From: epharmalert@email.[redacted].com
Sent: Wednesday, October 11, 2006 10:21 AM
To: [redacted]@alertmarketing.com; [redacted]@alertmarketing.com; [redacted]
Subject: TEST e-Pharm/alert Re: Clindesse™ at UnitedHealthcare® on Formulary Tier 2 Copay

e-Pharm / alert℠

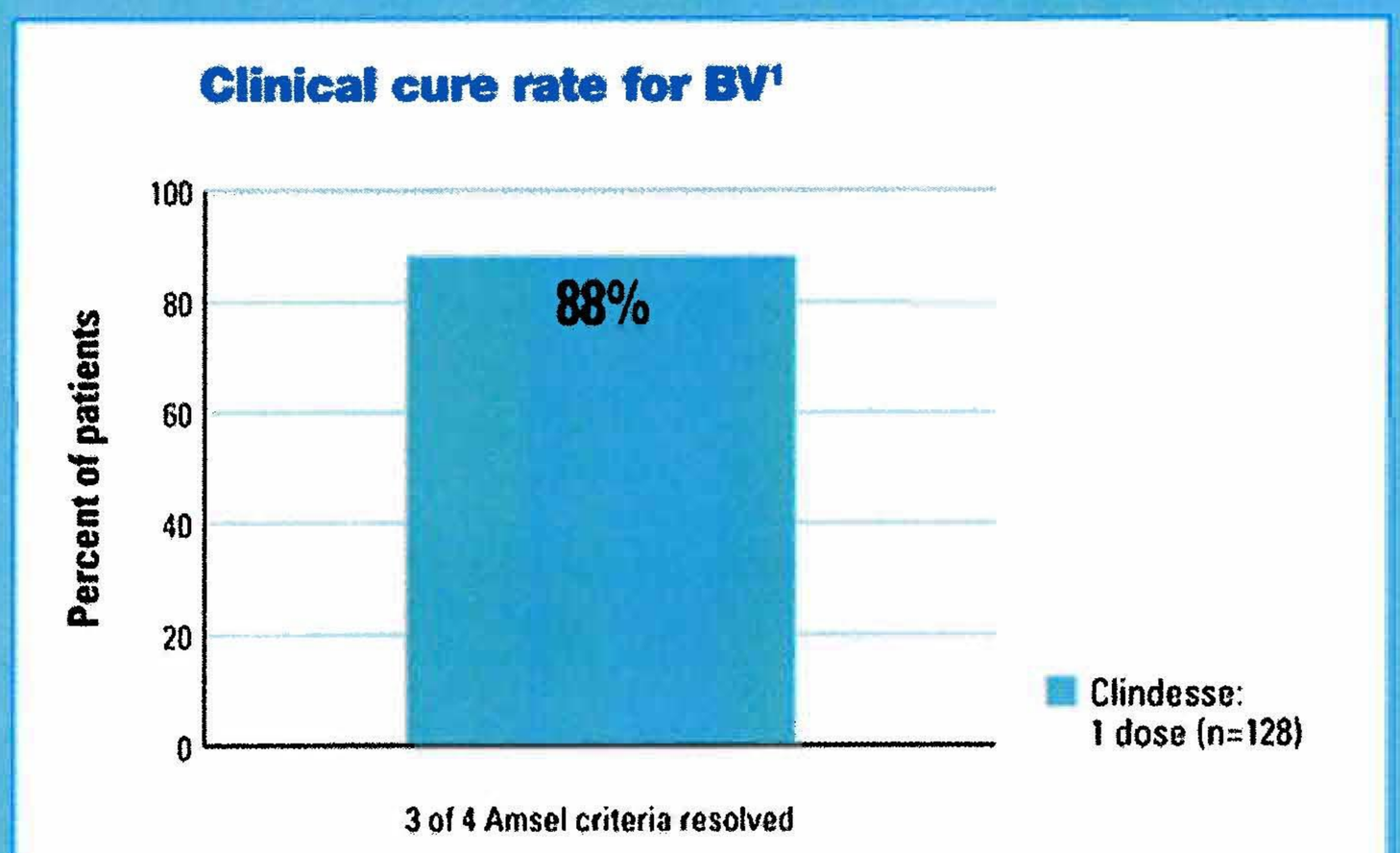
If you are unable to view this e-mail please click here.

[redacted]

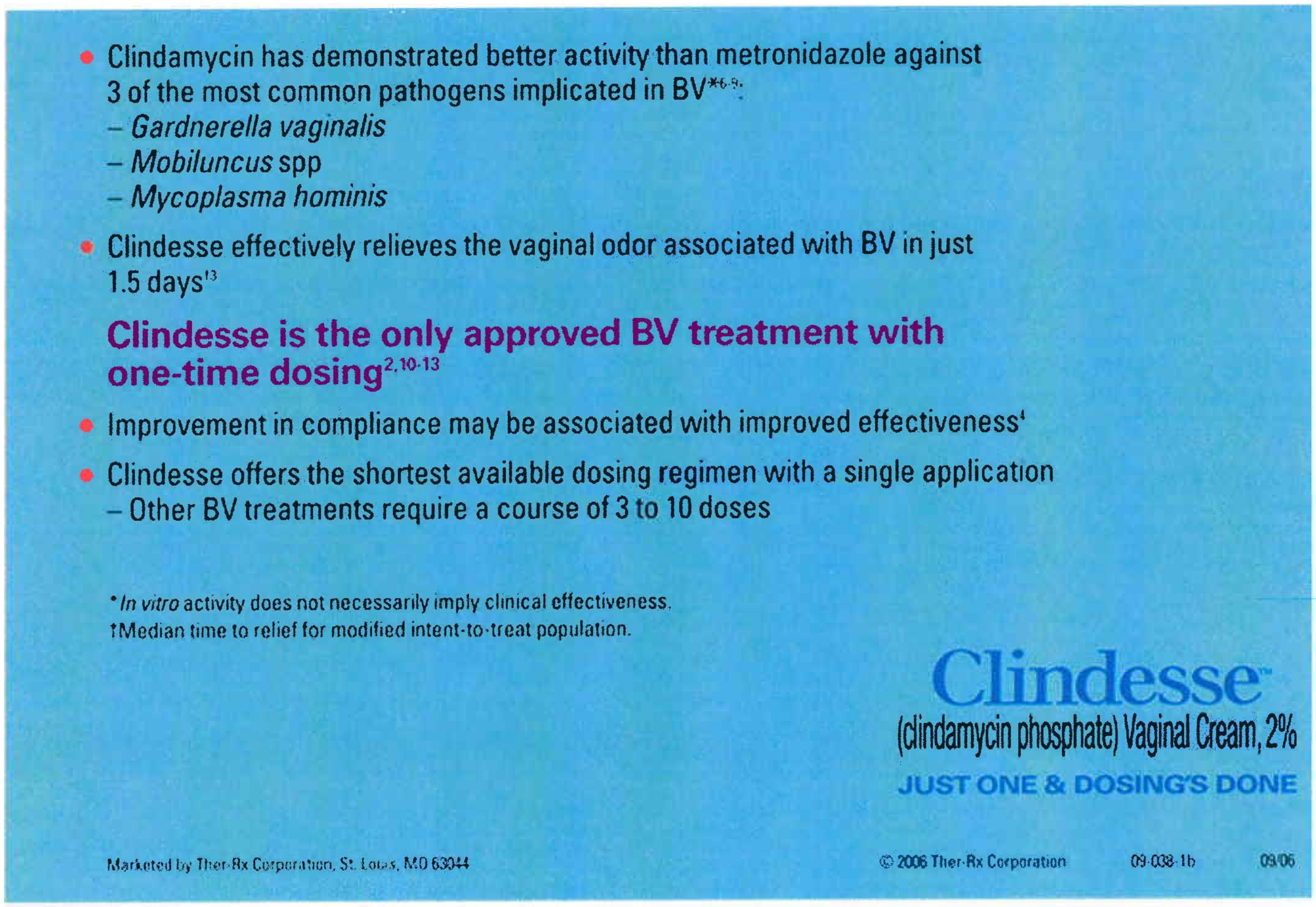
Clindesse™
(clindamycin phosphate) Vaginal Cream, 2%
JUST ONE & DOSING'S DONE

Just one & dosing's done

Clindesse™ delivers 88% efficacy and one-dose convenience[1,2]



Current CDC guidelines recommend evaluating BV based on resolution of 3 of 4 Amsel criteria.[3]
Multicenter, randomized, parallel-group study of patients with BV. 128 Clindesse patients were evaluated from the per-protocol population.[1]



Clindesse™ (clindamycin phosphate) Vaginal Cream, 2% is indicated for the treatment of bacterial vaginosis in non-pregnant wome Clindesse is Pregnancy Category B, which means there are no adequate and well-controlled studies in pregnant women. Therefor Clindesse should be used during pregnancy only if clearly needed.

Clindesse is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of thi vaginal cream, and in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

Important safety information for use of Clindesse:

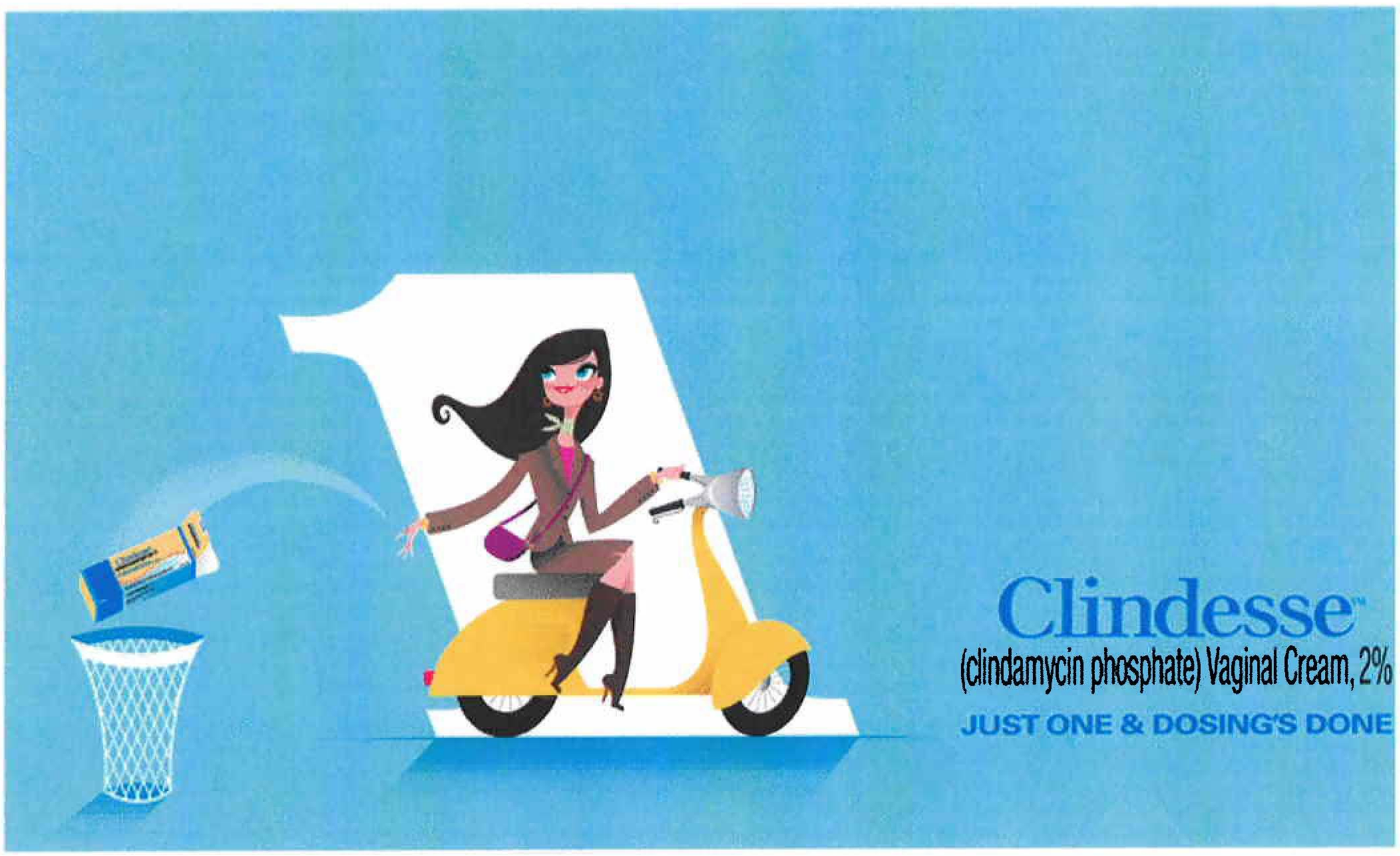
This cream contains mineral oil that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms Therefore, the use of such barrier contraceptives is not recommended concurrently or for 5 days following treatment with Clindesse. During this time period, condoms may not be reliable for preventing pregnancy or for protecting against transmission of HIV and other sexually transmitted diseases.

[redacted]

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin. Orally and parenterally administered clindamycin has been associated with severe colitis. Therefore, it is important to consider this diagnosis in patients wh present with diarrhea subsequent to the administration of Clindesse, even though there is minimal systemic absorption of clindamycin the vagina with administration of Clindesse Vaginal Cream.

In clinical trials (n=368), 1.6% of patients discontinued therapy due to adverse events. The most frequently reported adverse events we vaginosis fungal (14.1%), vulvovaginal pruritus (3.3%), and headache (2.7%).

References: 1. Faro S, Skokos CK. The efficacy and safety of a single dose of Clindesse™ vaginal cream versus a seven-dose regimen of Cleocin® vaginal cream in patie with bacterial vaginosis. *Infect Dis Obstet Gynecol.* 2005;13:155-160. **2.** Clindesse™ (clindamycin phosphate) Vaginal Cream prescribing information, Ther-Rx Corporation **3.** Data on file, Ther-Rx Corporation. **4.** Merabet J, Thompson D, Levinson RS. Advancing vaginal drug delivery. *Expert Opin. Drug Deliv.* 2005;2:769-777. **5.** Centers for Disc Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines. *MMWR Morb Mortal Wkly Rep.* 2002;51:42-44. **6.** Wilson J. Managing recurrent bacte vaginosis. *Sex Transm Infect.* 2004;80:8-11. **7.** Ugwumadu A, Manyonda I, Reid F, Hay P. Effects of early oral clindamycin on late miscarriage and preterm delivery in asymptor women with abnormal vaginal flora and bacterial vaginosis: a randomized controlled trial. *Lancet.* 2003;261:983-988. **8.** Hillier S, Krohn MA, Watts H, Wolner-Hanssen P, Eschenbach D. Microbiologic efficacy of intravaginal clindamycin cream for the treatment of bacterial vaginosis. *Obstet Gynecol.* 1990;76:407-413. **9.** Smayevsky J, Cani Lanza A, Bianchini H. Vaginal microflora associated with bacterial vaginosis in nonpregnant women: reliability of sialidase detection. *Infect Dis Obstet Gynecol.* 2001;9:1 **10.** MetroGel-Vaginal® (metronidazole vaginal gel) prescribing information, 3M Pharmaceuticals. **11.** Cleocin® (clindamycin phosphate vaginal cream) prescribing informat Pharmacia & Upjohn Company. **12.** Cleocin® Vaginal Ovules (clindamycin phosphate vaginal suppositories) prescribing information, Pharmacia & Upjohn Company. **13.** Flagyl® ER (metronidazole extended release tablets) prescribing information, G.D. Searle.



Clindesse™
(clindamycin phosphate) Vaginal Cream,* 2%

Rx Only
FOR INTRAVAGINAL USE ONLY
NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE

Brief Summary – See package insert for full prescribing information.

DESCRIPTION
Clindesse™ is a semi-solid, white cream, which contains clindamycin phosphate, USP, at a concentration equivalent to 20 mg clindamycin base per gram. The cream also contains edetate disodium, glycerol monoisostearate, lecithin, methylparaben, microcrystalline wax, mineral oil, polyglyceryl-3-oleate, propylparaben, purified water, silicon dioxide and sorbitol solution.

*Does not comply with the pH test of the USP monograph for clindamycin phosphate vaginal cream.

INDICATIONS AND USAGE
Clindesse™ is indicated for the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis) in non-pregnant women. There are no adequate and well-controlled studies of Clindesse™ in pregnant women.

Note: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, e.g., *Trichomonas vaginalis*, *Chlamydia trachomatis*, *N. gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus, should be ruled out.

CONTRAINDICATIONS
Clindesse™ is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of this vaginal cream. Clindesse™ is also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

WARNINGS
This cream contains mineral oil that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, the use of such barrier contraceptives is not recommended concurrently or for 5 days following treatment with Clindesse™. During this time period, condoms may not be reliable for preventing pregnancy or for protecting against transmission of HIV and other sexually transmitted diseases.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally and parenterally administered clindamycin, as well as with topical (dermal) formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of clindamycin, even though there is minimal systemic absorption of clindamycin from the vagina with administration of Clindesse™ cream.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.

PRECAUTIONS
General
Clindesse™ contains ingredients that will cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water and consult your physician.

The use of clindamycin may result in the overgrowth of nonsusceptible organisms in the vagina. In clinical studies involving a total of 368 women who received a single administration of Clindesse™, a vaginal fungal infection was diagnosed in 14.1% of women throughout the studies.

Information for the Patient
The patient should be instructed not to engage in vaginal intercourse, or use other vaginal products (such as tampons or douches) during treatment with this product.

Nursing Mothers
Clindamycin has been detected in human milk after oral or parenteral administration. It is n known if clindamycin is excreted in human milk following the use of vaginally administered clindamycin phosphate.

Because of the potential for serious adverse reactions in nursing infants from clindamycin ph a decision should be made whether to discontinue nursing or to discontinue the drug, taking account the importance of the drug to the mother.

Pediatric Use
The safety and efficacy of Clindesse™ in the treatment of bacterial vaginosis in post-menarchal females have been established on the extrapolation of clinical trial data fr adult women. The safety and efficacy of Clindesse™ in premenarchal females have n been established.

Geriatric Use
Clinical studies with Clindesse™ did not include sufficient numbers of subjects 65 years of ag older to determine whether they respond differently than younger subjects. Other reported cl experience has not identified differences in responses between the elderly and younger patie

ADVERSE REACTIONS
Clinical Trials
In clinical trials totaling 368 women treated with a single dose of Clindesse™, 1.6% of the pa discontinued therapy due to adverse events. Medical events judged to be definitely related, p related, or possibly drug-related were reported for 10.6% of the patients after receiving a sin of Clindesse™ and in 17.6% of patients treated with placebo. Adverse events occurred in 12 368 patients (34.2%) treated with Clindesse™ and in 32 of 85 patients (37.6%) treated with p Events occurring in ≥ 1% of patients receiving Clindesse™ in 3 clinical studies are shown in T

Table 1. All Adverse Events Reported in ≥ 1% of Patients Receiving Clindesse™ in Clinical Studies

Adverse Event	Clindesse N=368 n (%)	Placebo N=85 n (%)
Any adverse event	126 (34.2)	32 (37.6)
Vaginosis fungal NOS	52 (14.1)	7 (8.2)
Vulvovaginal pruritus	12 (3.3)	3 (3.5)
Headache NOS	10 (2.7)	2 (2.4)
Constipation	4 (1.1)	0 (0)
Nasopharyngitis	4 (1.1)	0 (0)
Back pain	6 (1.6)	1 (1.2)
Nausea	5 (1.4)	3 (3.5)
Urinary tract infection NOS	4 (1.1)	0 (0)
Vaginal discharge	4 (1.1)	2 (2.4)

N = number of patients in intent-to-treat population
n (%) = number and percentage of patients with reported adverse event
NOS = not otherwise specified

Other events not necessarily related to Clindesse™ but reported by < 1% of these women treated with Clindesse™:
Dermatologic: dermatitis, dry skin, pruritic rash
Gastrointestinal: diarrhea, dyspepsia, flatulence, hemorrhoids, vomiting
General: fatigue, pain, pyrexia, increased tendency to bruise, palpable lymph node
Immune System: hypersensitivity, food allergy
Infections: bladder infection, fungal infection, Herpes simplex, influenza, papilloma virus infection, sinusitis, tooth abscess, upper respiratory tract infection, vaginal infection, vulvovaginal trichomoniasis
Musculoskeletal: arthralgia, myalgia, neck pain, sciatica
Nervous System: dizziness, hypoesthesia
Psychiatric: anxiety disorder
Renal and Urinary Tract: bladder spasm
Reproductive System: pregnancy, cervical dysplasia, dysfunctional uterine bleeding, dysmen intermenstrual bleeding, pelvic pain, uterine cervical disorder, uterine spasm, vaginal burning irritation, atrophic vaginitis, vulvar erythema, vulvar laceration, vulvitis, vulvovaginal discomfo vulvovaginal dryness, vulvovaginitis
Respiratory Tract: cough, epistaxis, pharyngitis, rhinorrhea, sinusitis, wheezing

Other Clindamycin Formulations
Clindesse™ Vaginal Cream affords minimal peak serum levels and systemic exposure (AUCs) clindamycin compared to an oral or intravenous dose of clindamycin. Although these lower l exposure are less likely to produce the common reactions seen with oral clindamycin, the po of these and other reactions cannot be excluded presently. Data from well-controlled trials di comparing clindamycin administered orally to clindamycin administered vaginally are not ava

The following adverse reactions and altered laboratory tests have been reported with the ora **parenteral use of clindamycin:**

Gastrointestinal: Abdominal pain, esophagitis, nausea, vomiting, diarrhea, pseudomembranc (see WARNINGS)

The patient should also be advised that this cream contains mineral oil that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, the use of such barrier contraceptives is not recommended concurrently or for 5 days following treatment with Clindesse™. During this time period, condoms may not be reliable for preventing pregnancy or for protecting against transmission of HIV and other sexually transmitted diseases (see **WARNINGS**).

Drug Interactions
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative. Fertility studies in rats treated orally with up to 300 mg/kg/day (31 times the human exposure based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects
Pregnancy Category B
There are no adequate and well-controlled studies of Clindesse™ in pregnant women. Clindesse™ should be used during pregnancy only if clearly needed.

Another intravaginal formulation containing 2% clindamycin phosphate has been studied in pregnant women during the second trimester. In women treated for seven days, abnormal labor was reported in 1.1% of patients who received that clindamycin vaginal cream formulation compared with 0.5% of patients who received placebo.

Reproduction studies have been performed in rats and mice using oral and parenteral doses of clindamycin up to 600 mg/kg/day (62 and 25 times, respectively, the maximum human exposure based on mg/m²) and have revealed no evidence of harm to the fetus due to clindamycin. In one mouse strain, cleft palates were observed in treated fetuses; this outcome was not produced in other mouse strains or in other species and is, therefore, considered to be a strain specific effect.

(see **WARNINGS**).
Hematopoietic: Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindam therapy could be made in any of these reports.
Hypersensitivity Reactions: Maculopapular rash, vesiculobullous rash, and urticaria have bee observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are most frequently reported of all adverse reactions. Rare instances of erythema multiforme, so resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few case anaphylactoid reactions have been reported.
Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.
Musculoskeletal: Rare instances of polyarthritis have been reported.
Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed i rare instances.

OVERDOSAGE
Vaginally applied clindamycin phosphate vaginal cream 2% could be absorbed in sufficient a to produce systemic effects (see **WARNINGS** and **ADVERSE REACTIONS**).

DOSAGE AND ADMINISTRATION
The recommended dose is a single applicaterful of Clindesse™ (approximately 5 g of vaginal containing approximately 100 mg of clindamycin phosphate) administered once intravaginall time of the day.

HOW SUPPLIED
Clindesse™ (clindamycin phosphate) Vaginal Cream, 2%, is available in cartons containing o dose, pre-filled disposable applicator (NDC 64011-124-08). Each applicator delivers approxi 5 grams of vaginal cream containing approximately 100 mg of clindamycin phosphate.

Store at controled room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86 USP Controlled Room Temperature.] Avoid heat above 30°C (86°F).

U.S. Patent No. 5,266,329; Other patents pending.

Marketed by Ther-Rx Corporation
St. Louis, MO 63044 09-005 1