differed in this analysis from that of the applicant who reported 50 cases in Clindesse™-treated cases. This difference occurred because the applicant classified adverse events first by SOC then by PT. Several cases of vaginal candidiasis were classified under a different SOC and did not total  $\geq 1\%$  patients within that group.*

*It is not clear why abdominal pain occurred more frequently in the placebo-treated group. The applicant hypothesized that abdominal pain may occur more frequently in the*

*placebo group due to untreated bacterial vaginosis, however, abdominal pain is not usually associated with BV.*

#### 7.1.5.5 Identifying common and drug-related adverse events

The relationship of an adverse event to study medication was assessed by the investigator, and designated as possibly, probably, or definitely related, remote/unlikely related, and definitely not related. For this review, all adverse events considered possibly, probably, or definitely related were classified as drug-related.

The most common drug-related adverse event was “vaginosis fungal NOS”, which occurred in 16 (4.3%) Clindesse<sup>TM</sup>-treated patients, 12 (4.5%) Cleocin®-treated patients, and 2 (2.4%) placebo-treated patients. Additionally, 2 Clindesse<sup>TM</sup>-treated patients in the pilot study, 01-012, developed drug-related vaginal candidiasis. However, this was reported under the SOC, “Reproductive system and breast disorders” rather than under “Infections and Infestations”. No significant differences in drug-related adverse events were seen between treatment groups, except for abdominal pain, which was reported in 1 (0.4%) Clindesse<sup>TM</sup>-treated, and 4 (4.7%) placebo-treated patients ( $p=0.013$ ). Table 18 summarizes the drug-related adverse events reported in at least 2 patients in any treatment group.

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Table 18 . Most Commonly Reported Drug-Related Adverse Events\* by System Organ Class (SOC) and Preferred Term (PT) in Pooled Safety Database (Adapted from Applicant’s Table H, volume 21).

Adverse Event SOC and PT	Clindesse™ N=368	Cleocin® N=265	Placebo N=85
	n (%)	n (%)	n (%)
<b>Gastrointestinal disorders:</b>			
Abdominal pain NOS	0 (0)	1 (0.4)	4 (4.7)
Nausea	2 (0.5)	0 (0)	1 (1.2)
<b>Immune system disorders:</b>			
Drug hypersensitivity	2 (0.5)	0 (0)	0 (0)
<b>Infections and Infestations:</b>			
Vaginosis fungal NOS	16 (4.3)	12 (4.5)	2 (2.4)
<b>Reproductive system and breast disorders:</b>			
Vaginal burning sensation	2 (0.5)	0 (0)	1 (1.2)
Vaginal discharge	2 (0.5)	1 (0.4)	1 (1.2)
Vaginal irritation	1 (0.3)	1 (0.4)	2 (2.4)
Vaginosis fungal NOS	2 (0.5)	0 (0)	0 (0)
Vulvovaginal pruritis	5 (1.4)	2 (0.8)	3 (3.5)

\* Adverse events reported in 2 or more patients in any treatment group

N= total number of patients in treatment group

n = number of patients with specific adverse event

% = percentage of patients in treatment group

NOS= not otherwise specified

SOC and PT were coded using MedDRA® version 5.0

*Medical Officer Comments: When all reported cases of “vaginosis fungal NOS” are combined regardless of SOC term, 18 (4.9%) patients treated with Clindesse™, 12 (4.5%) treated with Cleocin®, and 2 (2.4%) patients treated with placebo, developed vaginal candidiasis. More cases of vaginal candidiasis were reported with Clindesse™ and Cleocin® than with placebo, suggesting a relationship to study medications. This finding is not unexpected because use of an antimicrobial agent could alter vaginal microflora, resulting in fungal overgrowth.*

#### 7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were performed.

### 7.1.6 Less Common Adverse Events

Adverse events occurring in < 1% of patients who received Clindesse™ were reviewed, and none appeared to be serious or potentially life-threatening.

### 7.1.7 Laboratory Findings

Except for laboratory data used in the efficacy analysis (Gram's stain for Nugent score, vaginal pH, "whiff" test, etc.), the only other laboratory data collected in these studies were cultures for *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Candida sp.*, and KOH preparation for yeast. These were considered "non-efficacy" laboratory data. Serum chemistry, hematology or other tests were not performed in these studies.

#### 7.1.7.1 Overview of laboratory testing in the development program

Specimens for non-efficacy laboratory data, described above, were obtained at study entry visit, and at the test-of-cure visit only if clinically indicated.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable

#### 7.1.7.3 Standard analyses and explorations of laboratory data

There were no statistically significant differences between treatment groups for baseline and test-of-cure "non-efficacy" laboratory and culture results, which included cultures for *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Candida sp.* However, a significant difference was noted at the TOC visit for the KOH preparation for yeast between the Clindesse™ and Cleocin® groups, with 56 patients (17.1%), 24 patients (10.3%), and 5 patients (8.3%) in the Clindesse™, Cleocin®, and placebo groups, respectively positive for yeast ( $p=0.027$ ). Vital signs were not recorded in these studies.

**Medical Officer Comments:** *The number of patients who had a positive KOH preparation for yeast at the TOC visit is similar to the numbers of cases of vaginal candidiasis reported as adverse events (Table 17 above).*

*7.1.7.3.1 Analyses focused on measures of central tendency*

Not applicable.

*7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Not applicable.

*7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities*

Not applicable.

7.1.7.4 Additional analyses and explorations

Not applicable

7.1.7.5 Special assessments

No special assessments were performed

7.1.8 Vital Signs

Vital signs were not recorded in the two pivotal studies, 01-025 and 02-005. Vital signs were recorded in the bioavailability study, but were not analyzed as part of this review.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not obtained in these studies.

7.1.10 Immunogenicity

No data regarding immunogenicity was collected in the clinical studies.

7.1.11 Human Carcinogenicity

No data regarding human carcinogenicity was collected in these studies.

7.1.12 Special Safety Studies

Because Clindesse<sup>TM</sup> is a topical product with minimal systemic absorption, no special studies were performed to assess safety concerns common to its pharmacologic class, specifically,

inhibition of neuromuscular activity. Similarly, no studies were performed to assess QT interval prolongation for this NDA.

No special clinical safety studies addressing cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity were performed.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Clindesse™ is a topical antimicrobial drug product and is not expected to have any abuse potential or to trigger withdrawal phenomena.

#### 7.1.14 Human Reproduction and Pregnancy Data

Pregnant women were excluded from study 02-005, but women in the second or third trimester of pregnancy could be enrolled in study 01-025. However, only 12 pregnant women were enrolled in this study, 3 patients received Clindesse™, and 9 received Cleocin vaginal cream. Because of the small number of pregnant women enrolled, a separate safety analysis would not accurately reflect safety concerns in this population. A total of 5 adverse events were reported among pregnant women enrolled. None of these events was serious or required study withdrawal. Additionally, six pregnancies which occurred during the these studies are discussed in section 7.1.3.3.

#### 7.1.15 Assessment of Effect on Growth

Not applicable because women under 18 years of age were excluded from these studies.

#### 7.1.16 Overdose Experience

No overdose experience with Clindesse™ was reported.

#### 7.1.17 Postmarketing Experience

There is no postmarketing experience with Clindesse™.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Data sources used for the safety analysis included the printed summaries provided by the Applicant, as well as safety information obtained directly from the electronic database.

The safety analysis for Clindesse<sup>TM</sup> was based on 4 clinical studies:

- e. KVP-214, a randomized, single-dose, two-way crossover relative bioavailability study of Clindesse<sup>TM</sup> vs. Cleocin® in normal volunteers;
- f. 01-012, a pilot multicenter single-dose bioavailability screening study;
- g. 01-025, a randomized, single-blind, active-controlled, phase 3 study comparing single dose Clindesse<sup>TM</sup> to 7 days of Cleocin® vaginal cream; and
- h. 02-005, a randomized, double-blind, placebo-controlled, phase 3 study comparing Clindesse<sup>TM</sup> to placebo and to metronidazole.

Because the study design differed and subjects were normal volunteers for KVP-214, the safety evaluation was performed separately; while an integrated safety analysis was performed on pooled data from studies 01-012, 01-025, and 02-005.

#### 7.2.1.1 Study type and design/patient enumeration

Please refer to section 10.1.5 for a summary table which includes a detailed description of the clinical studies submitted with this NDA.

#### 7.2.1.2 Demographics

For the studies pooled for the integrated safety analysis, most patients were between 18-39 years of age. More than half of the study population was Caucasian. There was no significant difference between the treatment groups in the pooled safety data with regard to race or age. These data are summarized in Table 19 below.

Table 19. Demographic Characteristics of Patients in Pooled Safety Database (Studies 01-012, 01-025, 02-005) (Adapted from Applicant's Table 2.7.4.1.4.1, volume 2).

Characteristic	Clindesse™ N=368	Cleocin® N=265	Metronidazole N= 85	Placebo N=85	Overall N=803
	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Race</b>					
Asian	5 (1.4)	2 (0.8)	0 (0)	3 (3.5)	10 (1.2)
African-American	131 (35.6)	95 (35.8)	32 (37.6)	25 (29.4)	283 (35.2)
Caucasian	186 (50.5)	136 (51.3)	37 (43.5)	48 (56.5)	407 (50.7)
Hispanic	38 (10.3)	25 (9.4)	16 (18.8)	9 (10.6)	88 (11.0)
Other	6 (1.6)	7 (2.6)	0 (0)	0 (0)	13 (1.6)
Unknown	2 (0.5)	0 (0)	0 (0)	0 (0)	2 (0.2)
<b>Age category (years)</b>					
18-39	257 (69.8)	195 (73.6)	66 (77.6)	53 (62.4)	571 (71.1)
40-64	108 (29.3)	68 (25.7)	19 (22.4)	32 (37.6)	227 (28.3)
65-75	2 (0.5)	2 (0.8)	0 (0)	0 (0)	4 (0.5)
>75	1 (0.3)	0 (0)	0 (0)	0(0)	1 (0.1)
Mean age (± SD)	34.6 (10.6)	33.9 (10.8)	32.5 (8.8)	35.8 (11.3)	NA
Median age	33.7	32.5	30.7	35.7	
Age range	18-78	18-75	18-60	19-60	18-78

N = Total number of patients in treatment group

n = number of patients with specific characteristic

%= percentage of patients in treatment group

SD = standard deviation

NA = not available

*Medical Officer Comments: The mean and median age of women enrolled in the placebo group was numerically higher than that of the other treatment groups. However, this difference is not likely to be clinically significant.*

### 7.2.1.3 Extent of exposure (dose/duration)

A summary of study drug exposure in studies 01-012, 01-025, and 02-005 for the integrated safety analysis is presented in Table 20. An additional 20 healthy volunteers received a dose in the KVP-214 bioavailability study.

Table 20. Patients Exposed to Clindesse™ or Comparators (Adapted from Applicant's Table 2.7.4.1.3.1, volume 2)

Study	Clindesse™	Cleocin®	Metronidazole	Placebo	Overall
	N	N	N	N	N
01-012	20	--	--	--	20
01-025	263	265	--	--	528
02-005	85	--	85	85	255
Total number of patients	368	265	85	85	803

N= total number of patients exposed to study drug

In study 01-012, all 20 subjects received a single dose (100 mg clindamycin phosphate) of Clindesse™. In study 01-025, a total of 251 of 268 patients administered a single dose (100 mg clindamycin phosphate) of Clindesse™, whereas 12 patients failed to report the number of doses administered. These 12 patients were included in the ITT analysis because there was no evidence that they did not administer the study medication. In the same study, 173 of the 265 patients randomized, administered 7 daily doses (100 mg clindamycin phosphate per dose) of Cleocin® vaginal cream. The mean dose of Cleocin® vaginal cream administered was 632.4 mg; while the mean dose of Clindesse™ administered was 100 mg. In study 02-005, 81 of 85 patients administered a single dose of Clindesse™; 83 of 85 patients in the placebo group, and 84 of 85 patients in the metronidazole group administered a single dose of study medication. Four patients in the Clindesse™ group, 1 patients in the metronidazole group, and 2 patients in the placebo group failed to report the number of doses administered, but were included in the ITT analysis.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were used to evaluate safety of Clindesse™ for this review.

#### 7.2.2.1 Other studies

None

#### 7.2.2.2 Postmarketing experience

There is no postmarketing experience with Clindesse™

#### 7.2.2.3 Literature

Literature regarding preclinical studies in support of this NDA was reviewed by the Pharmacology/Toxicology and Microbiology Reviewers. Literature pertaining to clinical studies was reviewed by the Medical Reviewer for background information, and selected references were cited in this review. See Reference section at the end of the review.

#### 7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects (368) were exposed to Clindesse™ to assess safety in a placebo-controlled study, an active-controlled study, and a pilot bioavailability study. The safety of Cleocin® vaginal cream was previously evaluated for NDA 50-680, and an additional 265 patients were exposed to Cleocin® in these studies for comparative safety analysis. Because only a few pregnant women and patients ages 65 and over were enrolled in these studies, conclusions regarding safety are not necessarily generalizable to these groups. Women under 18 years of age were excluded, but safety data from these studies was extrapolated to include post-menarchal females.

A single dose of clindamycin phosphate in Clindesse™ (100 mg) was compared to 7 daily doses of Cleocin vaginal cream (100 mg clindamycin phosphate per dose). Because the Clindesse™ vehicle is formulated for prolonged contact of the active drug with the vaginal mucosa, the actual duration of vaginal exposure to clindamycin is not known for single-dose Clindesse™. Pharmacokinetic studies with Clindesse™ showed minimal systemic absorption of clindamycin, with peak serum concentration occurring at 20 hours, compared to 6 hours post-dose for Cleocin® vaginal cream. A study with the same “sustained release” vehicle used for Gynazole-1 (NDA19-881) demonstrated that butaconazole nitrate was retained intravaginally for a median of 4.20 days in comparison to 2.57 days for butaconazole in the standard cream formulation (Weinstein, et al., 1994). Similar studies were not performed with Clindesse™ and Cleocin vaginal cream to compare the duration of intravaginal exposure.

#### 7.2.4 Adequacy of Special Animal and/or *In Vitro* Testing

One preclinical study was performed for this NDA submission. This study examined vaginal irritation in a rabbit model, and has been reviewed in detail by the pharmacology reviewer. This study appropriately addressed the potential for local adverse events attributable to intravaginal Clindesse™. A literature review was also provided by the applicant to address other aspects of preclinical pharmacology testing for this 505 (b)(2) application.

### 7.2.5 Adequacy of Routine Clinical Testing

Clinical testing of study subjects, performed at baseline, the interim visit at 7-10 days post-dosing (study 01-025 only), and the test-of-cure visit at 21-30 days post-treatment was adequate for assessing adverse events. An interim telephone contact to assess adverse events was also performed in study 02-005. Testing was adequate for assessing adverse events. Laboratory testing was not necessary in these studies because of the low systemic absorption of intravaginally-administered clindamycin.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Because intravaginally-administered Clindesse™ has minimal systemic absorption, these studies were not performed, as appropriate.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not Applicable

### 7.2.8 Assessment of Quality and Completeness of Data

Adverse event data was reported in descriptive form on case report forms and subsequently entered into the safety database, which included the same description of the event, and classification by MedDRA system organ class and preferred terms. Adverse event data from the case report forms provided for patients with serious or other significant adverse events were compared with the electronic database provided, and no irregularities were found. The overall quality and completeness of the safety data was adequate for these studies.

### 7.2.9 Additional Submissions, Including Safety Update

A 120-day safety update regarding pregnancy outcomes for patients enrolled in studies 01-025 and 02-005 was submitted July 23, 2003 upon the Agency's request. Information regarding pregnancy outcomes for patients who became pregnant during the study was incorporated into individual study reports (section 10.1). Pregnancy outcome data is not available from the investigative sites for 9 of the 12 pregnant women enrolled in study 01-025 at this time. For the 3 reported pregnancy outcomes, all were described as live births, with normal birth weight of the neonate. One of these deliveries was preterm (34 weeks).

*Medical Officer Comments: Because of the limited number of pregnant women enrolled in study 01-025, no conclusions can be drawn regarding safety of Clindesse™ in pregnancy.*

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The overall incidence of drug-related adverse events was 10.6% for single-dose Clindesse™, 7.9% with a therapeutic course of Cleocin® vaginal cream (up to 7 daily doses), and 17.6% for a single dose of placebo intravaginal cream. Most adverse events reported in these studies were transient, and mild- moderated in severity. No serious adverse events were attributed to Clindesse™ treatment. Vaginal candidiasis (“vaginosis fungal NOS”), was the most common drug-related adverse event for Clindesse™ and comparators.

The most common drug-related adverse event reported with Clindesse™ was vaginal candidiasis which occurred in 4.9% patients treated with Clindesse™, 4.5% of patients treated with Cleocin®, and 2.4 % patients treated with placebo.

*Medical Officer Comments: More emphasis is placed on all adverse events in this review, given the subjective nature of attributing an adverse event to a drug. In these studies, the relationship between the occurrence of vaginal candidiasis and treatment with either Clindesse™ or Cleocin® vaginal cream is not unexpected because of shifts in vaginal microflora with antimicrobial treatment.*

### 7.4 General Methodology

#### 7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

##### 7.4.1.1 Pooled data vs. individual study data

The integrated safety database used for this analysis included all patients who received at least one dose of study medication in the two pivotal clinical studies, 01-025 and 02-005, in addition to 20 patients enrolled in the pilot bioavailability study (01-012). The study population was similar in all 3 studies, including women  $\geq 18$  years old with the diagnosis of bacterial vaginosis. Although pregnant women were excluded in study 02-005, only 12 pregnant women were enrolled in study 01-025. These patients were included in the integrated safety analysis. Patient demographics were similar for the pooled safety population.

The 20 patients enrolled in the crossover bioavailability study (KVP-214) were not included in the integrated safety analysis because of the different study population in the latter (normal healthy volunteers). Description of adverse events that occurred in study KVP-214 were reported separately.

#### 7.4.1.2 Combining data

Safety data were pooled by simply combining adverse events (numerator) and denominators (numbers of patients) in each treatment group (Clindesse<sup>TM</sup>, Cleocin® vaginal cream, metronidazole or placebo) across studies.

#### 7.4.2 Explorations for Predictive Factors

Not applicable

##### 7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable

##### 7.4.2.2 Explorations for time dependency for adverse findings

Time dependency for adverse events was not assessed formally in this review.

##### 7.4.2.3 Explorations for drug-demographic interactions

###### Adverse Events by Race

No significant racial differences were noted when incidence of adverse events was analyzed by race in the integrated safety database.

###### Adverse Events by Age

The applicant analyzed incidence of adverse events by age category across treatment groups. A higher proportion of patients in the 18-39 year old category experienced adverse events in the Clindesse<sup>TM</sup> group (92 out of 257 patients, 35.8%) than in the Cleocin® group (53 out of 195 patients, 27.2%); while the proportion was similar to that in the placebo group (20 out of 53 patients, 37.3%). This difference between the Clindesse<sup>TM</sup> and Cleocin® groups was only of borderline significance ( $p= 0.054$ ).

##### 7.4.2.4 Explorations for drug-disease interactions

No specific explorations for drug-disease interactions were performed in these studies.

#### 7.4.2.5 Explorations for drug-drug interactions

No specific explorations for drug-drug interactions were performed in these studies.

#### 7.4.3 Causality Determination

Please refer to section 7.1.5.5 for discussion of drug-related adverse events. The most common adverse events in the study were vulvovaginal candidiasis and pruritis. As discussed above, development of vaginal candidiasis after treatment with intravaginal antibiotics could result from an alteration in vaginal microflora and fungal superinfection. Local reactions such vaginal pruritis, discharge, burning and irritation could be attributed to bacterial vaginosis itself, to a secondary fungal infection, or to the intravaginal medication, whether antibiotic or placebo.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The dose of clindamycin in Clindesse<sup>TM</sup> (100 mg clindamycin phosphate in a single intravaginal dose) was selected based on the dose of clindamycin in the approved product, Cleocin® vaginal cream (100 mg clindamycin phosphate administered daily for 3 to 7 days). In Clindesse<sup>TM</sup>, clindamycin is contained in a vehicle designed for prolonged contact with vaginal mucosa. However, the duration of intravaginal clindamycin retention after a single dose of Clindesse<sup>TM</sup> was not studied. Additionally, dose-response studies were not performed. Because the efficacy and safety of single dose Clindesse<sup>TM</sup> was demonstrated in the pilot study (01-012), the larger pivotal studies were conducting using that dosage regimen.

*Medical Officer Comments: Although the optimal dosing regimen was not evaluated, the Clindesse<sup>TM</sup> dosing regimen studied here is reasonable.*

### 8.2 Drug-Drug Interactions

Because the systemic absorption of clindamycin administered intravaginally as Clindesse<sup>TM</sup> is minimal, systemic drug-drug interactions would not be expected and were not studied. Local drug-drug interactions, such as interaction with other intravaginal medications or other topical agents, were not addressed in these studies.

*Medical Officer Comment:* \_\_\_\_\_  
\_\_\_\_\_

### 8.3 Special Populations

No studies were performed to address special dosing considerations based on age, race, pregnancy, lactation, or in patients with underlying renal or hepatic failure.

*Medical Officer Comments: Dosing in pregnant or lactating women would have to be addressed in a separate study to evaluate safety and efficacy of Clindesse™ in pregnancy. However, because Clindesse™ is a topical intravaginal product with minimal systemic absorption, special studies addressing dosing in patients with renal or hepatic failure are not necessary.*

### 8.4 Pediatrics

Adolescents under the age of 18 were excluded from these studies. However, because the pathophysiology of the disease is expected to be similar in all post-menarchal women, and because the safety and efficacy of Clindesse™ would be expected to be the same whether the patient is older or younger than 18, data from these studies can be extrapolated to include all post-menarchal females. Studies in pre-menarchal girls were not performed. However, because bacterial vaginosis is very uncommon in women who are not sexually active, a pediatric waiver will be granted to the applicant for premenarchal patients.

### 8.5 Advisory Committee Meeting

No advisory committee meeting was held in reference to this NDA submission.

### 8.6 Literature Review

Literature referenced in this review is listed in the References section at the end of the review. The literature regarding preclinical studies provided by the applicant in support of this 505(b)(2) application, specifically pharmacology, toxicology and microbiology references, were reviewed by the Pharmacology and Microbiology reviewers. All literature provided by the applicant pertaining to clinical studies was reviewed in the context of background information.

## 8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan was not submitted by the applicant, nor is one required.

## 8.8 Other Relevant Materials

None

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

Clindesse<sup>TM</sup> is safe and effective for the treatment of bacterial vaginosis in non-pregnant women. The pivotal clinical studies presented for this NDA demonstrated that Clindesse<sup>TM</sup> was superior to placebo and non-inferior to Cleocin® vaginal cream, approved previously for BV treatment. No significant safety concerns with Clindesse<sup>TM</sup> were raised in these studies.

## 9.2 Recommendation on Regulatory Action

APPROVAL of Clindesse<sup>TM</sup> for treatment of bacterial vaginosis in non-pregnant, post-menarchal women is recommended. In addition, a pediatric waiver should be granted because studies in pre-menarchal females are not appropriate.

The benefits of treatment with Clindesse<sup>TM</sup> include the relief of vaginal signs and symptoms of infection in women with symptomatic BV. Treatment of BV may also reduce the risk for infectious complications after abortion or hysterectomy, as well as reduce the risk for HIV and other sexually transmitted diseases (Workowski and Levine, 2002). Whether treatment with Clindesse<sup>TM</sup> affects those outcomes is unknown. Treatment of BV in pregnancy may reduce the risk of preterm delivery and postpartum infectious complications (Hillier and Holmes, 1999), however, Clindesse<sup>TM</sup> has not been studied in sufficient numbers of pregnant women to evaluate its efficacy for treatment of BV, or its safety in pregnancy.

The advantages of Clindesse<sup>TM</sup> over currently available therapy include its single-dose regimen, and minimal systemic absorption. Single-dose therapy should improve patient compliance, and its low systemic absorption should result in fewer systemic adverse events.

The risks of treatment with Clindesse<sup>TM</sup> appear to be minimal. Clindesse<sup>TM</sup> use has been mainly associated with treatable adverse events affecting the genital tract, such as vulvovaginal candidiasis, or vulvovaginal pruritis. However, Clindesse<sup>TM</sup> is formulated in a vehicle which

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contains mineral oil, which may damage rubber or latex products such as condoms or contraceptive diaphragms. This product will therefore carry a prominent WARNING concerning use of Clindesse™ concurrently and for 5 days following treatment with condoms, diaphragms, and other intravaginal products. This warning may be important in preventing the transmission of other sexually transmitted diseases and HIV, as well as preventing unplanned pregnancies.

*Medical Officer Comments: It is not known how long the mineral oil in Clindesse™ is retained intravaginally. In a study which examined intravaginal retention of butaconazole nitrate when applied in the standard cream formulation or in the same "sustained-release" formulation as used for Clindesse™, butaconazole was retained in the vagina for 2.6 days with the former, and 4.2 days with the latter formulation (Weinstein et al. 1994). Thus, the warning to avoid use of barrier contraceptive products concurrently and for 5 days following administration of Clindesse™ is warranted.*

### 9.3 Recommendation on Postmarketing Actions

#### 9.3.1 Risk Management Activity

Not applicable

#### 9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required of the Applicant.

#### 9.3.3 Other Phase 4 Requests

None

### 9.4 Labeling Review

Several major changes were made to the Applicant's proposed labeling for Clindesse™. The following sections were modified: Pharmacology, Warnings, Pregnancy, Nursing Mothers, Pediatric Use, Geriatric Use, and Clinical Studies. The proposed patient package insert was also modified to include the warning regarding mineral oil and to delete the instructions regarding use

\_\_\_\_\_ (See Appendix, section 10.2 for final labeling changes).

The Division of Medication Errors and Technical Support (DMETS) was consulted for an assessment of the proprietary name, \_\_\_\_\_ which was originally submitted by the applicant for this product. DMETS did not recommend the use of the name \_\_\_\_\_.

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mostly because of concerns related to “look-alike” similarity to Lindane, a topical formulation for the treatment of head lice, particularly because the misuse and overuse of Lindane has been associated with serious adverse events. DMETS also recommended changing the container, carton, and package insert labels to use “2%” rather than “2.0%” in regard to clindamycin phosphate vaginal cream, to prevent potential medication errors.

*Medical Officer Comments: The applicant subsequently submitted several trade names for review in lieu of \_\_\_\_\_, and DMETS found “Clindesse™” acceptable. Accordingly, the tradename “Clindesse™” will be used for this product*

## 9.5 Comments to Applicant

None

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## 10 APPENDICES

### 10.1 Review of Individual Study Reports

#### 10.1.1 Study 02-005: Safety and Efficacy Comparison of Clindamycin Vaginal Cream, 2% and Metronidazole Vaginal Cream, 0.75% versus Placebo in Patients with Bacterial Vaginosis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study

##### Study Objectives :

1. To demonstrate that a single dose of Clindesse™ vaginal cream is superior in efficacy and comparable in safety to placebo for treatment of bacterial vaginosis.
2. To demonstrate that a single dose of — metronidazole vaginal cream is superior in efficacy and comparable in safety to placebo for treatment of bacterial vaginosis.

##### Rationale

Clindamycin phosphate, 2% vaginal cream is an approved, commercially available and marketed for topical treatment of bacterial vaginosis as a 3- or 7- day course of therapy (Cleocin® vaginal cream, 2% NDA 59-680; Cleocin® vaginal ovules, NDA 50-767). Clindesse™ is formulated as a single-dose preparation for bacterial vaginosis. This product is formulated in the vehicle used in an approved product for vulvovaginal candidiasis, namely, Gynazole-1, which contains the active ingredient, butaconazole. The vehicle, using SITE RELEASE™ technology, provides for sustained contact of the product with the vaginal mucosa.

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##### Study Design

The study was a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study of 175 patients enrolled at 20 investigative sites in the U.S. The study was designed to compare safety and efficacy of Clindesse™ to placebo; and — metronidazole vaginal cream, 0.75%, to placebo, for the treatment of bacterial vaginosis. The study took place from October, 2002 through May, 2003.

##### Protocol Overview

Patients were required to meet the following inclusion and exclusion criteria for study participation:

**Inclusion Criteria:**

1. Females  $\geq$  18 years old
2. Clinical diagnosis of BV according to the Amsel criteria (Amsel, 1983), defined as having all the following:
  - a. Off-white (milky or gray), thin, homogeneous vaginal discharge with minimal or absent pruritis and inflammation of the vulva and vagina
  - b. Presence of "clue cells"  $\geq$  20% of total epithelial cells on microscopic examination of the "wet mount" preparation
  - c. pH of vaginal secretions  $>$  4.5
  - d. Positive "whiff" test, i.e. fishy odor of vaginal discharge with addition of a drop of 10% KOH
3. Willingness and ability to sign informed consent
4. Willingness to abstain from alcohol ingestion during the treatment phase of the study and for one day thereafter
5. Willing to abstain from vaginal intercourse during the 7 days after administration of the study medication
6. Willing to abstain from douching and from using other intravaginal products (e.g. diaphragm, contraceptive creams, gels, foams, sponges, tampons, feminine deodorant sprays, douche, nonoxynol-9 products, etc.) during treatment phase of study and follow up period.

*Medical Officer Comment: The inclusion criteria are appropriate for this study. The criteria for clinical diagnosis of BV are in accordance with the FDA Draft Guidance for Industry, "Bacterial Vaginosis- Development of Antimicrobial Therapy", 1998.*

**Exclusion Criteria:**

1. Other infectious causes of vulvovaginitis (e.g. *Candida*, *Trichomonas vaginalis*, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, etc.)
2. Other vulvar or vaginal condition such as condyloma, active *Herpes simplex* lesions, which could confound interpretation of clinical response
3. Nugent score  $<$  4 at study entry
4. Active menstruation at the time of study entry or expected menstruation within treatment period
5. Receipt of antifungal or antimicrobial therapy, systemic or intravaginal, within 14 days prior to treatment or during treatment and follow-up phases of the study

*Medical Officer Comment: Exclusion of patients who received antifungal or antibiotic therapy during the treatment or follow-up phases of the study is not valid. In fact, these patients were not excluded, but were considered non-evaluable in the Per Protocol analysis.*

6. Treatment for cervical intraepithelial neoplasia (CIN) or cervical carcinoma during the study period

7. Pregnancy (non-pregnant women were to use adequate form of birth control (hormonal birth control). Non-pregnant women using barrier methods of contraception could participate in the study if they agreed not to use intravaginal barrier methods, except for non-lubricated condoms, during the follow-up phase of the study.
8. History of hypersensitivity to metronidazole, clindamycin, lincomycin, or other ingredients of the formulation
9. Nursing mothers
10. Women with intrauterine devices
11. Use of disulfuram within 14 days prior to starting the study and during treatment and follow-up phases
12. Concomitant therapy with anticoagulants, lithium, neuromuscular blocking agents, or use of any investigational drug within 30 days of the start of the study
13. History of regional enteritis, ulcerative colitis, or "antibiotic-associated colitis"
14. Any significant medical disorder that would preclude accurate evaluation of the patient's condition

*Medical Officer's Comments: These exclusion criteria were appropriate for this study. Concomitant use of anticoagulants and lithium was excluded because of potential interaction with metronidazole. Despite the expectation for low systemic absorption of clindamycin from this intravaginal preparation, the concomitant use of neuromuscular blocking agents was excluded because clindamycin may enhance activity of such agents. Additionally, exclusion of patients with a history of enteritis or colitis was reasonable, in view of the labeled warning regarding development of pseudomembranous colitis with Cleocin® vaginal cream. All pregnant women were excluded from this study, presumably because of the metronidazole, which is contraindicated in the first trimester of pregnancy. Excluding the use of antimicrobial and antifungal drugs during the 14 day period prior to study entry was appropriate to eliminate potential confounding with study treatment effect.*

Randomization was accomplished by a sequential block permutation formulation. Patients were randomized within each block using a 1:1:1 ratio to receive either Clindesse™ vaginal cream, metronidazole vaginal cream, or placebo vaginal cream as follows:

- Clindamycin phosphate, 2% vaginal cream (Clindesse™) (100 mg clindamycin): Single-dose applicator administered intravaginally for one day; or
- Metronidazole, 0.75% vaginal cream (37.5 mg metronidazole): Single-dose applicator administered intravaginally for one day; or
- Matching placebo vaginal cream: Single-dose applicator administered intravaginally for one day.

Study medication was to be self-administered within 48 hours of the entry visit. Since this was a double-blind study, both patient and investigator were blinded to treatment. Study medication kits were packaged by an outside vendor and appeared identical. Numbered kits were dispensed to the patient by blinded personnel in numerical order to preserve randomization. Patients were instructed in self-administration of the study medication, and returned empty medication containers to unblinded personnel at the test-of-cure or early discontinuation visit.

**Medical Officer Comments:** *The dose of clindamycin in Clindesse™ was based on the FDA-approved formulation, Cleocin ® vaginal cream containing clindamycin phosphate, 2% (NDA 50-680). The latter was approved for use in BV as a 3- or 7-day course of therapy. Dose selection for metronidazole is not addressed in this review. The matching placebo vaginal cream is the vehicle used in the FDA-approved preparation, Gynazole-1, which contains butaconazole nitrate, 2% (KV Pharmaceuticals, NDA 19-881). The procedures used for double-blinding were acceptable.*

The study consisted of two phases:

- “Treatment phase” (period from entry visit to interim telephone contact at day 7-10 post-dose)
- “Follow-up” phase (period from interim telephone contact to the test-of-cure (TOC) visit at day 21-30).

The procedures and clinical assessments conducted at the entry visit, the interim telephone contact, the early discontinuation visit, and the test-of-cure visit are summarized in Table 1 shown below. Efficacy measurements were obtained at the test-of-cure or early discontinuation visit. Outcomes for patients discontinued early were carried forward to the test-of-cure visit.

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Table 1. Schedule of Assessments

Procedure	Entry Visit	Interim Telephone Contact (7-10 days)	Test of Cure Visit (21-30 days) or Early Discontinuation (EDC) Visit *
Physical Examination	X		X
Medical History	X		
OB/Gyn/Contraceptive/Sexual History	X		
Pelvic Examination	X		X
Pap Smear**	X		
Wet Mount	X		X
“Whiff” Test	X		X
Gram’s stain	X		X
Vaginal pH	X		X
KOH for yeast	X		X
Urine pregnancy test	X		X <sup>†</sup>
<i>Trichomonas vaginalis</i> wet mount	X		X <sup>§</sup>
<i>Chlamydia trachomatis</i> DNA probe	X		X <sup>§</sup>
<i>Neisseria gonorrhoea</i> DNA probe	X		X <sup>§</sup>
<i>Candida</i> culture	X		X <sup>§</sup>
<i>Herpes simplex</i> culture (if suspected)	X		X <sup>§</sup>
Study medication administration	X		
Return study medication			X
Adverse events		X	X
Concomitant medications	X	X	X
Assessment of clinical cure			X

Adapted from Applicant’s Table H, section 9.5.1.3

\* Non-evaluable patients due to baseline Nugent score < 4 were assessed at EDC visit for drug accountability, adverse events and concomitant medications.

\*\* If not done in preceding 12 months

† If patient not on hormonal birth control

§ If clinically indicated

### Removal of Patients from Study

Patients could be removed or disqualified from the study under the following conditions:

- Difficult to obtain laboratory samples
- Significant violation of study protocol

- Severe or serious adverse events
- Patient request
- Baseline Nugent score
- Lack of therapeutic effect

Patients withdrawn from the study were required to complete an “early discontinuation” visit. Assessments and procedures performed at the early discontinuation visit were the same as those done for the TOC visit.

*Medical Officer Comment: Patients discontinued due to lack of therapeutic effect are appropriately counted as treatment failures in the ITT analysis.*

### **Patient Evaluability**

The following were required for a patient to be considered clinically evaluable for the Per Protocol analysis:

- Clinical assessment and Gram’s stain (for Nugent score) completed at entry and test-of-cure visit
- No other antimicrobial therapy to treat conditions other than BV from entry visit to test-of-cure visit
- Study medication started within 48 hours of entry visit
- Inclusion/Exclusion criteria were met
- Complied with treatment regimen, with no significant protocol violations
- No additional intravaginal products during treatment phase of study (up to 7 days post-dose)

### **Primary Efficacy Outcome:**

Therapeutic Treatment Outcome was a composite of clinical outcome plus Nugent score. Therapeutic cure was defined as both a clinical cure and Nugent score cure (0-3). Therapeutic failure was defined as either a clinical failure or Nugent score >3 at the TOC visit. Additionally, any patient who required the use of an additional antimicrobial agent for treatment for BV during the study period (from the entry visit until the TOC visit at 21-30 days post-treatment) was considered a clinical failure. Table 2 shows the criteria for therapeutic treatment outcomes.

Table 2. Determination of Therapeutic Response at Test-of-Cure Visit (adapted from Applicant's Table F, section 9.5.1.1.6)

Clinical Outcome*	Nugent Score*	Therapeutic Outcome
Cure	0-3	Cure
Cure	>3	Failure
Failure	0-3	Failure
Failure	>3	Failure
Cure	NE	Failure
NE	0-3	Failure
NE	>3	Failure

NE= non evaluable

\* See definitions below

*Medical Officer Comments: Because therapeutic cure requires both clinical cure and Nugent score cure, the cure rates for these products would be expected to be lower than those seen in studies for Cleocin® vaginal cream licensing, or in published studies in the literature, where treatment outcome was based on clinical criteria alone.*

#### Secondary Efficacy Outcomes:

Clinical Outcome was based on evaluation of the Amsel criteria used in BV diagnosis (Amsel, et al. 1983) at the TOC visit. Clinical cure required resolution of all the following:

- Normal vaginal discharge
- Negative “whiff” test
- Negative clue cells (< 20% clue cells) on wet mount preparation
- pH of vaginal secretions < 4.7

*Medical Officer Comments: The 1998 FDA draft guidance for industry, Bacterial Vaginosis- Developing Antimicrobial Drugs for Treatment, recommends that for clinical cure “no clue cells” are seen on the wet mount preparation. The applicant, however, has classified patients with <20% clue cells as “clinical cure” in this study. This could potentially inflate the cure rates (both therapeutic and clinical cure) in all arms of the study. However, review of the electronic dataset, revealed only 2 patients in the  treatment arm, 4 in the metronidazole arm and none in the placebo arm who had between 1 and 19% clue cells at the TOC visit, and were classified as therapeutic cures. Thus, overall conclusions regarding efficacy should not be affected.*

A patient was considered a clinical failure under the following circumstances:

- The patient did not meet the definition of clinical cure; or
- The patient received additional antimicrobial therapy for BV because of lack of response to study medication; or
- The investigator answered “yes” to the question, “In your opinion, does the patient require additional treatment for BV infection at this time?”

Nugent score outcome: This is a 0-4 point scale based on the microscopic evaluation of vaginal microflora, using a weighted sum of the morphotypes for lactobacilli, gram-negative rods (*Gardnerella* and *Bacteroides*), and curved gram-variable rods (*Mobiluncus*). A score of 0-3 is normal; while a score > 3 is abnormal and indicative of BV (Nugent, et al. 1991). A Nugent score of 0-3 at the test-of cure visit was required for Nugent cure. A Nugent score >3 was considered a Nugent failure.

Investigator treatment outcome: The patient was considered a treatment cure if the patient was not lost to follow up, and the Investigator answered “no” to the question: “In your opinion, does the patient require additional treatment for BV?” If the Investigator answered in the affirmative, and if the patient was lost to follow-up the patient was considered a treatment failure.

Additional supporting efficacy analyses were provided by the applicant including the following:

- Signs of BV
- Study drug failures
- Symptoms of BV
- Primary and secondary treatment outcomes by site
- Demographic and historical characteristics
- Additional intravaginal/vulvovaginal product use

*Medical Officer Comments: Except for BV symptoms and the use of other intravaginal products, these additional analyses were not formally evaluated in this review.*

## Safety Evaluation

Safety assessment was performed at the interim telephone contact and test-of-cure visit or early discontinuation visit. All adverse events were reported on case report forms. All patients who received a dose of study medication were included in the ITT analysis for safety.

The relationship of adverse events to study medication was assessed by the investigator as definite, probable, possible, unlikely/remote, or definitely not related to study medication. The intensity of adverse events was rated as mild, moderate, or severe. A serious adverse event included any adverse event that was fatal or life-threatening, permanently disabling, requiring or extending hospitalization, or was a congenital anomaly, cancer, or overdose. All serious adverse events required immediate notification of the sponsor by telephone. Any serious adverse event that occurred up to two weeks following study participation required reporting.

## Statistical Considerations

The targeted enrollment for the study was 279 patients to ensure 195-252 evaluable patients. The study was designed to show superiority of the investigational products over placebo with a power of 80-90% at an alpha level of 0.05, assuming a 30% cure rate for each metronidazole and clindamycin vaginal creams, and 10% cure rate for placebo.

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The lower limit of the 95% 2-sided confidence interval for the treatment difference in cure rates for active drug minus placebo was used to determine if active drug was superior to placebo. Confidence intervals on differences in proportions were also utilized for safety analysis. Additional supporting statistical analyses are not discussed in this review.

Three patient populations were defined for analysis:

Intent to Treat (ITT) Population: All randomized patients who administered one dose of study drug.

Modified Intent to Treat (MITT) Population: Subpopulation of ITT population with Nugent score  $\geq 4$ .

Per Protocol Population: Randomized patients who complied strictly with protocol.

All three populations were used to analyze efficacy data and baseline demographic characteristics. The MITT population, however, was used in the primary analysis of efficacy; and the ITT population was used for safety analysis.

*Medical Officer Comments: The ITT set was appropriately designated for safety analysis. The MITT set included patients with a diagnosis of BV based on both Nugent and clinical criteria, and is appropriate for efficacy analysis. See further comments of statistical reviewer regarding sample size and statistical analysis of efficacy.*

## Study Results

### Patient Evaluability

A total of 262 patients were enrolled in the study. Seven patients did not administer the study medication. Exclusion of those patients left 255 patients in the ITT population, with 85 in each of the 3 treatment arms, Clindesse<sup>TM</sup>, metronidazole, and placebo. A summary of overall patient distribution by analysis population is shown in Table 3.

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Table 3. Overall Patient Distribution by Analysis Population (adapted from Applicant's Table I, section 10.1.4)

Population	Clindesse™ N=86	Metronidazole N= 87	Placebo N=89	Total N=262
	n	n	n	n
ITT	85	85	85	255
MITT	78	72	66	216
Per Protocol	53	48	42	143

N= number of patients enrolled

n= number of patients in each analysis set

The reasons for non-evaluability in the per protocol analysis are shown in Table 4 below.

Table 4. Reasons for Non-Evaluability in Per Protocol Population (adapted from Applicant's Figure 3, section 10.1.4.1)

Reason for Non-Evaluability	Clindesse™ N= 25	Metronidazole N=24	Placebo N=24
Study drug not taken within 48 h	5	1	2
Study duration <21 days and not treatment failure	10	12	8
Patient took other antimicrobial not for BV	3	6	5
Patient took additional vaginal product or had intercourse	1	--	1
Patient did not meet all inclusion/exclusion criteria	4	5	6
Study duration > 35 days	2	--	2

N = number of non-evaluable patients

**Medical Officer Comments:** *Approximately one-third of patients in each treatment arm were considered non-evaluable Per Protocol. The most common reason for non-evaluability in the Per Protocol population was "study duration < 21 days and not treatment failure", with a similar distribution among treatment arms. Patients not evaluated in the Per Protocol analysis were included in the MITT and ITT analyses.*

### Study Discontinuation

A total of 155 patients completed the study. Premature study discontinuation occurred with 107 patients, 43 in the placebo group (48.3 % enrolled patients), 37 in the — metronidazole group (42.5% enrolled), and 27 in the Clindesse™ group (31.4% enrolled). Seven of these patients did not receive study medication and were not included in the ITT analysis. Reasons for study discontinuation are shown in Table 5 below. The most common reason for early discontinuation for all three treatment groups was baseline Nugent score <4. A higher proportion of patients in the placebo group than in the Clindesse™ group were discontinued due to a baseline Nugent score < 4 or use of other antimicrobial products for BV.

Table 5. Reasons for Premature Study Discontinuation (ITT population) (adapted from applicant's summary Table 14)

Reason for DC	Clindesse™ N=26		— Metronidazole N=35		Placebo N=39	
	n	%	n	%	n	%
Baseline Nugent score <4	7	26.9	12	34.3	18	46.2
Other antimicrobial for BV	3	11.5	8	22.9	11	28.2
Treatment for other infection	1	3.8	0	0	1	2.6
Protocol violation	3	11.5	6	17.1	2	5.1
Adverse event	1	3.8	2	5.7	0	0
Study noncompliance	1	3.8	3	8.6	0	0
Lost to follow-up	5	19.2	2	5.7	4	10.3
Other	5	19.2	2	5.7	3	7.7

N= number of discontinued patients in each treatment arm

*Medical Officer Comments: The applicant does not specify "other" reasons for premature study discontinuation. However, the total numbers patients discontinued for "other" reasons are small and would not likely influence efficacy outcomes in this study.*

## Demographics

Comparison of age and race distribution for each treatment groups is shown in Table 6 .

Table 6. Baseline Demographics for ITT population\* (adapted from applicant's summary Tables 20a, 20b, 23a, 23b, 26, 29, 32)

Characteristic	Clindesse™ N=85	Metronidazole N= 85	Placebo N=85
<b>Age (years)</b>	n (%)	n (%)	n (%)
18-39	56 (65.9)	66 (77.6)	53 (62.4)
40-64	29 (34.1)	19 (22.4)	32 (37.6)
Mean	34.52	32.47	35.82
Median	33.40	30.69	35.68
Standard Deviation	10.67	8.78	11.29
Range	19.5-64.3	18.5-59.8	18.9-60.4
<b>Race/Ethnicity</b>			
African American	32 (37.6)	32 (37.6)	25 (29.4)
Asian	2 (2.4)	0 (0)	3 (3.5)
Caucasian	39 (45.9)	37 (43.5)	48 (56.3)
Hispanic	11(12.9)	16 (18.8)	9 (10.6)
Other	1(1.2)	0 (0)	0 (0)
<b>Height (in)</b>			
Mean	64.6	64.8	65.0
Standard deviation	3.10	2.79	2.56
Range	57-71	57-71.5	60-71
<b>Weight (lbs)</b>			
Mean	151.4	164.4	165.4
Standard deviation	38.00	41.18	37.37
Range	87-333	97-305	102-297

N= number of patients in ITT population

The Clindesse™ and placebo groups were similar with respect to age and height, and racial/ethnic distribution. The metronidazole treatment group differed significantly from the placebo group for age, with generally younger patients enrolled in the metronidazole group. In addition, racial distribution differed between the metronidazole and placebo treatment groups. However, this difference was not significant at the 95% confidence level (p-value= 0.061). No significant different was seen for height between the metronidazole and placebo groups.

For weight, a statistically significant difference was noted between the treatment groups in the ITT population, notably, mean weight was higher in the placebo group than in the Clindesse™

group (165 lbs and 151 lbs, respectively), while mean weight in the metronidazole group was not significantly different than placebo.

*Medical Officer's Comments: Most patients enrolled in the study were in the 18-39 year age range. Patients < age 18 and ≥ 65 years old were not enrolled, and pregnant women were excluded from this study. The difference in baseline weight between the Clindesse™ and placebo treatment groups is probably not clinically significant because the treatment is administered intravaginally and systemic absorption of Clindesse™ is low.*

No differences were noted between treatment groups for contraceptive methods in the ITT or MITT analyses. Additionally, no difference was observed between treatment groups for hysterectomy status, number of pregnancies, parity, sexual behavior, or prior BV episodes. Most patients had no prior BV episodes within the previous 12 months, with the mean number of episodes in the past 12 months ranging from 0.19-0.47 across treatment arms in the ITT population.

Patients were classified as “recalcitrant” if they had 3 or more episodes of BV within the past 12 months. Statistically significant differences in “recalcitrant status” were noted between treatment groups for all populations. No patients categorized as “recalcitrant” were enrolled in the placebo treatment arm, compared to the Clindesse™ treatment arm in which 5 patients (5.9%) in the ITT analysis set were considered “recalcitrant”. In the metronidazole treatment group, 3 patients (3.5%) in the ITT analysis set were considered “recalcitrant”.

*Medical Officer Comments: Because the numbers of recalcitrant patients were low for each analysis population, it is unlikely that the difference between treatment groups affected overall outcome.*

### **Disease Severity**

Patients were not stratified by disease severity in this study. Although not validated as a marker for disease severity, baseline Nugent scores were compared for each treatment group to further evaluate baseline patient characteristics. Baseline Nugent scores were similar for all treatment groups, with mean Nugent scores of 4.9, 5.2, and 5.3 in metronidazole, Clindesse™ and placebo groups, respectively, as shown in Table 7 below.

Table 7. Baseline Nugent Score analyzed by Treatment Group (ITT Population) (Reviewer's Analysis)

Nugent score	Placebo N=85	Metronidazole N=85	Clindesse™ N=85
Mean	5.3	4.9	5.2
Std. Dev.	3.335	3.479	3.528
Std. Error Mean	1.055	1.1	1.176
95% Confidence Interval	(2.914, 7.686)	(2.412, 7.388)	(2.511, 7.934)
Median	5.5	4.5	5.0

N= number of patients in ITT population

*Medical Officer Comments: The mean baseline Nugent scores in this study were somewhat lower than those in the non-inferiority study, 01-025. In that study, mean Nugent scores at baseline were 6.52 for the Clindesse™ treatment group and 6.18 for the Cleocin® vaginal cream group.*

### Concomitant Medications

Any medication or drug product taken by patients in the 30 days prior to study entry visit and throughout the study period was considered a concomitant medication. Patient use of concomitant medications was similar in Clindesse™, metronidazole, and placebo treatment groups, with 82.4%, 84.7%, and 78.8% patients reporting use in the respective group. The most commonly used medications included progestogens, estrogens and fixed combinations reported in 36.5%, 41.2%, and 37.6% of patients in the Clindesse™, metronidazole, and placebo groups, respectively. The use of systemic or intravaginal antibiotics or antifungal agents was contraindicated in the 14 days prior to study entry. Antibiotic use was reported for 11.8% patients who received Clindesse™, 8.2% of patients who received metronidazole, and 12.9% of patients who received placebo. The use of antifungal agents (including triazoles and imidazoles) was reported in 16.5%, 15.3%, and 9.4% of patients who received Clindesse™, metronidazole, and placebo, respectively.

*Medical Officer Comments: Patients who received another antibiotic for BV during the study period (entry visit- TOC visit) were classified as treatment failures; while patients who received antibiotics for other infections were evaluated for treatment outcome and included in the ITT and MITT analyses. Because certain systemic antibiotics could potentially treat BV, antibiotic use could be confounding factor in the efficacy analysis. However, antibiotic use was similar for each treatment arm; consequently overall conclusions regarding treatment should not be affected. The use of antifungal agents was higher in both active drug treatment groups in comparison to placebo. This most likely reflects the use of antifungal agents for treatment of treatment-emergent vaginal candidiasis. However, these data were not analyzed further for this review.*

### Use of Other Intravaginal Products $\geq$ 8 days after first treatment dose

Significantly more patients in the Clindesse<sup>TM</sup> and metronidazole treatment groups than in the placebo group reported use of other intravaginal products during the study (from day 8 to TOC visit). In the ITT population, intravaginal product usage during this time frame was reported in 12/85 (14.1%) patients in the Clindesse<sup>TM</sup> group, 1/85 (1.2%) patients in the placebo group, and 8/85 (9.4%) patients in the metronidazole group.

*Medical Officer Comments: Most of the intravaginal products used after treatment with study medication were intravaginal antifungal agents. Only 1 patient (in the Clindesse<sup>TM</sup> treatment arm) received another intravaginal product to treat BV. This patient was counted as a treatment failure. Because use of other intravaginal products could impact evaluation of treatment efficacy, a subset analysis of efficacy was performed (see section on Subset Analysis of Efficacy)*

### Treatment Compliance

Treatment compliance was assessed by study drug accountability and patient query. One patient in the Clindesse<sup>TM</sup> arm, 2 in the metronidazole arm, and 4 patients in the placebo arm did not administer the study drug, and were not included in the ITT analysis. Compliance with treatment was similar in each treatment group with 81 patients (94.2%), 84 patients (96.6%) and 83 patients (93.3%) who self-administered drug in Clindesse<sup>TM</sup>, metronidazole, and placebo groups, respectively. Treatment compliance was unknown in 4 (4.7%) patients in the Clindesse<sup>TM</sup> arm, 1 (1.1%) patient in the metronidazole arm, and 2 (2.2%) of patients in the placebo arm. These latter patients were included in the ITT and MITT analyses.

### Efficacy Analysis

The primary efficacy variable for this study was therapeutic treatment outcome, a composite outcome which combines clinical criteria and Nugent score. Therapeutic treatment outcome was measured at the TOC visit, which was 21-30 days after administration of study medication.

For therapeutic outcome, Clindesse<sup>TM</sup> was shown superior to placebo for treatment of BV for all analyses, as shown in Table 8 below. Similarly, for therapeutic treatment outcome, metronidazole was superior to placebo for all analyses, as shown in Table 9 below. Treatment differences between Clindesse<sup>TM</sup> or metronidazole and placebo groups were statistically significant. Treatment outcomes with metronidazole were not directly compared to those with Clindesse<sup>TM</sup> in this review.

Table 8. Therapeutic Treatment Outcome for Clindesse™ vs. Placebo (adapted from applicant's summary Table 66a)

Analysis Population	Clindesse™		Placebo		Treatment Difference (Clindesse™ cure rate minus Placebo cure rate)		
	N	n (%)	N	n (%)	%	95% Confidence Interval	Treatment p-value
Intent-to-Treat	85	23 (27.1)	85	3 (3.5)	23.5	[13.3, 33.8]	<0.001
MITT	78	23 (29.5)	66	2 (3.0)	26.5	[15.5, 37.4]	<.001
Per-Protocol	52	20 (38.5)	42	0 (0.0)	38.5	[25.2, 51.7]	<0.001

N= number of patients evaluated  
 n=number patients with therapeutic cure

Table 9. Therapeutic Treatment Outcome for Metronidazole vs. Placebo (adapted from applicant's summary Table 66b)

Analysis Population	Metronidazole		Placebo		Treatment difference*		p-value
	N	n (%)	N	n (%)	%	95% Confidence Interval	
ITT	85	13 (15.3)	85	3 (3.5)	11.8	[3.2, 20.4]	0.008
MITT	72	12 (16.7)	66	2 (3.0)	13.6	[4.1, 23.2]	0.006
Per Protocol	48	11 (22.9)	42	0 (0)	22.9	[11.0, 34.8]	0.001

N= number of patients evaluated  
 n=number patients with therapeutic cure  
 \* Treatment difference= metronidazole cure rate minus placebo cure rate

**Medical Officer's Comments:** Based on the primary outcome measure, therapeutic treatment outcome, both Clindesse™ and metronidazole were superior to placebo for treatment of BV. For Clindesse™, the favorable therapeutic outcome was supported by favorable secondary outcomes, including Nugent score, clinical outcomes, and Investigator outcome, as shown below. However, for metronidazole, a favorable therapeutic outcome was supported by a favorable Nugent score outcome, but not by clinical or Investigator outcomes (see secondary endpoints below).

Secondary outcomes measured in this study included Nugent score outcome, clinical outcome, and Investigator outcome. Tables 10-12 show the secondary outcomes for Clindesse™ and placebo for each analysis. In each case, a higher proportion of patients were cured with Clindesse™ compared to placebo. These treatment differences were statistically significant.

Table 10. Clinical Treatment Outcome for Clindesse™ vs. Placebo (Adapted from applicant's summary table 66a)

Analysis Population	Clindesse™		Placebo		Treatment Difference (Clindesse™ cure rate minus Placebo cure rate)		
	N	n (%)	N	n (%)	%	95% Confidence Interval	Treatment p-value
Intent-to-Treat	85	32 (37.6)	85	14 (16.5)	21.2	[8.2, 34.1]	0.001
Modified Intent-to-Treat	78	32 (41.0)	66	13 (19.7)	21.3	[6.8, 35.9]	0.007
Per-Protocol	52	25 (48.1)	42	9 (21.4)	26.6	[8.3, 45.0]	0.007

N= number of patients evaluated  
 n=number patients with therapeutic cure

Table 11. Nugent Score Treatment Outcome for Clindesse™ vs. Placebo (Adapted from applicant's summary table 66a)

Analysis Population	Clindesse™		Placebo		Treatment Difference (Clindesse™ cure rate minus Placebo cure rate)		
	N	n (%)	N	n (%)	%	95% Confidence Interval	Treatment p-value
Intent-to-Treat	85	36 (42.4)	85	5 (5.9)	36.5	[24.8, 48.1]	<0.001
Modified Intent-to-Treat	78	35 (44.9)	66	4 (6.1)	38.8	[26.4, 51.3]	<0.001
Per-Protocol	52	29 (55.8)	40	1 (2.5)	53.3	[38.9, 67.6]	<0.001

N= number of patients evaluated  
 n=number patients with therapeutic cure

Table 12. Investigator Treatment Outcome (Clindesse™ vs. Placebo) (Adapted from applicant's summary table 66a)

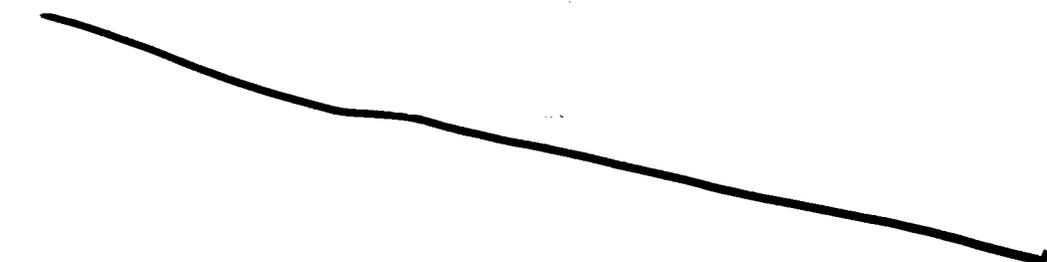
Analysis Population	Clindesse™		Placebo		Treatment Difference (Clindesse™ cure rate minus Placebo cure rate)		
	N	n (%)	N	n (%)	%	95% CI	Treatment p-value
Intent-to-Treat	75	52 (69.3)	68	26 (38.2)	31.1	[15.5, 46.7]	<0.001
Modified Intent-to-Treat	74	51 (68.9)	64	24 (37.5)	31.4	[15.5, 47.3]	<0.001
Per-Protocol	53	39 (73.6)	42	18 (42.9)	30.7	[11.6, 49.8]	0.001

N= number of patients evaluated  
 n=number patients with therapeutic cure

*Medical Officer Comments: As noted above, each of these secondary treatment outcomes support the conclusion that Clindesse™ is superior to placebo for treatment of BV.*

Secondary treatment outcomes for metronidazole in comparison to placebo are shown in Tables 13-15 below. Metronidazole was superior to placebo for BV treatment for only the Nugent score outcome, but not for clinical outcome or investigator outcome for all analyses.

Table 13. Clinical Treatment Outcome for Metronidazole vs. Placebo (Adapted from applicant's summary Table 66b)



N= number of patients evaluated  
 n=number patients with therapeutic cure  
 \* Treatment difference= metronidazole cure rate minus placebo cure rate



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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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### Reasons for Treatment Failure

The most common reasons for treatment failure were failure due to both Nugent score and clinical criteria, with approximately one-third of failures in each treatment arms attributed to this reason, as shown in Table 16 below. Overall, the reasons for failure differed between the Clindesse™ and placebo treatment groups (p-value = 0.012), but not between the metronidazole and placebo groups (p=0.354) in the ITT analysis.

Table 16. Reasons for Treatment Failure (ITT Population) (adapted from applicant's summary Table 84)

Reason for Failure	Clindesse™ N=62		Metronidazole N= 72		Placebo N=82	
	n	%	n	%	n	%
Lost to follow-up	5	8.1	2	2.8	4	4.9
Additional treatment for BV required	18	29	35	48.6	38	46.3
Failed due to Nugent score	9	14.5	6	8.3	11	13.4
Failed due to clinical criteria	9	14.5	5	6.9	1	1.2
Failed due to Nugent score + clinical criteria	21	33.9	24	33.3	29	34.1

N= number of patients classified as therapeutic failures  
 n= number of patients who failed due to specified reason  
 %= percentage of failures

*Medical Officer Comments: Not unexpectedly, a higher proportion of patients in the placebo group than in the Clindesse™ failed because additional treatment for BV was required. Most Clindesse™ failures were due to failure of both Nugent score and clinical criteria, although some patients failed due to either Nugent score or clinical criteria. Because of this discordance, further analysis was performed to determine the degree of correlation between Nugent score and clinical criteria for cure, as shown in the next section.*

### Correlation of Nugent score and other Criteria for Cure of BV

The electronic database was queried to construct a series of 2 x 2 tables to calculate the kappa statistic for the Nugent score outcome compared to clinical outcome, investigator outcome, and symptom resolution at the interim telephone contact. The MITT population was used to calculate the kappa statistics because patients in this group had BV based on clinical criteria and a Nugent score  $\geq 4$ . As shown in Table 17 below, the Nugent score outcome correlated best with clinical outcome and worst with symptom resolution at the time of the interim telephone contact. Because the time course of Nugent score conversion to normal range is not known, this latter comparison may not be valid because the outcomes were assessed at different times.

Table 17. Correlation of Nugent score Outcome to other Measures of BV Cure (all treatment groups) (Reviewer's Analysis)

"Gold Standard for BV Cure"	Kappa statistic ( 95% Confidence Interval)
Clinical cure	0.4608 (0.3296, 0.5920)
Investigator cure	0.3915 (0.2823, 0.5007)
Symptom resolution	0.0829 (-0.0022, 0.1679)

*Medical Officers Comments: These data show a relatively low correlation between the Nugent score outcome and the other clinical outcome measures. However, the "gold standard" for assessment of BV cure in the setting of a clinical trial is not known, and the use of composite criteria for cure, the therapeutic outcome, has been recommended in the 1998 FDA draft guidance for industry, "Bacterial Vaginosis- Developing Antimicrobial Agents for Treatment."*

### Symptom Resolution at Interim Telephone Contact (Reviewer's Analysis)

In the clinical setting, symptom resolution is most often used to determine whether BV has resolved, rather than strict assessment of the Amsel clinical criteria (Amsel, et al. 1983) or the Nugent score (Nugent, et al., 1991). Symptom resolution, based on patient query at the interim telephone contact at 7-10 days post-dose of study medication, was evaluated as an outcome measurement. For this outcome measurement, Clindesse<sup>TM</sup> was superior to placebo for treatment of BV, as shown in Table 18 below.

Table 18. Symptom Resolution at Interim Contact (data obtained from the electronic database)

Treatment Group	Symptoms Resolved (n/N)	Symptoms Resolved %
Placebo	40/84	47.6
Metronidazole	56/85	65.9
Clindesse™	51/81	63.0 †

† p value = 0.0476, and 95% confidence interval, [0.0016, 0.2982] for Clindesse™ vs. placebo (confidence intervals calculated using exact method). When missing data was treated as treatment failure (denominator = 85, the ITT population), the p-value = 0.09 for Clindesse™ vs. placebo with 95% confidence intervals, [-0.0193, 0.2781].

N= number of patients assessed

n = number of patients who reported symptom resolution

*Medical Officer Comments: Assessment of symptom resolution at the interim contact as an outcome for BV treatment resulted in similar overall conclusions to those drawn from the primary and secondary outcome analysis for Clindesse™ when missing data were excluded, but the difference was not significant when missing data were counted as treatment failures. The high rate of symptom resolution in the placebo arm suggests either a “placebo effect” or an effect attributable to the vehicle itself.*

The time to symptom resolution was analyzed by the applicant. No clinically significant difference was observed in time to symptom resolution between Clindesse™ (2.9 ± 1.5 days) or metronidazole (2.9 ± 1.5 days) and placebo (3.2 ± 1.4 days).

### Subset Analyses of Efficacy

#### Therapeutic Cure by baseline Nugent score (Reviewer’s Analysis)

Data from the electronic database was analyzed to evaluate therapeutic and clinical outcomes by baseline Nugent score. For the Clindesse™ treatment group, the rate of therapeutic cure was highest in patients with higher baseline Nugent scores as shown in Table 19 below. The treatment difference observed between the Clindesse™ and placebo groups was statistically significant only for patients with a baseline Nugent score of 8-10.

Table 19. Therapeutic Cure Analyzed by Baseline Nugent Score (ITT Population)

Baseline Nugent Score Category	Clindesse™ N=85	Placebo N=87	Treatment difference % (Clindesse™ minus placebo) [95% Confidence Intervals]*
	n /no. (% cure)	n/no. (%) cure	
<4	0/ 7 (0)	1/20 (5.0)	-5.0 [-46.7, 37.8]
4-7	3/15 (20.0)	1/18 (5.5)	14.5 [-20.7, 47.0]
8-10	20/64 (31.3)	1/51 (2.0)	29.3 [12.1, 46.1]

N = number of patients in Treatment Group

n = number of patients with therapeutic cure

no. = number of patients with specific baseline Nugent score category

\*Confidence intervals were calculated using exact methods.

*Medical Officer Comments: Patients with baseline Nugent scores <4 had the lowest rate of therapeutic cure, presumably because they did not have BV at study entry. Because this is a subset analysis, it is subject to a number of limitations. Additionally, categorization of Nugent scores as performed above may not be clinically significant.*

#### Therapeutic Cure by Age

Patients were categorized into 2 groups by age, 18-39 years old, and 40-64 years old. Patients < 18 or > 64 years old were not enrolled in this study. This analysis showed no significant differences in therapeutic outcome within each treatment group when analyzed by age category as shown in Table 20 below.

Table 20. Therapeutic Cure by age category (Reviewer's Analysis from electronic database)

Age Category (years)	Placebo n/N	% cure	Clindesse™ n/N	% cure	Treatment difference % (Clindesse™ minus placebo) [95% Confidence interval]*
18-39	2/56	3.6	14/56	25	21.4 [9.1, 33.8]
40-64	1/32	3.1	9/30	30	26.9 [2.5, 49.8]

n=number of patients with therapeutic cure

N= total number of patients in group

\*Confidence intervals were calculated using exact methods.

*Medical Officer Comments: No obvious age-related treatment effect was noted in this study. Statistically significant superiority of Clindesse™ relative to placebo was achieved in both age groups in this analysis.*

### Outcome Analysis by Race/Ethnic Group

Patients of Caucasian descent made up the largest proportion of the study population. When analyzed by race/ethnic group, proportionately more Caucasian patients were assessed as having therapeutic cure compared to patients in other racial/ethnic groups, as shown in Table 21 below.

Table 21. Therapeutic Cure by Race/Ethnic group (ITT Population) (adapted from applicant's summary Table 71a)

Treatment Group	African American	Asian	Caucasian	Hispanic	Other
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Placebo	0/25 (0)	0/3 (0)	3/48 (6.3)	0/9 (0)	0/0 (0)
Clindesse™	8/32 (25.0 %)	0/2 (0)	15/39 (38.5)	0/11 (0)	0/1 (0)

N= number of patients in ITT analysis

n =number of patients with therapeutic cure

% = percentage of patients cured within each racial/ethnic category

Because the numbers of patients classified as Asian, Hispanic, or "other" were small in this study, those groups were combined to compare therapeutic outcome with Caucasian patients, as shown in Table 22 below. Again, for Clindesse™, cure rates were higher among Caucasian patients for the combined patients in other racial categories. This difference was statistically significant, with a p-value = 0.0293. Clindesse™ remained superior to placebo, however, for both Caucasians and for the other combined racial groups.

Table 22. Therapeutic Outcome by Race/Ethnic Group (ITT Population) (Reviewer's Analysis)

Treatment Groups	Caucasian		Combined groups*	
	N	n(%)	N	n (%)
Placebo	48	3 (6.3)	37	0 (0)
Clindesse™	39	15 (38.5)	46	8 (17.4)

\*includes African-American, Asian, Hispanic, and "other"

N= number of patients in ITT analysis set

N= number of patients cured within racial category

*Medical Officer Comments: Whether these results point to true racial differences in treatment response to Clindesse™ would require further analysis of confounding factors and a study designed specifically to answer this question. Because the treatment is topical with minimal systemic absorption, metabolic differences between racial/ethnic groups probably do not explain the differences in efficacy noted here. Certainly, other factors, such as disease severity at baseline, small numbers of patients, and limited statistical power could contribute to the observed differences in efficacy.*

### Therapeutic cure by recalcitrant BV status

Only 8 patients with “recalcitrant” BV were enrolled in this study, none in the placebo group, 3 in the metronidazole group, and 5 in the Clindesse™ group. None of the “recalcitrant” patients in the metronidazole group, and 3 of 5 patients in the Clindesse™ group were considered therapeutic cures. Conclusions regarding treatment efficacy in patients with recalcitrant BV cannot be drawn from these data because of the small numbers of patients in this category.

### Therapeutic cure by investigative site

The applicant observed higher rates of therapeutic cure for Clindesse™- treated patients at investigative sites that enrolled more than 5 patients. Further analysis was not performed for this review.

### Therapeutic cure by intravaginal product use

The total number of patients who used other intravaginal products from day 8 post-treatment to TOC visit was relatively low. Rates of therapeutic cure for patients who used intravaginal products is compared to rates for those patients who did not in Table 23 below. Rates of cure were similar within treatment groups whether or not additional intravaginal products were used.

Table 23. Therapeutic Cure Analyzed by Intravaginal Product (IVP) Use (ITT Analysis)  
(Reviewer’s Analysis from electronic database)

Treatment Group	Patients who used IVP n/N (%)	Patients who did not use IVP n/N (%)
Placebo	0/1 (0)	3/84 (3.6)
Metronidazole	1/8 (12.5)	12/77 (15.6)
Clindesse™	3/12 (25.0)	20/73 (27.4)

N= number of patients in subgroup (IVP use) for each treatment group

n= number of patients with therapeutic cure

%= percentage of patients cured within subgroup

*Medical Officer Comments: Most of the intravaginal products used in this time frame were topical antifungal agents for treatment of vulvovaginal candidiasis, which would not be expected to affect efficacy of the study medication for BV treatment. Rates of therapeutic cure for these subsets did not differ significantly from those shown for the ITT analysis sets shown in Tables 8 and 9 above, suggesting that efficacy was not affected by other IVP use in this study.*

## Safety Analysis

### Drug Exposure

All patients who received a single-dose of study medication were analyzed for safety. A total of 248 patients (95% of enrolled patients) administered a single dose of study medication. Table 24 summarizes patient compliance with study medication. A total of 255 patients were included in the ITT analysis, which includes the 7 patients for whom there was no documentation of study drug administration.

Table 24. Study Medication Compliance (adapted from applicant's summary Table 65)

Drug Administration	Total Enrolled Patients N=262	Metronidazole N=87	Clindesse™ N=86	Placebo N=89
	n (%)	n (%)	n (%)	n (%)
Drug not administered	7 (2.7)	2 (2.3)	1 (1.2)	4 (4.5)
Unknown	7 (2.7)	1 (1.1)	4 (4.7)	2 (2.2)
Drug self-administered	248 (94.7)	84 (96.6)	81 (94.2)	83 (93.3)
Drug self-administered within 48 hr of entry visit	244 (93.1)	83 (95.4)	79 (91.9)	82 (92.1)

N= Total number of patients in each treatment group

n = number of patients for each drug administration group

### Adverse Events

A total of 166 adverse events were reported in this study. In the Clindesse™ group, 68 events were reported in 38 patients. In the metronidazole group, 52 events were reported in 34 patients, and in the placebo group, 46 events in 32 patients. Events were categorized by System Organ Class (SOC) and Preferred Term (PT). The most common adverse events reported by PT are listed in Table 25. The most common adverse event was "vaginosis fungal NOS" which occurred in 12 (14.1%) Clindesse™-treated patients, 10 (10.6%), metronidazole-treated patients, and 7 (8.2%) placebo-treated patients. No statistically significant differences were found between treatment groups for any adverse event classified by PT.

Table 25. Most Common Adverse Events\* Classified by Preferred Term (PT) (ITT Population)  
 (adapted from applicant's summary Tables 163a and 163b)

Adverse Event (PT)	Clindesse™ N=85	Metronidazole N=85	Placebo N=85
	n (%)	n (%)	n (%)
Abdominal pain NOS	1 (1.2)	2 (2.4)	5 (5.9)
Constipation	2 (2.4)	0 (0)	0 (0)
Diarrhea NOS	1 (1.2)	1 (1.2)	2 (2.4)
Nausea	3 (3.5)	3 (3.5)	3 (3.5)
Herpes simplex	2 (2.4)	0 (0)	1 (1.2)
Nasopharyngitis	2 (2.4)	0 (0)	0 (0)
Urinary tract infection NOS	2 (2.4)	1 (1.2)	0 (0)
Vaginosis fungal NOS	12 (14.1)	10 (11.8)**	7 (8.2)
Arthralgia	0 (0)	2 (2.4)	0 (0)
Back pain	4 (4.7)	0 (0)	1 (1.2)
Dizziness	1 (1.2)	2 (2.4)	1 (1.2)
Headache NOS	6 (7.1)	5 (5.9)	2 (2.4)
Pregnancy	0 (0)	2 (2.4)	0 (0)
Dysmenorrhea	1 (1.2)	2 (2.4)	2 (2.4)
Pelvic pain NOS	1 (1.2)	2 (2.4)	2 (2.4)
Vaginal discharge	2 (2.4)	2 (2.4)	2 (2.4)
Vaginal irritation	0 (0)	0 (0)	2 (2.4)
Vaginal odor	0 (0)	2 (2.4)	1 (1.2)
Vulvovaginal pruritis	1 (1.2)	2 (2.4)	3 (3.5)
Epistaxis	2 (2.4)	0 (0)	0 (0)
Rhinorrhea	2 (2.4)	0 (0)	0 (0)

\* Reported by > 2% patients in any treatment group

\*\* One case was reported as vaginal candidiasis and 9 were reported as vaginosis fungal NOS

N= total number of patients in treatment group

n= number of patients with reported adverse event

%= percentage of patients in treatment group with reported adverse event

NOS= not otherwise specified

**Medical Officer Comments:** The most common adverse event for all 3 treatment groups was vaginal candidiasis (vaginosis fungal NOS). For the 2 active drugs, Clindesse™ and metronidazole, fungal overgrowth or superinfection resulting in vaginal candidiasis is not unexpected. Theoretically, antibiotic therapy could alter the normal vaginal microflora, allowing superinfection by other commensal organisms, in this case, *Candida* sp. Vaginal candidiasis was also observed as the most common adverse event in the placebo group, suggesting a potential association with the product vehicle.

### Drug-Related Adverse Events

Adverse events were considered to be drug-related by the applicant in 9 (10.6%) Clindesse™-treated patients, 19 (22.4%) placebo-treated patients, and in 22 (25.8%) metronidazole-treated patients. The most common drug-related adverse events are summarized in Table 26. The most common drug-related adverse event reported for Clindesse™ and metronidazole groups was vaginal candidiasis (vaginosis fungal NOS); while abdominal pain was the most common in the placebo group. No significant differences were found between treatment groups.

Table 26. Most Common Drug-Related Adverse Events\* (ITT Population) (adapted from applicant's Tables 164a and 164b)

Adverse Event (Preferred Term)	Clindesse™ N=85	Metronidazole N= 85	Placebo N=85
	n (%)	n (%)	n (%)
Abdominal pain NOS	0 (0)	2 (2.4)	4 (4.7)
Nausea	1 (1.2)	3 (3.5)	1 (1.2)
Vaginosis fungal NOS	3 (3.5)	6 (7.1)**	2 (2.4)
Vaginal irritation	0 (0)	2 (2.4)	2 (2.4)
Vulvovaginal pruritis	0 (0)	2 (2.4)	3 (3.5)
Vaginal odor	0 (0)	2 (2.4)	0 (0)
Headache	1 (1.2)	2 (2.4)	1 (1.2)

\* Reported in >2% patients in any treatment group

\*\* Reported in 1 patient as vaginal candidiasis and 5 as vaginosis fungal NOS

N= total number of patients in treatment group

n= number of patients with reported drug-related adverse event

%= percentage of ITT patients

*Medical Officer Comments: For the active drug treatment groups, vaginosis fungal NOS was the most common adverse event. It is not clear why abdominal pain occurred more frequently in the placebo group, because abdominal pain is generally not a common symptom associated with untreated BV.*

### Severity of Adverse Events

Most adverse events were classified as mild-moderate in intensity. A total of 5 (5.9%) Clindesse™-treated patients reported 7 severe adverse events, 4 (4.7%) metronidazole-treated patients reported 4 severe adverse events, and 3 (3.5%) placebo-treated patients reported 4 severe adverse events. The adverse events characterized as severe, are listed in Table 27 below.

Table 27. Severe Adverse Events (ITT Population) (adapted from applicant's summary Table 167)

Severe Adverse Event Reported by Preferred Term	Clindesse™ N=85 N (%)	Placebo N=85 N (%)	● Metronidazole N=85 N (%)
Nausea	1 (1.2)	0 (0)	0 (0)
Vomiting	1 (1.2)	0 (0)	0 (0)
Bronchitis	0 (0)	1 (1.2)	0 (0)
Herpes simplex	1 (1.2)	0 (0)	0 (0)
Urinary Tract Infection	0 (0)	0 (0)	1 (1.2)
Vaginal candidiasis	0 (0)	0 (0)	1 (1.2)
Vaginosis fungal NOS	0 (0)	0 (0)	1 (1.2)
Headache	2 (2.4)	0 (0)	0 (0)
Dysmenorrhea	1 (1.2)	1 (1.2)	0 (0)
Vaginal odor	0 (0)	1 (1.2)	0 (0)
Vulvitis	1 (1.2)	0 (0)	0 (0)
Vulvovaginal pruritis	0 (0)	1 (1.2)	0 (0)
Skin irritation	0 (0)	0 (0)	1 (1.2)
Total Severe Adverse Events	7 (8.2)	4 (4.7)	4 (4.7)

N= Total number of adverse events

N= number of adverse events for Preferred Term

% = percentage ITT population

*Medical Officer's Comments: Although the total number and percentage of severe adverse events reported was somewhat higher in the Clindesse™ group, none of these events were considered serious and most occurred only once.*

#### Death or other Serious Adverse Events

No serious adverse events or deaths were reported in this study.

#### Study Withdrawal due to Adverse Events

One patient was withdrawn from the study due to abnormal vaginal bleeding that precluded completion of study procedures. This patient had been enrolled in the Clindesse™ arm. The event was considered to be moderate in severity, and was not thought to be drug-related.

#### Narrative Case Report for Patient Withdrawn from Study due to Adverse Event

Patient #143122 was a 47 year old Caucasian female, with a past medical history of nephrolithiasis and lithotripsy, ruptured right ectopic pregnancy, and therapeutic abortion. Baseline physical examination was normal except for abnormal vaginal discharge, described as a scant, thin white discharge with a strong odor, and mild vulvovaginal inflammation. Clindesse™ was dispensed on 1/22/03, and the patient developed abnormal uterine bleeding of moderate

severity on 2/11/03. The patient was seen 3/6/03 for an early discontinuation visit, but a physical examination and laboratory assessment were not performed at that time to assess outcome. The patient was considered a therapeutic failure for BV treatment, due to failure by both Nugent score and clinical criteria because these were not assessed. Aygestin was prescribed for the abnormal uterine bleeding and the event was noted to be ongoing at the time of the case report (3/15/03). The abnormal uterine bleeding developed by this patient was not attributed to the study medication.

Other adverse events listed on the case report form for this patient included severe menstrual cramping which developed on 3/2/03, treated with Ponstel and Midol, mild diarrhea which developed 3/3/03, moderate lower back pain, which started 3/3/03, and moderate generalized fatigue, beginning 2/28/03. The diarrhea and lower back pain resolved by 3/7/03, while the other all adverse events were noted to be ongoing at the time of the case report.

*Medical Officer Comments: The Investigator's assessment that this adverse event was unlikely to be related to the study medication is reasonable.*

#### Other Significant Adverse Events

Two patients in the metronidazole arm of the study, who had negative urine pregnancy tests on study entry, subsequently became pregnant during the study. Patient #103111 was discontinued from the study due to non-qualifying baseline Nugent score; while the other patient completed the study. Neither pregnancy was considered to be related to study medication. Table 28 below describes the information available regarding these two pregnancies.

Table 28. Pregnancies that occurred during Study

Patient Number	Study Medication	Date of Study Entry	Pregnancy Test on Entry	Contraceptive Method	Date of Positive Pregnancy Test	Therapeutic Treatment Outcome (BV)
103110	Metronidazole	1/28/03	negative	barrier	2/7/03*	failure
073307	Metronidazole	2/27/03	negative	barrier	3/21/03	failure

\*Date of interim telephone contact. Estimated date of conception was 1/23/03. No documentation was provided regarding positive pregnancy test.

*Medical Officer Comments: Patient #103110 had a normal vaginal delivery on [REDACTED]. Other than physiologic jaundice, the neonate was considered healthy. The pregnancy outcome for patient #073307 is unknown at this time.*

#### Time to Onset and Duration of Adverse Events

The time to onset of adverse events was shortest for the placebo group in comparison to the active drug treatment groups. The duration of adverse events was similar for all treatment groups. These data are summarized in Table 29 below.

Table 29. Time to Onset and Duration of Adverse Events (adapted from applicant's summary Table 154)

	Clindesse™	Metronidazole	Placebo
	N=67	N=51	N=46
Time to Onset of AE (days):			
Median	6.0	3.0	2.5
Mean ± standard deviation	11.4 ±11.55	8.3 ±9.48	5.2 ±6.25
Range	0-40	-5-33	0-30
	N=40	N=35	N=33
Duration of AE (days)			
Median	2.5	2.0	3.0
Mean ± standard deviation	3.2±2.28	4.1 ±4.68	4.8±4.66
Range	1-8	1-19	1-17

AE= adverse event

N= number of events analyzed

*Medical Officer Comments: The mean and median time to onset of adverse events was longer for Clindesse™ than for placebo. The later an adverse event occurs after administration of study drug, the more difficult it becomes to attribute that event to the study drug.*

### Demographic Analysis of Adverse Events

The applicant analyzed drug-related adverse events by patient demographic characteristics. No statistically significant treatment group differences were noted for age, height, weight, or race.

### Reviewer's Conclusions for Study 02-005

1. Clindesse™ was superior to placebo for the treatment of bacterial vaginosis for both primary and secondary endpoints in the ITT, MITT and Per Protocol analyses.
2. The safety profile of Clindesse™ was similar to that of the matching placebo vaginal cream.
3. No deaths or serious adverse events were reported in this study. One Clindesse™-treated patient was withdrawn from the study due to an adverse event that was not likely to be related to the study medication.
4. The most common adverse event associated with both Clindesse™ and placebo was vaginal candidiasis.

### 10.1.2 Study 01-025: Safety and Efficacy Comparison of Clindamycin Vaginal Cream, 2% (KV Pharmaceutical Company) and Cleocin® Vaginal Cream, 2% (Pharmacia and Upjohn) in Patients with Bacterial Vaginosis: A Multicenter, Randomized, Single-Blind, Parallel-Group Study

**Study Objective:** To demonstrate that dosing with one applicator full (5 grams containing 100 mg of clindamycin) of Clindesse™ (clindamycin phosphate vaginal cream, 2%) administered once on a single day is comparable in safety and efficacy to Cleocin® vaginal cream, 2% (Pharmacia and Upjohn) administered daily for seven days for the treatment of bacterial vaginosis (BV).

#### Rationale

Cleocin® vaginal cream, 2% is an FDA-approved, marketed product for treatment of bacterial vaginosis in pregnant women (7-day course of therapy), and non-pregnant women (3- or 7 days of therapy) (NDA 50-680). Clindesse™ contains the same active ingredient, clindamycin, as the active comparator in this study. However, the clindamycin in Clindesse™ is formulated in a different vehicle, a vaginal cream that allows for strong interfacial adhesion between the preparation and the vaginal mucosa. This vehicle allows for prolonged intravaginal retention of butaconazole, marketed as Gynazole-1® (NDA 19-881, butaconazole nitrate, 2% vaginal cream, KV Pharmaceuticals). For this NDA submission, Clindesse™ vaginal cream was studied for use as single-dose therapy for bacterial vaginosis.

#### Study Design

The study was a randomized, single-blind, parallel group, active-controlled phase 3 study of 540 patients enrolled at 27 investigative U.S. sites. The study was designed to show non-inferiority of Clindesse™ in comparison with Cleocin® vaginal cream, 2% for treatment of bacterial vaginosis. The study took place from June 11, 2002 to May 28, 2003.

#### Protocol Overview

Patients were required to meet the following inclusion and exclusion criteria for study participation:

#### Inclusion Criteria:

1.  $\geq 18$  years old
2. Clinical diagnosis of BV including all of the following: off-white, thin, homogeneous discharge with minimal or absent pruritis of vagina and vulva; the presence of  $> 20\%$  clue cells on wet mount preparation; pH of vaginal secretions  $> 4.5$ ; positive “whiff test” (fishy odor of vaginal discharge with addition of drop of 10% KOH);
3. Willing to provide informed consent;
4. Willing to abstain from vaginal intercourse from entry visit to interim safety evaluation visit at day 7-10 after dosing;

5. Willing to abstain from douching or use of other intravaginal products during treatment period and until after the test-of cure (TOC) visit.

*Medical Officer Comments: The inclusion criteria are appropriate for this study. Criteria for diagnosis of BV are in accordance with those recommended in the FDA draft guidance document, "Bacterial Vaginosis- Development of Antimicrobial Therapy", July 1998.*

**Exclusion Criteria:**

1. Patients with other infectious cause of vulvovaginitis (*Candida*, *Trichomonas vaginalis*, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, etc.)
2. Patients with another vulvar or vaginal condition which could confound interpretation of clinical response (e.g. active *Herpes simplex* (HSV), condyloma, etc.)
3. Gram's stain Nugent score < 4 at entry. If patients with a baseline Nugent score <4 receive study medication, they will be considered non-evaluable by per protocol and modified intent-to-treat (MITT) analyses.
4. Active menstruation at time of entry or expected within 7 days after dosing
5. Receipt of antimicrobial or antifungal therapy (systemic or intravaginal) within 14 days prior to treatment, or during treatment and follow-up phases of study.

*Medical Officer Comment: Exclusion of patients who received antifungal or antibiotic therapy during the treatment or follow-up phases of the study is not valid. In fact, these patients were not excluded, but were considered non-evaluable in the Per Protocol analysis.*

6. Treatment for cervical intraepithelial neoplasia (CIN) or cervical carcinoma during study period.
7. Women in the first trimester of pregnancy. Women who were not pregnant were to use an adequate birth control method (defined as hormonal birth control methods). However, if baseline pregnancy test was negative, study participation for those who use barrier methods of contraception was allowed if the patient agreed not to use intravaginal barrier methods (except for non-lubricated condoms) during follow-up phase of study (day 8 to TOC visit).
8. History of hypersensitivity to clindamycin, lincomycin or other ingredients of the formulation.
9. Nursing mothers.
10. Women with intrauterine devices.
11. History of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
12. Concomitant use of neuromuscular blocking agents.
13. Use of any investigational drug within 30 days of start of study.
14. Any significant medical disorder which would preclude accurate evaluation of the patient's condition.

*Medical Officer Comments: The exclusion criteria were appropriate for this study. Exclusion of pregnant females in the first trimester of pregnancy was appropriate.*

*Cleocin® vaginal cream, the comparator for the non-inferiority study, was previously approved for use only in the second and third trimesters of pregnancy. Despite the expectation for low systemic absorption of clindamycin from this intravaginal preparation, the concomitant use of neuromuscular blocking agents was excluded because clindamycin may enhance activity of neuromuscular blocking agents. Additionally, exclusion of patients with a history of enteritis or colitis was reasonable in view of the labeled warning regarding development of pseudomembranous colitis with Cleocin® vaginal cream, and other clindamycin preparations. Excluding the use of antimicrobial and antifungal drugs during the 14 day period prior to study entry was appropriate to eliminate potential confounding with study treatment effect.*

Randomization was accomplished by a sequential block permutation formulation. Patients were randomized 1:1 to receive either Clindesse™ vaginal cream or Cleocin® vaginal cream within each investigative site. Study medications were self-administered as either a single dose of Clindesse™ or as 7 consecutive single daily doses of Cleocin® vaginal cream. Study medication was to be administered within 48 hours of entry visit.

Because the dosing regimen differed for the two study medications, a single-blinded (investigator blind) design was utilized. The blinded investigator and nurse coordinator were responsible for performing pelvic examinations, determining study eligibility, and assessing efficacy and safety of treatment for study patients. An investigator and nurse coordinator at each site were unblinded to treatment assignment. These personnel dispensed the study medications to the patients, and performed medication accountability.

The study consisted of two phases: the “Treatment phase”, the period from the entry visit to the interim safety evaluation visit (day 7-10 post dosing, with day 1 designated as the first day the patient self-administered the study medication), and the “Follow-up” phase, the period from the interim safety evaluation visit to the Test-of-Cure (TOC) visit (day 21-30 days post-dosing). The assessments performed at the entry visit, the interim safety evaluation visit and TOC visit are shown in Table 1, below. Additional data collected and recorded at study visits included the following signs and symptoms of BV: color, odor, pH, and consistency of vaginal discharge, the presence and severity of vulvovaginal itching and irritation and the presence and severity of vulvovaginal inflammation.

Table 1. Schedule of Assessments and Procedures (adapted from Applicant’s Table H, section 9.5.1.3.4)

Procedure	Entry Visit	Interim Safety Evaluation Visit	Test-of-Cure Visit/Early Discontinuation Visit
Physical examination	X		X
Medical history	X		
OB/Gyn/Contraceptive/sexual history	X		
Pelvic examination	X	X	X
Pap smear*	X		
Wet mount preparation	X	X	X
“Whiff” test	X	X	X
Gram’s stain (Nugent score)	X		X
Vaginal pH	X	X	X
KOH preparation for yeast	X	X	X
Urine pregnancy test	X		
<i>Trichomonas vaginalis</i> wet mount	X		X†
<i>Chlamydia trachomatis</i> DNA probe	X		X†
<i>Neisseria gonorrhoea</i> DNA probe	X		X†
<i>Candida</i> culture	X		X†
<i>Herpes simplex</i> culture (if suspected)	X		X†
Study medication administration¶	X		
Return study medication			X
Assessment of adverse events		X	X
Concomitant medications	X	X	X
Assessment of clinical cure			X

† Only if clinically indicated

¶ Study medication self-administered within 48 hours of Entry visit

### Removal of Patients from Study

Patients could be removed or disqualified from the study under the following conditions:

- Difficult to obtain laboratory samples
- Significant protocol violation
- Severe or serious adverse event
- Patient request
- Baseline Nugent score <4
- Lack of therapeutic effect

Patients withdrawn from the study were to be evaluated at an “Early Discontinuation” visit. Assessments and procedures performed at the early discontinuation visit were the same as those

done for TOC visit, shown in Table 1 above. (Data from the early discontinuation visit was included for analysis with that from TOC visit.)

*Medical Officer Comments: Patient discontinued due to lack of therapeutic effect were appropriately counted as treatment failures in the ITT analysis.*

### Evaluability

The following were required for a patient to be considered clinically evaluable for the Per Protocol analysis:

- Clinical assessment and Nugent score (defined below) performed at the Entry visit and TOC visit;
- No other antimicrobial therapy was given to treat conditions other than BV during the study period (Entry visit to TOC visit);
- Self-administered medication within 48 hours of Entry visit;
- Met inclusion/exclusion criteria, complied with treatment regimen; and had no significant protocol violations;
- Additional intravaginal products were not used during the Treatment phase of the study (Entry visit to interim safety visit at 7-10 days post-dosing)

### Primary Efficacy Outcome:

The primary efficacy variable was Therapeutic Treatment Outcome, which is a composite endpoint. Therapeutic cure required both clinical cure and Nugent score cure (score of 0-3), as defined below. Therapeutic failure was defined as clinical failure or Nugent score >3 at TOC visit. Additionally, any patient who required the use of an additional antimicrobial agent for treatment of BV at any time during the study period (entry visit to TOC visit) was considered a clinical failure. Table 2 shows the criteria for therapeutic treatment outcome for the Per Protocol analysis.

Table 2. Determination of Therapeutic Response at TOC visit (adapted from Applicant's Table F, section 9.5.1.1.6)

Clinical Outcome*	Nugent Score*	Therapeutic Outcome
Cure	0-3	Cure
Cure	>3	Failure
Failure	0-3	Failure
Failure	>3	Failure
Cure	NE	NE
NE	0-3	NE
NE	>3	NE

NE= non evaluable

\*Terms defined below

*Medical Officer Comments: Because therapeutic cure requires both clinical cure and Nugent cure, expected cure rates for these products might be expected to be lower than those in studies for Cleocin® vaginal cream product licensing which relied on clinical criteria alone for study endpoints.*

### **Secondary Efficacy Outcomes:**

Clinical Outcome was based on evaluation of the Amsel criteria for BV (Amsel, et al. 1983) at the TOC visit. The following criteria were required for clinical cure at the TOC visit:

- Normal characteristics of vaginal discharge;
- Negative “whiff” test for amine (“fishy”) odor;
- Wet mount preparation with < 20% clue cells
- pH of vaginal secretions < 4.7.

Clinical failure was defined as a patient who did not meet the definition of clinical cure, or one of the following:

- Additional antimicrobial treatment for BV was received during the study period due to lack of response to study medication; or
- The Investigator answered in the affirmative to the question: “In your opinion, does the patient require additional treatment for BV infection at this time?”

*Medical Officer Comment: The 1998 FDA draft guidance for industry, Bacterial Vaginosis-Developing Antimicrobial Drugs for Treatment, recommends that “no” clue cells (rather than <20% clue cells) be seen on a wet mount preparation at the test-of-cure visit. In this review, outcome data were also analyzed using “no” clue cells as one of the clinical criteria for cure, in addition to the applicant’s analysis using < 20% clue cells.*

### **Nugent Score Outcome**

The Nugent score is a 0-4 point scale based on the microscopic examination of a Gram’s stain of vaginal microflora, using a weighted sum of the morphotypes for lactobacilli, gram-negative rods, and curved gram-variable rods (Nugent, et al. 1991)). A Nugent score of 0-3 at the TOC visit was required for Nugent cure. A Nugent score > 3 at the TOC visit was considered a Nugent failure.

### **Investigator Treatment Outcome**

The patient was considered a treatment cure if the patient was not lost to follow-up and the investigator answered “no” to the question: “In your opinion, does the patient require additional treatment for BV at this time?” The patient was considered a treatment failure if the investigator answered in the affirmative to this question, and the patient was not lost to follow-up.

*Medical Officer Comments: Because of the expected lower BV cure rates using therapeutic outcome, as noted above, evaluation of these secondary endpoints will be*

*helpful in comparing outcomes in this study with previously FDA-approved products, and with data from the literature. Additionally, because therapeutic outcome is a composite outcome using a surrogate marker for BV (Nugent score), demonstrating non-inferiority of the investigative drug to active control drug using the secondary endpoint, clinical outcome, which is based on Amsel criteria (Amsel, et al. 1983), the current clinical "gold standard" for BV diagnosis and cure, will be important to support approval of this product.*

The applicant provided additional supporting efficacy analyses including the following:

- Nugent score baseline to TOC, and score change from baseline;
- Individual Amsel criteria;
- Study drug failures
- BV symptoms
- Primary and secondary treatment outcome by investigative site
- Demographic/baseline characteristics
- Use of additional intravaginal/vulvovaginal products.

*Medical Officer Comments: Except for BV symptoms and the use of additional intravaginal products, these additional analyses were not formally analyzed for this review.*

### **Safety Evaluation**

Safety evaluation was performed at the interim safety evaluation visit, and the test-of-cure, or early discontinuation visit. All adverse events were reported on the case report form. All patients who received a dose of study medication were included in the ITT analysis for safety.

The relationship of adverse events to study medication was assessed by the investigator as definite, probable, possible, unlikely/remote, or definitely not related to study medication. The intensity of adverse events was rated as mild, moderate, or severe. A serious adverse event included any adverse event that was fatal or life-threatening, permanently disabling, cancer, or overdose. All serious adverse events required immediate notification of the applicant by telephone. Any serious adverse event that occurred up to two weeks following study participation had to be reported to the applicant within one working day of occurrence.

### **Statistical Considerations**

The targeted enrollment for the study was 500 patients, to ensure a total of 350 evaluable patients, 175 in each treatment group. Assuming a 55% cure rate for each treatment group, a sample size of 175 per group corresponded to 80% power to show a treatment difference of 15%. A two-sided 95% confidence interval was used to determine if Clindesse™ was non-inferior to Cleocin® vaginal cream for treatment of BV.

The primary safety analysis was performed using Fisher's exact test to evaluate potential treatment group differences, using system organ class (SOC) and preferred term (PT) to classify adverse events. Additional supporting statistical analyses were used, but are not discussed in this review.

***Medical Officer Comments:** In this submission, the applicant used the upper and lower bounds of the 95% confidence interval (non-inferiority margin) for treatment differences as  $\pm 20\%$  to show non-inferiority of Clindesse™ to Cleocin® vaginal cream for treatment of BV. However, the predetermined limits of the 95% confidence interval for treatment differences were set at  $\pm 15\%$  to reject the null hypothesis that the investigational drug is inferior to the active control drug, for this sample size. See further comments by the Statistical Reviewer regarding the non-inferiority margin.*

Three patient populations were defined for analysis:

Intent-to-Treat (ITT): This population included all randomized patients who administered at least one dose of study medication. This population was used for analysis of safety data.

Modified Intent-to-Treat (MITT): This was a subpopulation of the ITT population, including only patients with baseline Nugent score  $\geq 4$ .

Per Protocol (PP): This population included randomized patients with Nugent score  $\geq 4$ , who completed the study without significant protocol violations. The Applicant designated this population for primary efficacy analysis.

***Medical Officer Comments:** The ITT population was appropriately designated for safety analysis. The Per Protocol population was designated by the applicant as the primary population for efficacy analysis, however, only 125 patient in the Cleocin® group and 128 patients in the Clindesse™ group were evaluable for the Per Protocol analysis, making this analysis "under-powered" for determination of non-inferiority. The ITT and MITT populations were also evaluated for efficacy and this review will focus primarily on these analyses.*

## Study Results

### Patient Evaluability

A total of 540 patients were enrolled in this study, 271 patient were randomized to receive Clindesse™, and 269 patients were randomized to receive Cleocin® vaginal cream. Twelve patients did not administer study medication, 8 in the Clindesse™ arm, and 4 in the Cleocin® arm, leaving 528 patients for ITT analysis. A summary of overall patient distribution by analysis population is shown below in Table 3.

Table 3. Overall Patient Distribution by Analysis Population (Adapted from Applicant's Table I, section 10.1.3)

Analysis Population	Clindesse™ (N)	Cleocin® Vaginal Cream (N)	Total (N)
ITT	263	265	528
MITT	221	211	432
PP	128	125	253

N= number of patients

The primary reason for non-evaluability in the Per Protocol analysis is shown in Table 4 below. There were no statistically significant differences in reasons for non-evaluability between treatment groups.

Table 4. Primary Reasons for Patient Non-Evaluability for Per Protocol Analysis (Adapted from Applicant's Figure 3, section 10.1.3.2)

Reason for Non-Evaluability	Clindesse™ N=93 n (%)*	Cleocin® Vaginal Cream N=86 n (%)*
Study drug not taken within 48 hours	34 (6.3)	18 (3.3)
Study duration <21 days and not treatment failure	37 (6.9)	27 (5.0)
Did not dose on 3 consecutive days	N/A	14 (2.6)
Took other antimicrobial not for BV	7 (1.3)	14 (2.6)
Took additional intravaginal product or intercourse	11 (2.0)	9 (1.7)
Did not meet inclusion/exclusion criteria	3 (0.6)	3 (0.6)
Study duration > 40 days	1 (0.2)	1 (0.2)

N/A= not applicable

\*Percentage of total randomized patients (540)

N= total number of non-evaluable patients

n= number of patients non-evaluable for specified reason

**Medical Officer Comments:** Patients non-evaluable for the Per Protocol analysis comprised 35.4 %, and 32.4 % of the ITT population, for Clindesse™, and Cleocin® treatment groups, respectively. The total number of non-evaluable patients was similar in each group. The most frequent reasons for non-evaluability was "study drug not taken within 48 hours", and "study duration < 21 days and not treatment failure."

## Study Discontinuation

The total number of patients discontinued from the study was similar in both treatment groups, with 97 patient discontinuations in the Clindesse™ group, and 95 in the Cleocin® group. The reasons for study discontinuation are listed in Table 5 below. Although some differences were noted in reasons for discontinuation between treatment groups, these differences were not statistically significant.

Table 5. Reasons for Early Study Discontinuation (ITT analysis) (Adapted from Applicant's Table L, section 10.1.4.2.3)

Reason for Discontinuation	Clindesse™ N=97	Cleocin® Vaginal Cream N=95	Overall N=192
	n (%)	n (%)	n (%)
Nugent score < 4	38 (39.1)	48 (50.5)	86 (44.8)
Lost to follow-up	20 (20.6)	14 (14.7)	34 (17.7)
Protocol violation	17 (17.5)	7 (7.4)	24 (12.5)
Other	7 (7.2)	9 (9.5)	16 (8.3)
Other antimicrobial for BV	5 (5.2)	5 (5.3)	10 (5.2)
Antimicrobial for other infection	5 (5.2)	3 (3.2)	8 (4.2)
Adverse event	3 (3.1)	2 (2.1)	5 (2.6)
Patient request	1 (1.0)	3 (3.2)	4 (2.1)
Study noncompliance	1 (1.0)	4 (4.2)	5 (2.6)

N= Total number of patients discontinued

n= Number of patients discontinued for each reason

%= percentage discontinued

*Medical Officer Comments: The data shown in Table 5 was obtained directly from the electronic database, and differs slightly from the applicant's summary Table L which did not include 3 patients in the Cleocin® arm and 5 patients in the Clindesse™ arm who did not complete the study and were not evaluated for outcome. Further details regarding "other" reasons for study discontinuation were not provided by the applicant. However, the numbers of patients discontinued for "other" reasons were similar for the 2 treatment groups in this study.*

## Demographics

Comparison of the age and race distribution for Clindesse™ and Cleocin® treatment groups is shown below in Table 6.

Table 6. Baseline Demographic Characteristics (ITT Population)(Adapted from Applicant's Table M, section 11.2.1)

Characteristic	Clindesse™ N=263		Cleocin® Vaginal Cream N=265	
	n	(%)	n	(%)
<b>Age category (years)</b>				
18-39	186	70.7	195	73.6
40-64	74	28.1	68	25.7
65-75	2	0.8	2	0.8
>75	1	0.4	0	0
Mean ± SD	34.6 ± 10.7	--	33.9 ± 10.8	--
Range (min-max)	18-77	--	18-75	--
<b>Race/Ethnicity</b>				
Asian	3	1.1	2	0.8
African-American	91	34.6	95	35.8
Caucasian	137	52.1	136	51.3
Hispanic	27	10.3	25	9.4
Other	5	1.9	7	2.6

N= Total number of patients in treatment group

n= number of patients in each category

***Medical Officer Comments:** Most patients enrolled in this study fall into the 18-39 year old category, with similar distribution for all age categories between the treatment groups. Women under age 18 were not enrolled in this study. Additionally, only 5 patients who were older than 65 were enrolled in the study, 3 patients in the Clindesse™ group, and 2 patients in the Cleocin® group. The majority of enrolled patients were Caucasian, followed by those of African-American origin. The overall racial/ethnic distribution between treatment groups was similar.*

Baseline height and weight did not differ significantly between patients enrolled in the Clindesse™ or Cleocin® vaginal cream treatment groups. However, contraceptive methods differed significantly between the two treatment groups as shown in Table 7. A higher proportion of patients in the Cleocin® treatment group used barrier methods of contraception, and fewer used hormonal or surgical methods of contraception than in the Clindesse™ group. Similar differences were noted in the MITT, but not in the Per Protocol population.

Table 7. Primary Contraceptive Method (ITT Population) (Adapted from Applicant’s Table N., section 11.2.2.1)

Contraceptive Method	Clindesse™ N=263	Cleocin® vaginal cream N=265
	n (%)	n (%)
Hormonal	96 (36.5)	83 (31.3)
Surgical	84 (31.9)	75 (28.3)
Barrier	68 (25.9)	87 (32.8)
Post-menopausal	11 (4.2)	7 (2.6)
Other	4 (1.5)	13 (4.9)

p value = 0.045 for difference between treatment groups using Cochran-Mantel-Haenszel (CMH) statistics

*Medical Officer Comments: These differences noted between treatment groups in baseline contraceptive methods would not be expected to affect treatment outcomes. The applicant determined that primary contraceptive method was not predictive of primary or secondary outcome measures using binary logistic regression analysis. For inclusion in the study, patients agreed to abstain from vaginal intercourse from the entry visit to the interim safety evaluation. Additionally, participants who used barrier methods of contraception agreed not to use intravaginal barrier methods (except for non-lubricated condoms) during the follow-up phase of the study (day 8 to TOC visit). However, 34 patients treated with Cleocin® and 50 patients treated with Clindesse™ used intravaginal products during this time frame. This difference between groups was of borderline statistical significance (p value=0.054 for the ITT analysis. Because intravaginal product use could have an effect of the efficacy evaluation, this subset of patients was also analyzed separately below.*

Treatment groups did not differ significantly in hysterectomy status, number of prior BV episodes within 12 months prior to study entry, number of pregnancies, number of live births, sexual behavior, or “recalcitrant” BV status, defined as 3 or more episodes of BV within 12 months of study entry.

### Disease Severity

Except for subjective symptom severity, there is no method for determination of BV severity, and for this study, participants were not categorized by any disease severity index. Although the Nugent score is not a validated biomarker for BV severity, we compared the baseline Nugent score distribution for the two treatment groups, in an effort to compare patient characteristics at study entry. These data, derived from the electronic database, are shown in Table 8. The distribution of baseline Nugent scores was similar for each group.

Table 8. Baseline Nugent Scores Analyzed by Treatment Groups (ITT Analysis)

Nugent Score	N=263	Cleocin® vaginal cream N=265
Mean	6.52	6.18
Standard deviation	2.9045	3.9066
Standard error mean	0.1768	0.1895
95% Confidence interval	(6.1742, 6.8702)	(5.8073, 6.5536)
Median	8.0	8.0

**Medical Officer Comments:** *It is notable that the mean and median baseline Nugent scores are somewhat higher in this study than in the placebo-controlled study, 02-005 (see Table 7 Appendix 10.1.1, 02-005 study report). This may have significance when data from the two studies are pooled for analysis of efficacy, but whether differences in Nugent score actually reflect the severity of BV is not known.*

### Concomitant Medications

All medications taken by patients in the 30 days prior to study entry visit and throughout the study period were considered concomitant medications. Overall use of concomitant medications was reported in 84% of patients who received Clindesse™, and 79% of patients who received Cleocin® vaginal cream. The most frequent concomitant medications were progestins and estrogens in fixed dose combinations, taken in 33.1% and 27.2% of patients in the Clindesse™ and Cleocin® vaginal cream groups, respectively. The use of antifungal use agents was reported in 15.2%, and 12.1% of patients in the Clindesse™ and Cleocin® vaginal cream treatment groups, respectively. Antibiotic use was reported in 10.6%, and 9.9% patients in the Clindesse™ and Cleocin treatment groups, respectively. These data were derived directly from the electronic database.

**Medical Officer Comments:** *The use of antibiotics and antifungal agents reported in this database includes those used up to 30 days prior to study entry and throughout the study period. Patients who used these agents within 14 days of study entry were excluded from the study. Patients who received another antibiotic for BV during the study period were classified as treatment failures; while patients who received antibiotics for other infections were evaluated for treatment outcome and included in the ITT and MITT analyses. Because certain systemic antibiotics could potentially treat BV, antibiotic use could be confounding factor in the efficacy analysis. However, antibiotic use was similar in the two treatment groups; and consequently it is unlikely that conclusions regarding efficacy were affected. The more frequent use of antifungal agents in the Clindesse™ group could reflect the higher incidence of vaginal candidiasis as an adverse event, or could reflect more frequent prior use of antifungal agents, presumably for vulvovaginal candidiasis, however, these data were not analyzed further for this review.*

## Treatment Compliance

Treatment compliance was assessed by patient query and drug accountability data. Patients returned used the study medication container to unblinded study personnel at the TOC or early discontinuation visit. The study drug kits (used or unused) were then returned to the clinical supplies vendor at the end of the study for inventory. Clindesse was administered as a single dose; while Cleocin® vaginal cream was administered as a single dose administered daily for 7 days. Eight patients assigned to Clindesse™, and 4 patients assigned to Cleocin® did not administer study medication. Administration of study drug was unknown for 12 patients in each treatment group. These latter patients were included in the ITT analysis. The total number of patients who self-administered treatment was similar for the two study arms, 251 (92.6%) in the Clindesse™ group, and 253 (94.1%) in the Cleocin® group. The study drug was administered within 48 hours of entry visit in 227 Clindesse™-treated patients (83.8%), and in 238 Cleocin®-treated patients (88.5%).

*Medical Officer Comments: Treatment compliance was similar in the two treatment groups.*

## Efficacy Analysis

The primary efficacy variable for this study was therapeutic treatment outcome, a composite outcome, which combines clinical outcome and Nugent score outcome. Therapeutic cure required cure by both clinical and Nugent score criteria. Therapeutic outcome was assessed at the TOC visit, 21-30 days post initial dose of study medication. Table 9 shows the therapeutic treatment outcome for all study populations. For the ITT and MITT analyses, Clindesse™ was non-inferior to Cleocin® vaginal cream for treatment of bacterial vaginosis. For the per protocol analysis, the point estimate of the treatment difference was -3.5%, with a 95% confidence interval of [-15.8, 8.7], which lies outside the pre-specified non-inferiority margin of  $\pm 15\%$ .

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Table 9. Therapeutic Treatment Outcome (All Analyses) (Adapted from Applicant's Summary Tables W and X, section 11.4.1.1.1)

Population	Clindesse™			Cleocin® vaginal cream			Treatment difference* %	95% Confidence Interval
	N	n	% cure	N	n	% cure		
ITT	263	78	29.7	265	80	30.2	-0.5	[-8.3, 7.3]
mITT	221	73	33.0	211	78	37.0	-3.9	[-12.9, 5.1]
Per Protocol	126	53	42.1	125	57	45.6	-3.5	[-15.8, 8.7]

N is the number of patients in each treatment group

n is number of patients cured for each group

% cure is the percentage of patients cured for each group

\*Treatment difference is the difference in cure rates for Clindesse™ minus Cleocin® vaginal cream.

**Medical Officer Comments:** For this submission, the applicant proposed using a non-inferiority margin of  $\pm 20\%$  for the treatment difference between investigative drug (Clindesse™) and active control (Cleocin® vaginal cream). However, the pre-specified non-inferiority margin for this study was  $\pm 15\%$ , which should be used as the non-inferiority limit for analysis of this data. Clindesse™ was non-inferior to Cleocin® vaginal cream in the ITT and MITT analyses. Although the confidence interval for the treatment difference between Clindesse™ and Cleocin® vaginal cream in the per protocol analysis (-15.8, 8.7), lies just outside the pre-specified limit, the Per Protocol analysis set was not adequately powered to evaluate non-inferiority. Based on the MITT and ITT analyses alone, we can conclude that Clindesse™ is non-inferior to Cleocin vaginal cream for treatment of BV. This conclusion is supported by the results of the secondary treatment outcomes shown below.

### Reviewer's Analysis of Efficacy

As discussed previously, the 1998 FDA draft guidance, *Bacterial Vaginosis, Developing Antimicrobial Drugs for Treatment*, recommends that no clue cells be observed on a wet mount preparation for clinical (and therapeutic) cure. The electronic database was queried to determine the number of patients classified as therapeutic or clinical cures actually had from 1 to 19 % clue cells observed on the wet mount preparation at the test of cure visit. These patients were reclassified as treatment failures, and are listed in Table 10 below. The number of patients reclassified as therapeutic failures based on clue cells seen at the TOC visit was similar in both treatment groups. Most patients in this category had 5-10 % clue cells reported at the TOC visit.

Table 10. Patients Reclassified as Therapeutic Failures Based on % Clue Cells

Analysis Population	Clindesse™	Cleocin® Vaginal Cream
	N	N
ITT	20	19
MITT	19	18
Per Protocol	15	14

N= number of patients previously classified as therapeutic cures who had between 1 and 19 % clue cells reported at TOC visit

Therapeutic treatment outcomes, calculated removing these reclassified patients from the “cure” category, are shown in Table 11 below. The same methods were used to analyze clinical outcomes (see secondary outcomes below).

Table 11. Revised Therapeutic Treatment Outcome (Reviewer’s Analysis)

Analysis Population	Clindesse™			Cleocin® Vaginal Cream			Treatment Difference*	95% Confidence Interval
	N	n	%	N	n	%		
ITT	263	58	22.1	265	61	23.0	-0.9	[-8.1, 6.2]
MITT	221	54	24.4	211	60	28.4	-4.0	[-12.3, 4.3]
Per Protocol	126	38	30.0	125	43	34.4	-4.4	[-15.8, 7.3]

\* Revised outcomes based on reclassification of patients with 1-19 % clue cells at the TOC visit as treatment failures

N is the number of patients in each treatment group

n is number of patients cured for each group

% cure is the percentage of patients cured for each group

\*Treatment difference is the difference in percentage cured for Clindesse™ percentage cured - for Cleocin® vaginal cream.

*Medical Officer Comments: Similar cure rates were observed for the two treatment groups. Absolute rates of cure, however, were somewhat lower than those observed using the applicant’s analysis (Table 9). Nevertheless, the same conclusions can be drawn regarding efficacy of Clindesse™ in comparison to Cleocin® vaginal cream as discussed for Table 9 above even with the stricter criteria for therapeutic cure used in this analysis.*

### Secondary Outcome Measures

For each of the secondary outcome measures, clinical outcome, Nugent score outcome, and investigator outcome, Clindesse™ was shown to be non-inferior to Cleocin® vaginal cream for treatment of bacterial vaginosis (using the non-inferiority margin of ± 15%), by ITT, MITT, and Per Protocol analyses. These data are summarized in Tables 12-15 shown below.

Table 12. Clinical Outcome (All Analyses) (adapted from Applicant's Summary Table Y section 11.4.1.2.1).

Population	Clindesse™			Cleocin® vaginal cream			Treatment difference*	95% Confidence Interval
	N	n	% cure	N	n	% cure		
ITT	263	130	49.4	265	126	47.5	1.9	[-6.6, 10.4]
mITT	221	118	53.4	211	114	54.0	-0.6	[-10.0, 8.8]
Per Protocol	126	81	64.3	125	79	63.2	1.1	[-10.8, 13.0]

N is the number of evaluable patients in each group

n is number of patients cured for each group

% cure is the percentage of patients cured for each group

\*Treatment difference is the difference in cure rates for Clindesse™ minus cure rates for Cleocin® vaginal cream.

### Reviewer's Analysis of Clinical Outcome

Patients who were classified as clinical cures but who had between 1 and 19% clue cells on the wet mount preparation at the TOC visit, were reclassified as clinical failures as shown in Table 10 above. Clinical cures were then recalculated after reassigning these patients as clinical failures. Revised clinical outcomes are shown in Table 13 below.

Table 13. Revised Clinical Outcomes (Reviewer's Analysis)

Analysis Population	Clindesse™			Cleocin® vaginal cream			Treatment Difference*	95% Confidence Interval
	N	n	%	N	n	%		
ITT	263	93	35.4	265	94	35.5	-0.1	[-8.3, 8.1]
MITT	221	86	38.9	211	85	40.3	-1.4	[-10.6, 7.9]
Per Protocol	126	56	44.4	125	56	44.8	-0.4	[-12.7, 11.9]

N is the number of evaluable patients in each group

n is number of patients cured for each group

% cure is the percentage of patients cured for each group

\*Treatment difference is the difference in cure rates for Clindesse™ minus cure rates for Cleocin® vaginal cream.

**Medical Officer Comments:** Although reclassifying patients who had between 1 and 19% clue cells on the wet mount preparation at the TOC visit as failures reduced the rate of clinical cure, the relative reduction was similar in both treatment groups. Clindesse™ remained non-inferior to Cleocin® vaginal cream for clinical outcome in this analysis, despite the stricter criteria for clinical cure.

Table 14. Nugent Score Outcome (All Analysis Populations) (adapted from Applicant's Table Z)

Population	Clindesse™			Cleocin® vaginal cream			Treatment difference* %	95% Confidence interval
	N	n	% cure	N	n	% cure		
ITT	263	124	47.1	265	112	42.3	4.9	[-3.6, 13.4]
MITT	221	101	45.7	211	104	49.3	-3.6	[-13.1, 5.8]
Per Protocol	124	70	56.5	123	71	57.7	-1.3	[13.6, 11.1]

N is the number of evaluable patients in each group

n is number of patients cured for each group

% cure is the percentage of patients cured for each group

\*Treatment difference is the difference in cure rates for Clindesse™ minus cure rates for Cleocin® vaginal cream.

Table 15. Investigator Outcome (All Analysis Populations) (adapted from Applicant's Summary Table AA)

Population	Clindesse™			Cleocin® vaginal cream			Treatment difference* %	95% Confidence interval
	N	n	% cure	N	n	% cure		
ITT	263	213	81	253	215	85	-4.0	[-10.5, 2.5]
MITT	221	178	80.5	206	170	82.5	-2.0	[-9.3, 5.4]
Per Protocol	128	114	89.1	125	108	86.4	2.7	[-5.4, 10.7]

N is the number of evaluable patients in each group

n is number of patients cured for each group

% cure is the percentage of patients cured for each group

\*Treatment difference is the difference in cure rates for Clindesse™ minus cure rates for Cleocin® vaginal cream.

95% CI is 95% confidence interval

**Medical Officer Comments:** These data from the secondary study endpoints support the conclusions reached by analysis of the primary outcome measure, therapeutic treatment outcome regarding non-inferiority of Clindesse™ in comparison to Cleocin® vaginal cream for treatment of BV.

### Symptom Resolution as an Outcome Measure

Patients were asked to record presence or absence of vaginal itching or irritation, vaginal odor, vaginal discharge and product leakage in the patient diary during the first 7 days of the study. Most patients in each treatment group reported no vaginal itching, odor on day 1, and vaginal discharge was present in only 47% of patients treated with Clindesse™ and 55% patients treated with Cleocin® on the first day of treatment. Except for product leakage, no statistically significant differences were noted between treatment groups for patient-reported symptoms on day 1 or day 7 of the study. Product leakage, which was not analyzed further by the applicant for this study, was similar in both treatment groups on day 1, but at study day 7 was present in more patients in the Cleocin® group than in the Clindesse™ treatment group. This difference is not unexpected because treatment with Clindesse™ was administered as a single dose on day 1, while Cleocin® was administered once daily for 7 days. These data are summarized in Table 16.

Table 16. Patient-Reported Symptoms\*(ITT Population)(Adapted from Applicant’s summary Tables 63, 73,85 and 97)

Symptom	Clindesse™		Cleocin® Vaginal cream	
	Day 1 (% present)	Day 7 (% present)	Day 1 (% present)	Day 7 (% present)
Vaginal itching/irritation	25.5	17.0	24.1	12.5
Vaginal odor	25.5	7.5	29.2	2.4
Vaginal discharge	47.0	21.0	55.3	17.8
Product leakage	63.3	3.5	67.2	58.2

\*Patients recorded symptoms in diary for study days 1-7, where day 1 was the day on which the patient first administered study medication.

% present = percentage of patients reporting presence of symptom

*Medical Officer Comment: Because the symptoms associated with BV are so variable, the difficulties inherent in assessing outcomes for BV based on clinical assessment alone are obvious, and justify the need for clinical markers such as the Amsel clinical criteria and surrogate markers such as the Nugent score as study endpoints. Nevertheless, these data, showing a decrease in reported symptoms during the first 7 days of the study for both treatment groups, support the conclusions drawn from the measured outcome variables regarding efficacy of Clindesse™ and Cleocin® vaginal cream for BV treatment.*

The time to symptom resolution, based on patient-reported information, is shown in Table 17. Time to resolution of symptoms was similar for the two treatment groups, with no statistically significant differences noted except for product leakage which lasted longer in the Cleocin® treatment group, as expected with the longer duration of treatment.

Table 17. Time to Symptom Resolution (ITT Population) (Adapted from Applicant's summary Tables 70, 82, 94, and 106)

Symptom	Clindesse™			Cleocin® vaginal cream		
	Mean days*	Std. deviation	Median days*	Mean days*	Std. deviation	Median days*
Vaginal itching/irritation	2.3	1.5	2.0	2.6	1.7	2.0
Vaginal odor	2.0	1.4	1.0	2.1	1.4	2.0
Vaginal discharge	3.0	1.8	3.0	2.6	1.7	2.0
Product leakage	2.3	1.5	2.0	3.3	1.9	4.0

\*mean or median days to patient-reported symptom resolution  
 Std. deviation= standard deviation of the mean

### Reasons for Treatment Failure

A significant difference in the reason for failure was noted between treatment groups in the ITT analysis; however, no significant difference between groups was observed in the MITT or Per Protocol analyses. Using the applicant's analysis, the primary reason for therapeutic treatment failure in the ITT population was failure due to both Nugent score and clinical criteria, in 45 patients (24.3%) treated with Clindesse™, and 73 patients (39.5%) treated with Cleocin® vaginal cream. The reasons for therapeutic treatment failure are shown in Table 18 below.

Table 18 . Reasons for Therapeutic Treatment Failure (ITT Population) (Adapted from Applicant's summary Table 177)

Reason for Failure	Clindesse™	Cleocin® vaginal cream
	N=185	N=185
	n (%)	n (%)
Lost to follow-up	20 (10.8)	14 (7.6)
Additional treatment for BV required	30 (16.2)	24 (13.0)
Failed due to Nugent score alone	52 (28.1)	46 (24.9)
Failed due to clinical criteria alone	38 (20.5)	28 (15.1)
Failed due to Nugent score <b>and</b> clinical criteria	45 (24.3)	73 (39.5)

N= total number of patients in treatment group

n= number of patients who failed treatment for each category

% = percentage of patients in treatment group who failed treatment for each category

p value = 0.035 for difference between treatment groups

*Medical Officer Comments: It is not clear why proportionately more failures occurred due to failure of both Nugent score and clinical criteria in the Cleocin® than in the Clindesse™ arm.*

When reasons for clinical failure were analyzed, the most common reason for failure was failure of a single clinical (Amsel) criterion. This occurred in 63 (47.4% of clinical failures) patients in the Clindesse™-treated group, and in 68 (48.9% of clinical failures) patients in the Cleocin® vaginal cream-treated group.

### Correlation of Nugent Score Outcome with other criteria for BV treatment outcome

The electronic database was queried to construct a series of 2 x 2 tables to calculate the kappa statistics to correlate Nugent score outcome with clinical outcome and investigator outcome as “gold standards” for cure. A low correlation (kappa statistic < 0.40) was noted between the Nugent score outcome and other clinical outcome measures, as summarized in Table 19 below.

Table 19. Comparison of Nugent Score Outcome to other Outcome Measures (Reviewer’s Analysis)

“Gold Standard” for BV Cure	Kappa statistic† [95% Confidence interval]
Clinical Outcome	0.3773[0.2908, 0.4638]
Investigator Outcome	0.2826 [0.2149, 0.3504]

†Kappa statistic is a measure of agreement between two measurements. Kappa statistics were calculated for combined treatment groups (Clindesse™ and Cleocin®) using the MITT populations.

*Medical Officer’s Comments: In the clinical setting, the gold standard for cure of bacterial vaginosis is symptom resolution or clinical assessment based on the Amsel criteria (Amsel, et al. 1983). Because BV may be asymptomatic in more than half of affected patients, use of subjective symptom resolution as an outcome measure is probably not feasible in the setting of a clinical trial, and more objective measures of cure are necessary to document cure. In this study, the Nugent score outcome did not correlate closely with clinical measures of outcome. However, the FDA draft guidance, “Bacterial Vaginosis- Developing Antimicrobial Drugs for Treatment”, 1988, recommends the use of a composite outcome including clinical outcome plus Nugent score outcome, to evaluate drugs for treatment of BV. The use of the Nugent score in the composite outcome, therapeutic cure, reduces the rates of BV cure when compared to cure rates based on clinical endpoints alone, as shown in this study. For example, in the Clindesse™-treated group, cure rates were 29.7%, 49.4%, and 81% measured by therapeutic outcome, clinical outcome, and investigator outcome, respectively, in the ITT analysis. Thus, direct comparison of Clindesse™ cure rates to other marketed products for BV, or to studies in the literature, will be difficult if the Nugent score was not used as an efficacy endpoint (alone or as part of a composite endpoint) in those studies.*

## Subset Analyses of Efficacy

### Therapeutic Cure by baseline Nugent Score

Data from the electronic database was analyzed to determine whether baseline Nugent score affected therapeutic outcome. This analysis is shown in Table 20. Patients with a baseline Nugent score of <4 were included in the ITT analysis if they received a dose of study medication before the results of the Nugent score were available.

Table 20. Therapeutic Cure analyzed by Nugent Score at Entry Visit (All randomized patients) (Reviewer's Analysis)

Baseline Nugent Score Category	Clindesse™ N= 271	Cleocin® Vaginal Cream N= 269	Treatment Difference % (Clindesse™ minus Cleocin®) [95% confidence interval]
	n/no. (% cure)	n/no. (% cure)	
< 4	5/44 (11.4)	2/54 (3.7)	7.7 [-10.1, 27.1]*
4-7	18/57 (31.5)	17/55 (30.9)	0.6 [-16.5, 17.8]
8-10	55/170 (32.3)	61/160 (38.1)	5.8 [-16.1, 4.5]

N = total number of patients in treatment group

n = number of patients cured for each category of baseline Nugent score

% = percentage of patients with therapeutic cure within each baseline Nugent score category

\*Confidence interval was calculated by the exact method.

**Medical Officer Comments:** *Those enrolled with baseline Nugent scores of < 4 had lower rates of therapeutic cure for each treatment group than those with higher Nugent scores, possibly because they did not actually have BV at study entry. For patients with a baseline Nugent score of ≥ 4, therapeutic outcome did not differ significantly with baseline Nugent score, whether the score was in the intermediate range (4-7) or higher range (8-10). The lower bound of the confidence interval for comparing efficacy of Clindesse™ with Cleocin® Vaginal Cream exceeds the 15% non-inferiority margin in the subsets of patients with Nugent score in the 4-7 and 8-10 range. However, these data are subject to the limitations of subset analysis and should be considered exploratory.*

### Therapeutic Cure by Age

Therapeutic cure rates were similar in patients 18-39 years old or 40-64 years old for both treatment groups as shown in Table 21 below.

Table 21. Therapeutic Cure Analyzed by Age Category (All randomized patients) (Reviewer's Analysis)

Age Category	Clindesse™ N= 271	Cleocin® N=269
	n/no. (% cure)	n/no. (% cure)
18-39	54/191(28.8)	58/199 (29.1)
40-64	24/77 (31.2)	22/68 (32.4)
65-75	0/2 (0)	--
>75	0/1 (0)	--

N= total number of patients in treatment group

n= number of patients with therapeutic cure

no. = number of patients in age category

% = percentage of patients with therapeutic cure in age category

*Medical Officer Comments: Although cure rates were similar for the two age groups which contain most of the enrolled patients, too few patients over 64 years old were enrolled to draw any conclusions regarding efficacy in the geriatric population. Additionally, patients < 18 years old were not enrolled in this study, so no conclusions can be drawn regarding efficacy of Clindesse™ in women under age 18.*

#### Therapeutic Cure by Race/Ethnic Group

Table 22 summarizes therapeutic outcome by race/ ethnic origin for this study. Although the total number and proportion of Hispanic patients cured was higher for Cleocin® than Clindesse™, these differences were not statistically significant. When cure rates for Caucasian patients were compared with all non-Caucasian patients combined, no significant differences within treatment groups were observed. For those who received Clindesse™, 43 of 141 (30.5%) Caucasian patients, compared to 35 of 130 non-Caucasian (26.9%) patients had a therapeutic cure (p-value = 0.5163). For patients treated with Cleocin®, 44 of 136 (32.4%) Caucasians, compared to 36 of 133 (27.1%) non-Caucasians were cured (p-value = 0.3431).

Race or ethnic background were also not significant predictors of therapeutic outcome, when analyzed by the applicant using logistic regression comparing cure rates for Caucasians vs. all non-Caucasians.

Table 22. Therapeutic Cure Analyzed by Race/Ethnic Group (Adapted from Applicant's Summary Table 150)

Race/Ethnic Group	Clindesse™ N= 271	Cleocin® N= 269
	n/no. (% cure)	n/no. (% cure)
African American	29/93 (31.2)	28/99 (28.3)
Asian	1/3 (33.3)	0/2 (0)
Caucasian	43/141 (30.5)	44/136 (32.4)
Hispanic	5/28 (17.9)	7/25 (28.0)
Other	0/6 (0)	1/7 (14.3)

**Medical Officer Comments:** Unlike the placebo-control study reviewed above, race/ethnic background was not significantly associated with rate of therapeutic cure in this study. Whether this inconsistency between studies occurred because more patients were enrolled in this study or because of true racial treatment differences is not known at this time. No racial difference in treatment outcome was noted in the integrated efficacy analysis.

#### Therapeutic Cure by Recalcitrant BV status

Only one patient in the Clindesse™ treatment group, and 5 patients in the Cleocin® treatment group were considered as having "recalcitrant" BV (i.e. 3 or more episodes within 12 months of study entry), so a meaningful subset analysis could not be performed.

#### Therapeutic Cure by Investigative Site

No statistically significant differences were observed for therapeutic outcome for any of the investigative sites in the ITT analysis. Similarly for clinical outcome and investigator outcome no significant differences were seen between any of the study centers in the ITT analysis. For Nugent score outcome however, a significant treatment difference was noted for investigative site #62, where Nugent cure was observed in 13 of 18 patients (72.2%) treated with Clindesse™, and in 6 of 17 patients (35.3%) treated with Cleocin® in the ITT analysis. This treatment difference was statistically significant (p-value = 0.043). This difference was not significant in the MITT or per protocol analyses (applicant's summary table 144).

**Medical Officer's Comments:** Nugent scores were determined from Gram's stains read by a central laboratory, so bias related to the investigative site seems unlikely. Additionally, because no site-related treatment differences were noted for outcome measures other than the Nugent score, the difference in Nugent score outcomes for investigative site # 62 is not likely due to bias.

#### Therapeutic Treatment Outcome in Patients who used other Intravaginal Products

Patients who used other intravaginal products from day 8 post-treatment until the end of the study were analyzed as a subset because these could potentially reduce efficacy or interfere with

efficacy analysis. These data were obtained directly from the electronic database, and are shown in Table 23 below.

Table 23. Therapeutic Treatment Outcome in Patients who used other Intravaginal products (Reviewer's Analysis)

Analysis Population	Clindesse™			Cleocin® Vaginal Cream			Treatment Difference	95% Confidence Interval
	N	n	%	N	n	%		
ITT	50	11	22.0	34	16	47.1	-25.1	[-45.4, -4.7]
MITT	41	10	24.4	34	16	47.1	-22.7	[-44.0, -1.4]
Per Protocol	23	7	30.4	21	10	47.6	-17.2	[-45.6, 11.3]

N= number of patients in treatment group who used other intravaginal products from day 8 to TOC visit.

n= number of patients cured

%= percentage of patients who used intravaginal products classified as therapeutic cure

Treatment Difference= cure rates for Clindesse™ minus Cleocin® treatment groups

*Medical Officer Comments: In this study, the most common intravaginal products used after study medication were tampons and condoms, followed by topical antifungal preparations. Only one patient received another intravaginal product for treatment of BV and was classified as a therapeutic failure. Interestingly, in this subset analysis of patients who used other intravaginal products after the study medication (day 8 until TOC visit), Clindesse™ was inferior to Cleocin® vaginal cream in the ITT and MITT analysis sets, and indeterminate in the Per Protocol set. According to the applicant, the treatment difference noted in the Per Protocol set was not statistically significant when controlled for pooled investigative sites. However, because subset analyses are subject to a number of limitations (including no randomization to post-treatment IVP use), and because there is no plausible biological explanation for the treatment differences seen here, these results should be considered exploratory.*

Therapeutic outcome was also compared within treatment groups for patients who used other intravaginal products from day 8 to TOC visit, as shown in Table 23a below. For those treated with Clindesse™, therapeutic cure rates were lower in the subset of patients who used other intravaginal products than in those who did not; while the reverse was true for the Cleocin®-treated group.

Table 23a. Therapeutic Treatment Outcome Analyzed by Intravaginal Product (IVP) Use (ITT Analysis) (Reviewer's analysis)

Treatment Group	Patients who used IVP	Patients who did not use IVP
	n/N (%)	n/N (%)
Cleocin® vaginal cream	16/34 (47.1)	64/231 (27.7)
Clindesse™	11/50 (22.0)	67/213 (31.5)

N= number of patients in subgroup of IVP use

n= number of patients with therapeutic cure

%= percentage of patients cured within subgroup

*Medical Officer Comments: No further analysis was performed for this review to determine reasons for lower rates of therapeutic cure in patients who used other intravaginal products after treatment with Clindesse™, and these results should be considered exploratory.*

## Safety Analysis

### Drug Exposure

All patients who received at least one dose of study medication were included in the safety analysis. A total of 251 patients (95.4%) administered one dose of Clindesse™ (100 mg clindamycin phosphate). A total of 253 patients (95.5%) administered at least one dose of Cleocin® vaginal cream (mean dose administered was 100 mg). The number of Cleocin® vaginal cream doses administered in this study is shown in Table 24. The mean dose administered in the Cleocin® treatment group was 632.4 mg clindamycin phosphate, administered over a mean of 6.3 days (standard deviation  $\pm$  1.36). Twelve patients in each treatment group who did not report the number of doses administered were included in the ITT analysis because there was no evidence that they had not administered the study medication.

Table 24. Number of Cleocin® Vaginal Cream Doses Administered (ITT Analysis)  
(Adapted from Applicant's summary Table 189).

Number of Doses Administered	Cleocin® Vaginal Cream N=265
Unknown	12
1	8
2	2
3	7
4	3
5	16
6	44
7	173

N= Total number of patients in treatment group

n= number of patients who received specified number of doses

***Medical Officer Comments:** Note the significant difference in drug exposure between treatment groups (mean 632 mg for Cleocin® and 100 mg for Clindesse™) because of the differences in dosing regimens (1 day vs. 7 day treatment). Adverse events in the Clindesse™ treatment group might be expected to occur at a lower frequency than in the Cleocin® group because of lower total active drug exposure, yet more total events and total patients with adverse events were reported for the Clindesse™ group, as shown below.*

#### Adverse Events

A total of 115 adverse events in 80 Clindesse™-treated patients (30.4%) were reported; while a total of 97 adverse events in 71 Cleocin®-treated patients (26.8%) were reported in this study.

Adverse events were categorized by System Organ Class (SOC) and by Preferred Term (PT). The most common adverse event reported by PT was "Vaginosis Fungal NOS (not otherwise specified), followed by vulvovaginal pruritis. No statistically significant difference was found for the incidence of the most common adverse events between the two treatment groups. The most commonly reported Adverse Events classified by Preferred Term are shown in Table 25.

Table 25. Most Commonly Reported\* Adverse Events Classified by Preferred Term (Adapted from Applicant's Table GG, section 12.2.3)

Adverse Event	Clindesse™ N= 263 n (%)	Cleocin® Vaginal Cream N= 265 n (%)
Vaginosis fungal NOS	38 (14.4)	27 (10.2)
Vulvovaginal pruritis	11 (4.2)	8 (3.0)
Headache	4 (1.5)	4 (1.5)
Urinary tract infection NOS	2 (0.8)	3 (1.1)
Vaginal discharge	2 (0.8)	3 (1.1)
Pregnancy NOS	3 (1.1)	1 (0.4)
Vaginal hemorrhage	0 (0)	3 (1.1)

\* Reported by > 1% patients in any treatment group

N= total number of patients in treatment group

n= number of patients with reported adverse event

*Medical Officer Comments: Similar to the adverse event profile seen in the placebo-control study (02-005), fungal overgrowth or superinfection, manifested as vaginal candidiasis, was the most frequent adverse event associated with BV treatment. The incidence of vaginal candidiasis was similar with both Clindesse™ and Cleocin® treatment in this study, despite the higher total exposure to clindamycin with Cleocin® vaginal cream.*

### Drug-Related Adverse Events

Adverse events were considered by the applicant to be drug-related in 27 (10.3%) Clindesse™-treated patients, and in 21 (7.9%) Cleocin®-treated patients. The most frequent drug-related adverse event was vaginal candidiasis, which occurred in 13 (4.9%) of Clindesse™-treated, and in 12 (4.5%) of Cleocin®-treated patients. No significant differences were observed between treatment groups for drug-related adverse events classified by either system organ class or by preferred term (data not shown).

### Severity of Adverse Events

Most adverse events reported in this study were mild or moderate in intensity. A total of 8 patients (3 patients who received Clindesse™, and 5 patients who received Cleocin® experienced 9 severe adverse events,). Severe adverse events are listed in Table 26 shown below.

Table 26. Severe Adverse Events (Adapted from Applicant's summary Table 212)

Severe Adverse Event	Clindesse™ N=263	Cleocin® vaginal cream N=265
	n (%)	n (%)
Diarrhea	0	1 (0.4)
Seasonal Allergy	0	1 (0.4)
Pelvic Inflammatory Disease	0	1 (0.4)
Vaginal burning sensation	1 (0.4)	0 (0)
Vulvovaginal pruritis	3 (1.1)	1 (0.4)
Cellulitis	0 (0)	1 (0.4)
Total severe adverse events	4 (1.5)	5 (1.9)

N= Total number of patients in treatment group

n= number of patients who experienced severe adverse event

#### Death or Serious Adverse Events

No deaths were reported in this study. One serious adverse event was reported in this study, cellulitis of the left lower extremity, which occurred in a patient who received Cleocin® vaginal cream. This adverse event, which was noted to be severe in intensity, was not considered to be related to the study medication, and resulted in patient hospitalization, with subsequent resolution. The case report for this adverse event is summarized below:

#### Case Report Narrative for Patient #612580, with Serious Adverse Event:

This patient was a 53 year-old Caucasian female with a past medical history significant for reflex sympathetic dystrophy, skin sensitivity to light, depression, gastroesophageal reflux disease, endometriosis, cholecystectomy, total abdominal hysterectomy, and arthroscopic knee surgery (knee not specified), benign breast cyst excision, discography, and "cyst removed from spine". Physical exam was noted to be normal at study entry, except for an abnormal vaginal discharge, with no associated vulvovaginal inflammation. The study medication, Cleocin® vaginal cream, was dispensed 4/9/03, and the patient subsequently developed cellulitis in the left lower extremity on 4/14/04. The cellulitis was severe, requiring hospitalization for intravenous antibiotics and leg elevation. The cellulitis resolved by 4/17/03. The patient completed the study visits, and was considered a therapeutic cure for BV. The cellulitis was considered unlikely to be related to the study medication.

*Medical Officer's Comments: Although assigning causality to an adverse event is difficult, it seems unlikely that this adverse event was related to use of the intravaginal study medication. The patient's lower extremity edema and underlying reflex sympathetic dystrophy, which could predispose to lower extremity cellulitis, are more likely related to this event.*

### Study Withdrawal Due to Adverse Events

Three patients from the Clindesse™ treatment group and 2 patients from the Cleocin® treatment group were withdrawn from the study due to adverse events. These are tabulated in Table 27.

Table 27. Adverse Events Resulting in Study Withdrawal

Patient Number	Adverse Event	Study Medication	Severity	Time after Receipt of Study Medication	Relationship to Study Drug*
842294	Allergy	Clindesse™	moderate	3 days	definite
512389	Vaginosis fungal NOS	Clindesse™	moderate	13 days	possible
602137	Vaginosis fungal NOS	Clindesse™	mild	0 days (study entry)	not related
512390	Vaginosis fungal NOS	Cleocin® vaginal cream	mild	9 days	not related
742557	Vaginosis fungal NOS	Cleocin® vaginal cream	mild	12 days	probable

\*Relationship of adverse event as judged by Investigator

NOS= not otherwise specified

### Narrative Case Reports for Patients Withdrawn from Study due to Adverse Events

1. Patient # 842294 was a 26 year old Caucasian female with a past medical history significant for asthma, seasonal allergies, and allergies to "sulfa" and codeine, a previous miscarriage, and an episode of BV in the 12 months prior to study entry. Baseline physical examination was normal, except for vaginal discharge, without vulvovaginal inflammation. Clindesse™ was dispensed on 1/6/03. The patient was seen at an early discontinuation visit on 1/9/03, where she was found to have vulvar and vaginal erythema, tenderness and mild edema, attributed to allergy/hypersensitivity to study medication. The investigator indicated that further treatment for BV was necessary, and the patient was treated at that time with metronidazole 500 mg PO bid for 7 days. The overall outcome for treatment of BV was therapeutic failure, because the investigator felt that further treatment for BV was required. The vaginal itching and burning resolved 1/16/03. This adverse event was considered to be definitely related to the study drug.
2. Patient #512389 was a 43 year old African American female with a past medical history significant for central nervous system microadenoma. Baseline physical exam was reported as normal, except for abnormal vaginal discharge, with no vulvovaginal inflammation. Study medication, Clindesse™, was dispensed 1/6/03. At the interim safety visit on 1/16/03, vaginal discharge was white and thick, but considered normal, and vulvovaginal inflammation was absent. On 1/20/03, the early discontinuation visit, the vaginal discharge was described as abnormal, with mild vulvovaginal inflammation, and severe vulvovaginal

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Clindesse (clindamycin phosphate 2% vaginal cream)

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itching/irritation present. At that time, yeast forms were noted on a wet mount preparation. The patient was then treated with terazol-7 vaginal cream. At the time this adverse event was reported, the adverse event was noted to be ongoing, with no further indication of outcome. The outcome for treatment of BV was therapeutic failure, due to both Nugent score and clinical outcome failure.

3. Patient #602137 was a 43 year old African American female with a past medical history significant for urethral stricture, urethral dilatation, and incomplete miscarriage with dilatation and curettage. Baseline physical examination was normal except for an abnormal vaginal discharge, described as yellow-white, moderately thick, with a fishy, stale odor. No vulvovaginal inflammation was present. Study medication, Clindesse™, was dispensed 8/8/02. The patient was withdrawn from the study due to “protocol violation” because the *Candida* culture obtained at the entry visit was positive. At the early discontinuation visit, the physical exam was unchanged from baseline, with an abnormal vaginal discharge present, described as white and thick, without vulvovaginal inflammation. A KOH preparation for yeast was positive at the early discontinuation visit, and the patient was treated with terazol-7 for vaginal candidiasis at that time. The adverse event was ongoing at the time of case report form recording. The patient was considered a therapeutic failure for treatment of BV because of both Nugent score and clinical outcome failure.
4. Patient # 512390 was a 37 year old African American female with a past medical history of headaches, endometrial ablation, total abdominal hysterectomy, and therapeutic abortion. Baseline physical examination was normal except for an abnormal vaginal discharge, with no vulvovaginal inflammation present. Study medication, Cleocin® vaginal cream, was dispensed on 1/8/03. The patient was seen for an early discontinuation visit on 1/16/03, at which time, the physical exam was not changed from baseline. The vaginal discharge, described as white and thick, was considered normal, and no vulvovaginal inflammation was present. However, yeast forms were observed on a wet mount preparation at that time, and the patient was treated with a single dose of Gynazole-1 for vaginal candidiasis, which was reported to be ongoing at the time of the case report. Notably, a culture was positive for *Candida* on study entry. This patient was considered a therapeutic cure for BV treatment.
5. Patient # 742557 was a 35 year old African American female with a past medical history of hypertension, and an abnormal PAP smear (atypical cells of uncertain significance). Baseline physical examination was normal, except for abnormal vaginal discharge, described as white, and thin, with a slightly fishy odor. Vaginal inflammation was absent. Study medication, Cleocin® vaginal cream was dispensed on 1/14/03. At the early discontinuation visit on 1/28/03, the patient was noted to have an abnormal vaginal discharge, described as white, and “chunky”, with associated moderate vulvovaginal inflammation and severe vulvovaginal itching/irritation. A KOH preparation was positive for yeast at that time, and a single dose diflucan was prescribed for vaginal candidiasis. The adverse event was considered to be ongoing at the time of the case report. The patient was considered a therapeutic treatment failure for BV, based on both Nugent score and clinical criteria.

**Medical Officer Comments:** Patient# 602137 may have had BV with *Candida* colonization at baseline, because no vulvovaginal inflammation was present at that time to suspect vulvovaginal candidiasis. It is also questionable as to whether she actually had vulvovaginal candidiasis at the early discontinuation visit, for the same reason. Although the patient was considered a therapeutic failure based on Nugent and clinical criteria, review of the electronic database and case report form revealed that the Nugent score was not assessed at the early discontinuation visit. In the case report form, for the early discontinuation visit on 8/15/02, a vaginal pH of 5.3 was reported, the whiff test was reported as negative, and 3% clue cells were noted on wet mount preparation. These data were not recorded in the electronic database. Nevertheless, the patient would still be considered a clinical failure based on vaginal pH and abnormal vaginal discharge at the early discontinuation evaluation.

### Other Significant Adverse Events

Four pregnancies occurred during the study, 3 in the Clindesse™ group and 1 in the Cleocin® group. None of the pregnancies was considered to be related to the study medication. Three pregnancies were followed to conclusion. The fourth pregnancy was electively terminated. Pertinent information regarding these pregnancies is shown in Table 28.

Table 28. Pregnancies that Occurred during Study 01-025

Patient Number	Study Medication	Date of Study Entry	Pregnancy Test on Study Entry	Contraceptive Method	Date of Positive Pregnancy Test	Pregnancy Outcome†
522250	Clindesse™	9/12/02	negative	barrier	(5 weeks pregnant on 10/11/02)	Normal delivery — normal infant
602413	Clindesse™	11/6/02	negative	barrier; tubal ligation 11/02	11/02	Elective Abortion
622491	Cleocin® vaginal cream	11/21/02	negative	oral contraceptives	12/5/02	42 week delivery — hematemesis in neonate*
812129	Clindesse™	8/27/02	negative	barrier	9/23/02	Unknown

† Pregnancy outcomes were reported in the 120-day safety update (7/23/04)

\* Neonate required 5 days in neonatal intensive care unit, but subsequently recovered.

**Medical Officer Comments:** None of the patients who became pregnant during the study reported sexual intercourse in the patient diary during the 7 days after receipt of the study medication; and none of these pregnancies was attributed to the study drug. However, the Cleocin® vaginal cream label contains the following information for the patient: "The patient should be instructed not to engage in vaginal intercourse, or use

*other vaginal products (such as douches) during treatment with this product. This cream contains mineral oil, which may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms; therefore use of such products following treatment with clindamycin phosphate vaginal cream, 2%, is not recommended". A similar warning was proposed by the applicant for the Clindesse™ label. However, the recommendation that patients not use condoms or diaphragms within 72 hours of a Clindesse™ dose may not be appropriate based on the data showing prolonged vaginal retention of butaconazole in the same vehicle. That study demonstrated that butaconazole was found in vaginal secretions for a median of 4.2 days in comparison to 2.57 days for the standard cream formulation (Weinstein, et al. 1994).*

### **Time to Onset and Duration of Adverse Events**

The mean time to the onset of an adverse event after study drug administration was 11.1 days  $\pm$  9.09 days, with a range of 0-30 days for Clindesse™-treated patients, and 10.2 days  $\pm$  9.09 days, with a range of 0-32 days for Cleocin®-treated patients. The mean duration of an adverse event was 3.7  $\pm$  3.18 days, and 5.3  $\pm$  5.24 days, for Clindesse™-treated, and Cleocin-treated patients, respectively (from applicant's summary Table 199).

### **Demographic Analysis of Adverse Events**

The applicant analyzed drug-related adverse events by race, age, and recalcitrant BV status. No significant differences between treatment groups were noted for age, age category, race, recalcitrant BV status for drug-related adverse events in the applicant's analysis.

### **Conclusions for Study 01-025**

1. Clindesse™ is non-inferior to Cleocin® vaginal cream for the treatment of BV for both primary and secondary study endpoints in the ITT and MITT analyses.
2. The safety profile for Clindesse™ is similar to Cleocin® vaginal cream.
3. No deaths were reported in the study, and no serious adverse events occurred in patients treated with Clindesse™. The most common adverse event reported in both treatment groups was vaginal candidiasis.

### **10.1.3. Study 01-012: The Evaluation of a Single Dosage Regimen of KV Pharmaceutical Company Site-Release® Clindamycin Vaginal 2% Cream in the Treatment of Bacterial Vaginosis: A Pilot Multicenter Bioavailability Screening Study**

#### **Study Objectives:**

To evaluate the clinical utility and bioavailability of dosing with one applicator full of Clindesse™ (100 mg clindamycin phosphate) administered once on a single day for the treatment of bacterial vaginosis (BV).

*Medical Officer Comments: This review primarily addresses the safety data obtained in this study because only 20 patients were enrolled, and because a full analysis of the efficacy data was not provided with this submission.*

#### **Rationale**

Clindesse™ contains clindamycin phosphate, in a patented drug delivery system (Site Release®). This vehicle has been used previously in an FDA-approved intravaginal product, Gynazole-1®, which contains butaconazole nitrate 2% (NDA 19-881), used for treatment of vulvovaginal candidiasis. In Gynazole-1®, butaconazole is present in the vagina 63% longer than butaconazole nitrate 2% administered in the convention formulation. Using the same rationale, the intravaginal retention of clindamycin is expected to be longer than clindamycin administered in the conventional cream preparation (Cleocin® vaginal cream), allowing for use as a single dose, theoretically improving patient compliance, and potentially reducing systemic exposure to clindamycin.

#### **Study Design**

Study 01-012 was a multicenter, open-label, single-dose, phase 2 pilot study, designed to assess bioavailability, efficacy and safety of Clindesse™ for treatment of BV. Twenty patients were enrolled at 3 investigative sites. Bioavailability was assessed by assessment of clinical efficacy endpoints. The study took place from January through July, 2002.

#### **Protocol Overview**

Eligible patients with protocol- defined BV were dispensed a single dose of Clindesse™ (100 mg clindamycin phosphate) for intravaginal self-administration within 48 hours. Efficacy and safety evaluations were performed at the interim evaluation clinic visit at 7-10 days, and at 21-30 days for the test-of-cure (TOC) visit.

#### **Inclusion Criteria**

1. Females  $\geq$  18 years old
2. Clinical diagnosis of BV defined as follows:

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{NDA 50-793 N-000}

Clindesse (clindamycin phosphate 2% vaginal cream)

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- a. Off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritis and inflammation of the vulva and vagina
  - b.  $\geq 20$  % clue cells on microscopic examination of wet mount preparation
  - c. pH of vaginal secretions  $>5.0$
  - d. Positive "whiff test" (a fishy odor of the vaginal discharge with addition of 10% KOH)
3. Willingness and ability to give signed informed consent
  4. Willing to abstain from vaginal intercourse during the treatment phase of the study (period between dosing and interim evaluation clinic visit), and to have their partner using a non-lubricated condom for intercourse within 48 hours preceding the TOC visit
  5. Willing to abstain from douching, and from using intravaginal products (e.g., a diaphragm, contraceptive creams, gels, foams, sponges, tampons, etc.) during the treatment phase and follow-up period (period between the interim evaluation clinic visit and TOC Visit).

**Exclusion Criteria**

1. Patients with other infectious causes of vulvovaginitis (e.g. *Candida*, *Trichomonas vaginalis*, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, etc.)
2. Patients with another vaginal or vulvar condition which could confound the interpretation of clinical response (e.g. condyloma, active *Herpes simplex* virus lesions, etc.)
3. A Gram's stain Nugent score  $< 4$  at entry
4. Patients who are actively menstruating at the time of study entry or are expected to begin menstruation within 7 days after dosing.
5. Patients who received antifungal or antimicrobial (systemic or local) therapy within 14 days prior to treatment or during the treatment and follow-up phases of the study.

*Medical Officer Comments: Patients who received antifungal or antibiotic therapy during the study period (treatment and follow-up phases of the study) were non-evaluable Per Protocol.*

6. Patients who are under treatment during the study period for cervical intraepithelial neoplasia or cervical carcinoma
7. Pregnant women
8. History of hypersensitivity to clindamycin, lincomycin, or other ingredients of the formulation
9. Nursing mothers
10. Patients with intrauterine devices
11. Patients with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis
12. Concomitant use of neuromuscular blocking agents
13. Use of any investigational drug within 30 days of study entry
14. Any significant medical disorder which would preclude accurate evaluation of the patient's condition
15. More than 3 episodes of BV within the last 12 months

*Medical Officer Comments: The inclusion and exclusion criteria are essentially identical to those used in study 02-005 and 01-025 with the exception of the criterion excluding those with more than 3 episodes of BV in the year prior to study entry. Additionally, in study 01-025, pregnant women could be enrolled in the study after the first trimester.*

## Study Procedures

The study consisted of 2 phases:

- “Treatment Phase”, the period from the entry visit (visit 1) to the interim evaluation clinic visit (visit 2, at 7-10 days post-dose); and
- “Follow Up Phase”, the period from the interim evaluation clinic visit to the TOC Visit (visit 3, at 21-30 days post-dose).

The treatment day was defined as the day on which the patient self-administered the study medication. This was to occur within 48 hours of the entry visit. The procedures and evaluations conducted at each study visit are outlined in Table 1 below. Patients were also given a diary to record time of study drug administration, symptoms, and adverse events.

Table 1. Schedule of Study Procedures and Evaluations (Adapted from Applicant’s Appendix C, Schedule of Events)

Procedure	Entry Visit	Interim Visit	Test-of-Cure Visit
Physical examination	X		X
Medical history	X		
Ob/Gyn/contraceptive/sexual history	X		
Pelvic examination	X	X	X
Wet mount preparation (clue cells)	X	X	X
Whiff test	X	X	X
Gram’s stain (for Nugent score)	X		X
KOH preparation for yeast	X	X	X
Urine pregnancy test	X		
<i>Chlamydia trachomatis</i> culture	X		
<i>Neisseria gonorrhoea</i> culture	X		
<i>Candida</i> culture	X		
<i>Herpes simplex</i> culture (if suspected)	X		
Study medication administration	X		
Adverse events		X	X
Concomitant medications	X	X	X
Assessment of Clinical cure		X	X
Dispense diary	X	X	

### Study Discontinuation

Patients could withdraw from the study at any time. Patients could be removed from the study for the following reasons:

- Difficult to obtain laboratory samples
- Protocol violations
- Severe or serious adverse events

Patients withdrawn from the study were to complete the follow-up evaluations listed for the Test-of-Cure visit.

### Definitions for Study Populations

- **Intent-to-Treat (ITT) Population:** All patients enrolled and treated in the study
- **Per Protocol Population:** All patients who complied strictly with the protocol and who were classified as clinically evaluable

### Patient Evaluability

Patients were considered clinically evaluable if the following criteria were met:

- a. Clinical assessment and Gram's stain Nugent score result were done between study days 21-30
- b. Nugent score  $\geq 4$  at study entry
- c. No other antimicrobial therapy was given to treat conditions other than BV
- d. Patient administered study medication within 48 hours of entry visit
- e. Patient met inclusion/exclusion criteria, complied with treatment regimen, and had no significant protocol violations
- f. Patient used no additional intravaginal products during the first 7 days of the study.

Patients who discontinued the study prematurely or who were deemed clinically not evaluable due to treatment with an antimicrobial agent for conditions other than BV, or who used other intravaginal products during the first 7 days of the study, could be replaced at the sponsor's discretion.

### Study Endpoints

Therapeutic outcome was the primary study endpoint. Therapeutic outcome was a composite outcome based on clinical outcome and Nugent score outcome. Clinical cure was defined as resolution of abnormal clinical findings: vaginal discharge, "whiff" test, percentage of clue cells on a saline wet mount, and vaginal pH of  $<4.5$ . A Nugent score of 0-3 was considered a cure.

Secondary outcomes included the clinical outcome, Nugent score outcome, investigator outcome, and analysis of patient diary information.

*Medical Officer Comments: See reviews of studies 01-025 and 02-005 for detailed definitions of primary and secondary endpoints, Nugent score and clinical outcomes.*

## Study Results

### Patient Demographics

In this study, 10 patients (50%) were Caucasian, 8 (40%) were African-American, and 2 patients were of unknown racial/ethnic origin. The mean patient age in this study was  $34.1 \pm 9.95$  years, with an age range of 18.9-56.8, and a median of 33.1 years.

### Patient Disposition

Twenty patients were enrolled in the study, and 16 patients completed the study through the test-of-cure visit. Two patients were lost to follow-up, and 2 patients discontinued the study early because of baseline Nugent score  $<4$ .

Twenty patients were included in the ITT analysis, and 15 in the per protocol analysis.

### Synopsis of Efficacy Data

In the ITT analysis, 7 of 20 patients (35%) were classified as therapeutic cures, 12/20 (60%) were classified as clinical cures, 9/20 (45%) were classified as Nugent score cures.

In the per protocol analysis 7 of 15 evaluable patients (46.7%) were classified as therapeutic cures, 12/15 (80%) patients were classified as clinical cures, and 9/15 (60%) were classified as Nugent score cures.

*Medical Officer Comments: These data supported further evaluation of Clindesse™ for treatment of BV in phase 3 studies.*

### Safety Analysis

Safety assessment was performed at the interim evaluation visit and the TOC visit. The relationship of adverse events to study medication and the severity of adverse events was determined by the Investigator, using the same definitions described for studies 01-025 and 02-005. All patients who received a dose of study medication were included in the safety analysis.

*Medical Officer Comments: Data for this safety review were obtained directly from the electronic database provided by the Applicant.*

## Drug Exposure

Clindesse™ was self-administered as single dose (100 mg clindamycin phosphate) in 20 patients enrolled in this study.

## Adverse Events

There were 10 adverse events reported in 8 patients (40%). All adverse events reported in this study are summarized in Table 2. No deaths or serious adverse events were reported, but two patients were withdrawn from the study prematurely due to adverse events. One patient developed a dermatitis which was treated and resolved within 10 days; and the second patient developed human papilloma virus infection and cervical dysplasia. All adverse events were reported as “mild”.

Table 2. Adverse Events Reported in Pilot Study 01-012 Classified by System Organ Class (SOC) and Preferred Term (PT)

Adverse Event SOC and PT	Clindesse™ N=20 n	Relationship to Study Drug
<b>Infections and Infestations:</b>		
Papilloma viral infection NOS	1	Definitely not
<b>Reproductive System and Breast Disorders:</b>		
Cervical Dysplasia	1	Definitely not
Vaginosis fungal NOS	2	Possible
Vulvovaginitis Trichomonal	1	Definitely not
Uterine cervical disorders NOS	1	Definitely not
<b>Respiratory, Thoracic and Mediastinal Disorders:</b>		
Sinusitis NOS	1	Definitely not
Wheezing	1	Definitely not
<b>Skin and Subcutaneous Tissue Disorders:</b>		
Dermatitis	1	Possible
Dry skin	1	Unlikely/remote

N= total number of patients in treatment group

n = number of patients with reported adverse event

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*Medical Officer Comments: Because of the small number of patients enrolled in this study, the proportion of patients with reported adverse events was not calculated. The overall percentage of patients with adverse events is similar to that reported in studies 01-025 and 02-005. The safety data from this study was pooled with data from those studies for the Integrated Safety Summary (section 7).*

#### **Reviewer's Conclusions Regarding Safety**

Application of a single intravaginal dose Clindesse™ was not associated with any serious or severe adverse events in this pilot study. The overall incidence of adverse events associated with Clindesse™ use in this study (40%), was similar to that seen in the two pivotal clinical studies for this NDA, the placebo-controlled study (02-005), and the active-controlled study (01-025).

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#### **10.1.4 Study KVP-214: A Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Clindamycin Vaginal Cream Formulations in Normal, Healthy Women**

##### **Study Objective**

To compare the relative bioavailability of clindamycin vaginal cream 2% (KV Pharmaceutical Company) to Cleocin® vaginal cream (Pharmacia and Upjohn) following a single intravaginal dose in fasted, normal, healthy female subjects.

*Medical Officer Comments: This review addresses the safety data obtained in this study. Please refer to the Clinical Pharmacology review for study results and conclusions regarding bioavailability.*

##### **Study Design**

This was an open-label, randomized, single-dose two-period, two-treatment, two-sequence crossover study in which study subjects received a single dose of one of two drug formulations, either Clindesse™ or Cleocin® vaginal cream. After a two-week washout period, the subject received a single dose of the other drug formulation.

A total of 20 patients received the study medication(s). These patients constituted the Intent-to-Treat (ITT) population, which was used for the safety analysis.

##### **Protocol Overview**

##### **Inclusion Criteria:**

1. Normal, healthy adult female volunteer
2. Age  $\geq$  18 years
3. Body mass index in the range of 19-35
4. Subject is willing to avoid pregnancy by abstaining from sexual intercourse, or by the use of an IUD or barrier methods of contraception (diaphragm, condom, foams/jellies, sponge), or subject is surgically sterile or post-menopausal for at least 6 months prior to study entry
5. Subject is considered reliable and capable of understanding her role and responsibilities in the study
6. Subject is willing to abstain from vaginal intercourse and the use of intravaginal products for 72 hours following each study drug administration
7. Subject has provided informed consent

##### **Exclusion Criteria:**

1. History of allergy or hypersensitivity to clindamycin or vaginal creams

2. Clinically significant laboratory abnormalities that would interfere with the conduct or interpretation of the study or jeopardize safety
3. Significant history or clinical evidence of autoimmune, cardiovascular, gastrointestinal, hematological, hematopoietic, hepatic, neurological, ongoing infection (including vaginal infection), pancreatic or renal diseases that would interfere with the conduct or interpretation of the study or jeopardize safety
4. History of regional enteritis, ulcerative colitis, or “antibiotic-associated colitis”
5. Nursing mothers
6. Serious psychological illness
7. Significant history (within the past year) or clinical evidence of alcohol or drug abuse
8. Positive urine drug screen, or positive HIV-1 or hepatitis B screen, or positive pregnancy test
9. Subject is unable to refrain from use of alcohol or xanthine-containing foods or beverages during the 48 hours prior to study drug administration until the last blood sample has been taken
10. Subject has used systemic prescription drug during the 14 day period prior to study initiation, or any systemic OTC drug during the 72 hour period preceding study initiation
11. Subject is unable to refrain from the use of all concomitant medications during the study
12. Subject has donated or lost blood, or participated in a clinical study which involved withdrawal of a large volume of blood (more than 480 ml) during the six week period prior to study initiation
13. Subject has donated plasma during the 2 week period preceding study initiation
14. Subject has received an investigational drug during the 30 day period preceding study initiation

*Medical Officer Comments: Inclusion and exclusion criteria were appropriate for this study.*

### **Randomization**

Subjects were numbered sequentially in the order in which they reported to the investigational site.

### **Study Dropouts**

Study dropouts were not replaced. Participation in the study could be discontinued for the following reasons:

- Adverse reaction
- Intercurrent illness
- Pregnancy
- Non-compliance with study requirements
- Subject decision not to continue participation
- Judgement by the Principal Investigator that it was not in the subject’s best interest to continue

## Study Procedures

Study procedures and screening laboratory tests are shown in Table 1 below. Subjects were sequestered at the study site starting the evening prior to study drug administration, and until a 36-hour blood sample post-treatment was obtained. Subjects received study or reference drug on day 1 and day 15. There was a 2 week wash out period between administration of study or reference drug.

Table 1. Schedule of Study Procedures

Procedure	Screening visit	Days 1 and 14	Days 1 and 15	Days 2 and 16	Days 3 and 4, 17 and 18
Informed consent	X				
Medical/Social History	X				
Hematology, chemistry, UA	X				
Urine drug screen	X				
Urine pregnancy test	X	X			
HIV screen	X				
Hepatitis B screen	X				
12-lead ECG	X				
Physical exam	X				
Admit to dormitory		X			
Check-in questionnaire		X			
Dose administration			X		
PK blood samples			X	X	X
Vital signs			X		
Adverse event monitoring			X	X	X
Release from dormitory				X	

ECG= electrocardiogram; UA= urinalysis

PK= pharmacokinetic

## Safety Analysis

Adverse events reported by subjects or observed by staff at the study site where patients were sequestered for 36 hours after receipt of each study medication. The relationship of adverse events to study medication was determined by the investigator.

## Patient Demographics

Most subjects were of Hispanic origin (17/20, 85%). Two African-American and one Caucasian subject were also enrolled. The mean age for enrolled subjects was  $43.3 \pm 12.6$  years. The median age was 43.5 years; while the range was 18-66 years.

*Medical Officer Comments: The racial/ethnic and age distributions differed between this study and the other studies submitted for this NDA. In each of the other studies, patients were predominantly Caucasian and in the 18-39 year age category. See individual study reports for details. Because of these differences in patient demographics, because patients in this study were healthy at baseline, and because subjects in this study received two study medications, safety data from this study was not pooled with the other clinical studies for the Integrated Safety Summary.*

## Drug Exposure

Ten subjects received a single dose of Clindesse™, and 10 subjects received a single dose of Cleocin® vaginal cream in the first study period. In the second study period, after the 14 day washout period, 10 subjects received a single dose of the Clindesse™; and 9 received Cleocin® vaginal cream. One subject withdrew from the study and did not receive a dose of Cleocin® vaginal cream during the second study period.

A single dose of drug in this study was defined as one applicator full (5 grams) of Clindesse™ (clindamycin vaginal cream, 2%) or Cleocin® vaginal cream 2%.

## Adverse Events

A total of 18 adverse events were reported in 9 subjects, 4 of whom received Clindesse™, and 5 of whom received Cleocin®. No deaths or serious adverse events were reported. Only 1 adverse event was considered possibly “drug-related”, abdominal fullness in a subject who received Cleocin® vaginal cream. Two subjects who had received Cleocin® vaginal cream reported severe headaches. All other adverse events were reported as mild or moderate in severity. No patients were withdrawn from the study due to an adverse event. All adverse events that occurred in this study are summarized below in Table 2.

Table 2. Adverse Events Reported in Bioavailability Study KVP-214 Classified by System Organ Class (SOC) and Preferred Term (PT) (adapted from applicant's Table 7, section 5.5).

Adverse Event SOC and PT	Clindesse™ N= 20	Cleocin® N=19
	n	n
General disorders and administration site conditions:		
Pain NOS	1	0
Gastrointestinal disorders:		
Vomiting NOS	0	2
Abdominal distension	0	1
Investigations:		
Body temperature increased	1	0
Nervous System disorders:		
Headaches	2	5
Dizziness postural	0	1
Vascular disorders:		
Hypertension NOS	1	0
Hypotension NOS	1	0

N= Total number of subjects in treatment group  
 n = number of subjects with reported adverse event  
 NOS= not otherwise specified

**Medical Officer Comments:** *The total number of events noted in Table 2 above, differs slightly from the applicant's accounting of events. For this review, an adverse event was counted only once per patient (for example, 3 episodes of vomiting occurred in 1 subject within a short time period. This was counted as 3 adverse events by the applicant, but as 1 event for this review. Similarly, 2 episodes of headache in the same subject were counted as two events by the applicant, but as a single even in this review.)*

*Some of the adverse events seen in this study, notably fever, hypotension, and hypertension, were not observed in the pilot study (01-012) or the two large pivotal studies (01-025 and 02-005). In those studies, vital signs were not obtained, and patients self-administered study medication as outpatients, so those adverse events would not have been observed had they occurred.*

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#### **Reviewer's Conclusions Regarding Safety for Study KVP-214**

A single dose of Clindesse<sup>TM</sup> was not associated with any serious or severe adverse events in the comparative bioavailability study. Conclusions regarding incidence of specific adverse events associated with Clindesse<sup>TM</sup> cannot be drawn from this study because of the small number of patients exposed to the drug.

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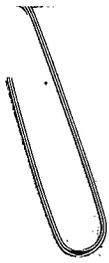
### 10.1.5. Summary Table for Clinical Studies

Study	Study Design	Study Location	Treatment Groups/Dosing Regimen	Study Population	N
02-005	Multicenter, randomized, placebo-controlled, double-blind, parallel group, phase 3	20 U.S. sites	Clindesse™ (100 mg clindamycin phosphate), single dose  KV Metronidazole vaginal cream, 0.75%, single dose  Placebo (matching vaginal cream), single dose	Non-pregnant females ≥ 18 years old with BV	262
01-025	Multicenter, randomized, active-controlled, single blind, parallel group, phase 3	27 U.S. sites	Clindesse™ (100 mg clindamycin phosphate), single dose  Cleocin® vaginal cream (100 mg clindamycin phosphate), once daily for 7 days	Females ≥ 18 years old with BV; women in second or third trimester of pregnancy included	540
01-012	Multicenter pilot bioavailability study, phase 2	3 U.S. Sites	Clindesse™ (100 mg clindamycin phosphate), single dose	Non-pregnant females ≥ 18 years old with BV	20
KVP-214	Open-label, randomized, single-dose, 2-way crossover, relative bioavailability study	1 U.S. site	Clindesse™ (100 mg clindamycin phosphate), single dose  Reference: Cleocin® vaginal cream (100 mg clindamycin phosphate), single dose	Healthy female volunteers ≥ 18 years old	20

N= number of patients enrolled in study

### 10.2 Line-by-Line Labeling Review

The following package insert was proposed by the applicant with the submission of NDA 50-793:



20 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓ \_\_\_\_\_ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1

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/s/

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