Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product concerned (brand names):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.2
Date of final sign off	05 June 2014		

LIST OF ABBREVIATIONS

Abbreviation	Term
AAD	antibiotic-associated diarrhea
AUC	area under the (time-concentration) time curve
BV	bacterial vaginosis
CDAD	*Clostridium difficile*-associated diarrhea
CDI	*Clostridium difficile* infection
C. difficile	*Clostridium difficile*
CEU	Clinical Effectiveness Unit
CI	confidence interval
Cmax	maximum concentration
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
g	gram
GVP	Guideline on Good Pharmacovigilance Practices
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IMS	Intercontinental Marketing Services
IIP	International Infections in Pregnancy
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NDA	New Drug Application
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PhV	pharmacovigilance
PIL	patient information leaflet
PL	package leaflet
PMC	pseudomembranous colitis
PT	Preferred Term
RMP	Risk Management Plan
ROW	rest of the world
RR	relative risk
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
STD	sexually transmitted disease
STI	sexually transmitted infection
tRNA	transfer ribonucleic acid
US	United States
VVC	vulvovaginal candidiasis
WBC	white blood cell or white blood cell count
WHO	World Health Organization

PART I: PRODUCT OVERVIEW

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
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Data lock point for current RMP	31 July 2013	Version number	1.2
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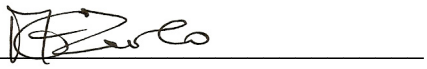
Administrative Information on the RMP

Part	Module/Annex	Date Last Updated for Submission (Sign Off Date)	Version Number of RMP When Last Submitted or Not Applicable
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	26 November 2013	1.0
	SII Non-clinical part of the safety specification	Not applicable	Not applicable
	SIII Clinical trial exposure	Not applicable	Not applicable
	SIV Populations not studied in clinical trials	Not applicable	Not applicable
	SV Post-authorisation experience	26 November 2013	1.0
	SVI Additional EU requirements for the safety specification	30 April 2014	1.1
	SVII Identified and potential risks	05 June 2014	1.2
	SVIII Summary of the safety concerns	30 April 2014	1.1
Part III Pharmacovigilance Plan		30 April 2014	1.1
Part IV Plan for Post-Authorisation Efficacy Studies		26 November 2013	1.0
Part V Risk Minimisation Measures		30 April 2014	1.1
Part VI Summary of RMP		30 April 2014	1.1
Part VII Annexes	**ANNEX 2** Current or proposed SmPC/PIL	26 November 2013	1.0
	ANNEX 3 Worldwide marketing status by country	26 November 2013	1.0
	ANNEX 4 Synopsis of clinical trial programme	Not applicable	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not applicable	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	Not applicable
	ANNEX 8 Protocols for studies in Part IV	Not applicable	Not applicable

Part	Module/Annex	Date Last Updated for Submission (Sign Off Date)	Version Number of RMP When Last Submitted or Not Applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable
	ANNEX 11 Mock up examples	Not applicable	Not applicable
	ANNEX 12 Other supporting data	05 June 2014	1.2

QPPV name	MariaGrazia Zurlo, MD
QPPV signature	
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Overview of versions:

Version number of last agreed RMP:

Version number	Not applicable
Agreed within	Not applicable

Current RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Submitted Within
1.1	16 May 2014	IE/H/119/01/II/27

Invented names in the European Economic Area (EEA)	Cleocin Dalacin
Authorisation procedure	Mutual Recognition Procedure
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	Clindamycin phosphate is a lincosamide antibiotic which inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.
Indication in the EEA	Clindamycin phosphate vaginal ovule is indicated for the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis).
Posology and route of administration in the EEA	The recommended dose is one ovule intravaginally at bedtime for three consecutive days.
Pharmaceutical form and strength	Clindamycin phosphate equivalent to 100 mg clindamycin. Semisolid, white to off-white pessaries.

Country and date of first authorisation worldwide	Ireland	21 December 1998
Country and date of first launch worldwide	Sweden	16 October 1999
Country and date of first authorisation in the EEA	Ireland	21 December 1998

Is the product subject to additional monitoring in the EU? Yes [ ] No [X]

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.0
Date of final sign off	26 November 2013		

Indication

Clindamycin phosphate vaginal ovules is indicated for the treatment of bacterial vaginosis (BV) (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis).

Bacterial vaginosis represents a complex change in vaginal flora characterized by a reduction in the prevalence and concentration of hydrogen peroxide-producing lactobacilli and an increase in the prevalence and concentration of *Gardnerella vaginalis;* mobiluncus species; *Mycoplasma hominis;* anaerobic gram-negative rods belonging to the genera prevotella, porphyromonas, and bacteroides; and peptostreptococcus species.[1]

This Risk Management Plan is specifically focused on clindamycin phosphate vaginal ovules. Clindamycin is also available as capsules, oral solution, and solution for injection for the following indications: infections when caused by susceptible anaerobic bacteria; susceptible strains of gram positive aerobic bacteria such as streptococci, staphylococci, and pneumococci; and susceptible strains of *Chlamydia trachomatis*. The topical solution, lotion, and gel are indicated in the treatment of acne vulgaris.

Brand names of concerned products (with this indication)

Cleocin, Dalacin, Dalacin V

1.1. EPIDEMIOLOGY OF THE DISEASE

The United States National Library of Medicine PubMed database and Google Scholar were searched for primary research and literature reviews in humans between 2000 and 2013. The following search terms were used: Bacterial vaginosis AND (incidence OR prevalence OR risk factors OR mortality OR morbidity). Bacterial vaginosis as the therapeutic search term was selected because it has been widely used and accepted since 1984. A supplementary search on studies published since 2000 using the terms *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, and anaerobic vaginosis did not result in epidemiological findings.

INCIDENCE AND PREVALENCE

Incidence

Literature defining the incidence of BV is sparse, since the condition can be asymptomatic in up to 75% of the women and its natural history is unclear.[2,3]

A longitudinal cohort study published in 2008 identified 773 sexually active, non-pregnant women between the ages of 18 and 30 years without BV at enrollment to investigate risk factors associated with BV during an accumulated 619 woman-years of follow-up.[4] The incidence of BV was 36 cases per 100 woman-years. The incidence of new cases was higher among Black women compared with White women (62.8% versus 28.1%), corresponding to

a hazard ratio (HR) of 2.4 for acquiring BV (95% confidence interval [CI]: 1.8, 3.1). The number of new cases also increased by age groups: 32.5% among women 18 to 20 years, 37.4% among women 21 to 25 years, and 43.4% among women 26 to 30 years.

To identify risks of BV among women who have sex with women, a prospective cohort study was conducted among 199 women aged 16 to 35 years (median age 25 years), free of BV, recruited through media, advertisements and community referrals from October 2003 to December 2006.[5] The women were followed for an average of one year. There were 40 episodes of BV over a total of 172.6 woman-years at risk for an overall incidence of 23 episodes per 100 woman-years. Most of the women (70%) were asymptomatic.

Prevalence

BV is a prevalent vaginal disorder in adult women worldwide.[6] Epidemiologic studies show that the prevalence varies by subject population: 5.8% to 24.4% of pregnant women worldwide,[7] 9.1% among those attending general practices,[8] and 15% to 42% of women attending health clinics[9,10] have been found to be BV-positive.

Global

The International Infections in Pregnancy (IIP) study, a multicenter, international study, enrolled 1466 pregnant women (mean age 26 years) from July 1999 to September 2001, to determine the prevalence of BV and the distribution of associated morphotypes among asymptomatic pregnant women in seven countries.[7] The prevalence ranged from a high of 24.4% in Zimbabwe and 15.6% in Myanmar to a low of 5.9% in Ireland and 5.8% in the US.

A systematic review by Kenyon and colleagues (2013) described the global epidemiology of BV among women to vary by ethnic groups within a country.[11] In the US and UK, BV prevalence was found to be highest in Blacks and lowest in Whites. The highest prevalence was found in southern and eastern Africa: 34% to 58.3% range in South Africa, 38.1% in Botswana, and 34.3% in Uganda. In Eastern Europe, the ranges were between 17.5% in Bulgaria to 28.5% in Poland. In East Asia, the prevalence in China ranged from 5.9% to 51.6%, and 18.2% in Japan.

Detailed study descriptions are given below for large European and US studies.

Europe

A prospective cohort study recruited 1,201 pregnant women presenting before 10 weeks gestation (mean age 31 years) from 32 general practices and five family planning clinics in south London during a two-year period.[12] The prevalence of BV in this group was 14.5%. In another study from UK involving three general practice surgeries that serve a predominantly middle-class population with a low incidence of sexually transmitted diseases, the frequency of BV was lower.[8] Among the 287 women examined in the study (mean age 33 years), the prevalence of BV was 9.1%.

Cauci and colleagues consecutively enrolled 1,486 non-pregnant women aged 40 to 79 years during routine gynecologic examinations in three clinics in northern Italy from 1998 to 2001

to determine the changes in vaginal flora and the prevalence of BV as a function of reproductive condition.[13] The prevalence of BV in premenopausal (n = 328; mean age 45 years), perimenopausal (n = 237; mean age 50 years) and postmenopausal women (n = 921; mean age 57 years) were 9.8%, 11% and 6%, respectively.

To describe the prevalence and age distribution of BV, a study was conducted among a cross-sectional population on the Åland Islands during a 15-year period (1993 to 2008).[14] A total of 3,204 women aged 20 to 60 years provided samples for examination. The prevalence of BV declined from 15.6% in 1993 to 8.6% in 2008. The prevalence was greater in 1993, especially in the age groups of 45 and 50 years. After five years, the greatest prevalence was among 55-year-old women. In 2003 and 2008, the greatest prevalence was among 35-year-old women.

United States

A cross-sectional study enrolled 496 non-pregnant women, aged 18 to 40 years, from one of three healthcare clinics in central Michigan from March through November 1998.[9] The prevalence of BV ranged from 15% to 30% across the three clinics. Depending on the clinic site, the frequency of BV among Black women ranged from 19% to 42%, while the range among White women was 14% to 25%.

Yen and colleagues conducted a cross-sectional study of 1,938 non-pregnant women (mean age 19 years) who were in recruit training for the United States Marine Corps between 1999 and 2000 to estimate the prevalence of BV of both sexually experienced (defined as having had vaginal intercourse at least once) and inexperienced young women.[15] The overall prevalence of BV in the study population was 27%. The prevalence of BV was statistically significant when stratified by sexual experience: 28% among sexually experienced and 18% among those sexually inexperienced (p = .001). The frequency of BV by race was 34% in Native Americans, 32% in Blacks, 30% in Hispanics, 25% in Whites and 11% in Asian/Pacific Islanders.

Koumans and colleagues conducted a cross-sectional study which utilized the National Health and Nutrition Examination Survey (NHANES) 2001–2004, a nationally representative sample of the US civilian non-institutionalized population, to examine symptoms and risk factors for BV.[16] Women aged 14 to 49 years (n = 3,739) were interviewed and provided specimens for the study. The prevalence of BV was 29.2%, which corresponds to 21.4 million women with BV. The prevalence of symptomatic BV was 4.4% while the prevalence of asymptomatic BV was 27.7%. Stratified by age groups, the prevalence among 14- to 19-year-old women was 23.3%, 20- to 29-year-old women 31.1%, 30- to 39-year-old women 28.1%, and 40- to 49-year-old women: 31.3%. Stratified by race, the prevalence among non-Hispanic White women was 23.2%, non-Hispanic Black women 51.4%, and Mexican-American women 31.9%. In addition, another study using the same dataset (NHANES 2001-2004) found an association between race and age: among non-Hispanic White women, the BV prevalence increases with age, and among non-Hispanic Black women, higher prevalences of BV were found in those aged 20 to 49 years.[17]

DEMOGRAPHICS OF THE TARGET POPULATION – AGE, SEX, RACE/ETHNIC ORIGIN

While BV is common among women of reproductive age, information is limited regarding the prevalence of BV in older women.[18] Substantial differences in BV prevalence by race have been reported. Prevalence is higher in Black women and lowest in White women, with Hispanic women having an intermediate prevalence.[15,16,17]

Prevalence of BV among women in the US by age and race, NHANES 2001-2004[17]

Age	White	Black	Hispanic*
14-19 years	16.8	40.2	33.1
20-29 years	23.3	55.4	33.4
30-39 years	22.5	52.4	31.0
40-49 years	26.6	53.4	30.6

Source: Allsworth 2007
* NHANES specifies Mexican-American

RISK FACTORS FOR THE DISEASE

Currently, the risk factors for BV are unknown and reasons for its varying global prevalence are not clear.[11,19] There is substantial debate about whether BV is a sexually transmitted disease.[20,21] A systematic review and meta-analysis of the association between sexual risk factors and BV, found BV to be significantly associated with sexual contact with new and multiple male and female partners, and that decreasing the number of unprotected sexual encounters may reduce incident and recurrent infection.[20] On the other hand, other studies have found a prevalence of BV of 18% to 19% among women who reported never having had sex.[15,16]

Besides sexual behavior, other risk factors include race,[16,22] vaginal douching,[9,23] and dietary factors.[10,24] Recent studies describing the effect-estimate of these risk factors are given below.

Prior research suggests Black women are more likely to have BV compared with White women.[9,15,16,17,22] The NHANES study by Koumans and colleagues described previously reported race as an independent risk factor for BV.[16] The risk of BV among non-Hispanic Blacks was 2.8 times higher compared with non-Hispanic Whites (odds ration [OR]: 2.75; 95% confidence interval [CI]: 2.2, 3.5).

A prospective cohort study, the Longitudinal Study of Vaginal Flora, enrolled 3,620 non-pregnant women between the age of 15 to 44 years (median age 24 years) from 12 health clinics who were followed up for one year, to assess the risk of BV conferred by douching.[23] The risk of BV was 21% higher among women who reported regular douching, compared with those who did not douche (relative risk [RR]: 1.21; 95% CI: 1.08, 1.38). A subset of women (n = 1,521) was evaluated in a cross-sectional analysis to examine the association between diet and the presence of BV.[10] The risk of BV was 50% higher among women with

increased dietary fat intake, compared with other macronutrients (i.e., protein, carbohydrate) (OR: 1.5; 95% CI: 1.1, 2.4).

MAIN TREATMENT OPTIONS

The main treatment options for the treatment of BV are oral/vaginal metronidazole, clindamycin, and tinidazole. Several guidelines on BV recommend these drugs.

Vaginal *Lactobacillus acidophilus* probiotic is also used, but has not demonstrated significant benefit to date. The results of a study that was performed to determine the comparative efficacy of probiotic yogurt and clindamycin in pregnant women showed that probiotics could be as effective and safe as the standard antibiotic therapy.[25] However, in the investigators' conclusions of the study, it was noted that success or failure of treatment in this study was based solely on the patient's symptoms, rather than by objective criteria, and, as such, was a significant limitation of the study.

Combining the recommended first-line therapies of oral metronidazole and vaginal clindamycin, or oral metronidazole with an extended course of a commercially available vaginal *L.acidophilus* probiotic, has not reduced BV.[26]

Guidelines

UK National Guideline for the Management of Bacterial Vaginosis
This guidance recommends oral metronidazole 400 mg twice daily for five to seven days or metronidazole 2 g single dose, or intravaginal metronidazole gel (0.75%) once daily for five days, or intravaginal clindamycin cream (2%) once daily for seven days. Alternative regimens include oral tinidazole 2 g single dose or oral clindamycin 300 mg twice daily for seven days.[27]

New York State Department of Health AIDS Institute
This guidance recommends the following regimen for the treatment of BV in non-pregnant human immunodeficiency virus (HIV)-infected women: metronidazole 500 mg orally twice daily for seven days or metronidazole gel, 0.75%, one full applicator (5 g) intravaginally once a day for five days or clindamycin cream, 2%, one full applicator (5 g) intravaginally at bedtime for seven days. Alternate regimens include clindamycin 300 mg orally twice daily for seven days or clindamycin ovules 100 mg intravaginally once at bedtime for three days.[28]

Note: For the treatment BV in HIV-infected pregnant women, clindamycin cream should not be used; instead, either oral metronidazole or oral clindamycin should be used. Metronidazole 500 mg orally twice daily for seven days, or metronidazole 250 mg orally three times daily for seven days, or clindamycin 300 mg orally twice daily for seven days are recommended regimens for treatment of BV in pregnant HIV-infected women.[28]

Faculty of Sexual & Reproductive Healthcare Clinical Guidance for Management of Vaginal Discharge in Non-Genitourinary Medicine Settings

The Clinical Effectiveness Unit (CEU) guidance recommends oral metronidazole 400 mg twice daily for five to seven days or 2 g single dose for BV. Alternate regimens include intravaginal metronidazole gel (0.75%) once daily for 5 days, or intravaginal clindamycin cream (2%) once daily for seven days, or clindamycin 300 mg capsule twice daily for seven days or tinidazole tablet 2 g single dose. For recurrent infections, oral suppressive therapy with oral metronidazole 400 mg twice daily for three days is recommended at the beginning and end of menstruation.[29] Intravaginal therapy includes metronidazole (0.75%): 5 g applicator twice weekly for four to six months after an initial 10-day course, or lactic acid gel (4.5%), 5 ml tube at night for two to three nights after menstruation.[29]

Women with BV who are pregnant or breastfeeding may use oral metronidazole 400 mg twice daily for five to seven days or intravaginal therapies. In the treatment of non-pregnant women with BV, clindamycin and metronidazole treatments show comparable efficacy in terms of eradication of symptoms, irrespective of dosing regimen or route of administration.[29]

Oral metronidazole is the recommended first-line treatment for BV in the UK because it is less expensive than vaginal preparations and safer than oral clindamycin, which has been associated with pseudomembranous colitis.[29]

For women with recurrent BV, suppressive treatment with metronidazole vaginal gel may be considered.[29]

Compared with clindamycin vaginal cream 5 g per night for seven nights, acidic vaginal gel used for three weeks following tinidazole 2 g stat dose resulted in a higher percentage of women “clinically cured” and with vaginal pH <4.5.[30]

National Guideline for the Management Of Bacterial Vaginosis (2006) Clinical Effectiveness Group, British Association for Sexual Health and HIV
This guidance recommends metronidazole 400 to 500 mg twice daily for five to seven days or metronidazole 2 g single dose. Intravaginal metronidazole gel (0.75%) once daily for five days (A) or intravaginal clindamycin cream (2%) once daily for seven days or oral clindamycin 300 mg twice daily for seven days or oral tinidazole 2 g single dose are recommended as alternative regimens. For women who are allergic to metronidazole, 2% clindamycin cream is recommended.[31]

For recurrent cases:
Suppressive therapy with metronidazole gel 0.75% twice weekly four to six months to decrease symptoms, after an initial daily treatment for 10 days, is being evaluated.[31]

Metronidazole 400 mg orally twice daily for three days at the start and end of menstruation, combined with fluconazole 150 mg as a single dose, is recommended if there is a history of candidiasis also.[31]

A recent observational study reported that Aci-Jel vaginal jelly, used at the time of menstruation and following unprotected sexual intercourse, was associated with a reduction in relapse rate following a course of metronidazole.[31]

Sexually Transmitted Diseases Treatment Guidelines, 2010
Recommended Regimens:
Metronidazole 500 mg orally twice a day for seven days or metronidazole gel, 0.75%, one full applicator (5 g) intravaginally once a day for five days or clindamycin cream, 2%, one full applicator (5 g) intravaginally at bedtime for seven days.[32]

Alternative Regimens:
Tinidazole 2 g orally once daily for two days, or tinidazole 1 g orally once daily for five days, or clindamycin 300 mg orally twice daily for seven days, or clindamycin ovules 100 mg intravaginally once at bedtime for three days.[32]

Small studies of live yogurt or *L. acidophilus* have not demonstrated benefit.[31]

Other treatments being studied at present include the use of combinations of antibiotics with probiotic therapy and hydrogen peroxide.[31]

MORTALITY AND MORBIDITY (NATURAL HISTORY)

Bacterial vaginosis is not a life-threatening condition, but it has been associated with pelvic inflammatory disease, sexually transmitted infections, and various adverse reproductive health outcomes such as spontaneous pre-term birth and miscarriage.[12,33,34,35]

Epidemiological studies have reported a wide range of estimates for BV as a risk factor for HIV acquisition and transmission. A meta-analysis identified 23 published studies since 1995 through 2008 representing a total of 30,739 women.[36] BV was associated with an increased risk of acquiring HIV in HIV incidence studies (RR: 1.61; 95 percent CI: 1.21, 2.13). Among women with BV, the prevalence ORs for HIV acquisition ranged from 0.77 (95% CI: 0.64, 0.93) to 3.70 (95% CI: 1.10, 13.2).

1.2. CONCOMITANT MEDICATION(S) IN THE TARGET POPULATION

Clindamycin or metronidazole or tinidazole are usually prescribed as monotherapy, and there are no concomitant medications that are used in the treatment of BV. However, the use of combinations of antibiotics with probiotics and hydrogen peroxide are being studied.

1.3. IMPORTANT CO-MORBIDITIES FOUND IN THE TARGET POPULATION

BV-affected women are more susceptible to acquiring other sexually transmitted diseases (including HIV and herpes simplex virus).[37]

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PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product concerned (brand names):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.0
Date of final sign off	26 November 2013		

5.1. ACTION TAKEN BY REGULATORY AUTHORITIES AND/OR MARKETING AUTHORISATION HOLDERS FOR SAFETY REASONS

Table 1. Cumulative List -- Clindamycin Phosphate Vaginal Ovules (in reverse chronological order)

Safety Concern 1			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries where clindamycin phosphate vaginal ovules are approved and marketed.	**Patient Labeling** *Countries with active registration of the vaginal ovules presentation were instructed to include the following language concerning directions for use:* Do not use this product if the foiled pouches containing vaginal ovules are torn, opened, or incompletely sealed. *For countries that do not have a patient information leaflet (PIL), countries were instructed to update their Local Product Documents (LPDs) with the information below:* Advise patients not to use this product if the foiled pouches containing vaginal ovules are torn, opened, or incompletely sealed.	In November 2012, a product complaint was reported by a pharmacist in Estonia for Dalacin Ovules who noted that product residue was present on the outside of the foil packaging. The appearance of the defect led to the assumption that the primary package leaked, resulting in a pharmacy level market action for Dalacin ovules, lot number OBTU4.	12 February 2013

Safety Concern 2			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries in the European Economic Area [EEA] where clindamycin phosphate vaginal ovules are approved and marketed.	**4.4 Special warnings and precautions for use** *Text added:* Caution is advised in patients when prescribing Dalacin 100 mg Vaginal Ovule to individuals with Inflammatory Bowel Disease such as Crohn's Disease or Ulcerative Colitis.	Added as a new warning in the Reference Member State (RMS) Summary of Product Characteristics (SmPC).	22 July 2011

Safety Concern 3			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries where clindamycin phosphate vaginal ovules are approved and marketed.	**4.3 Contraindications** *Text added:* Clindamycin vaginal cream and clindamycin vaginal ovules are also contraindicated in individuals with a history of antibiotic-associated colitis.	Added as a new contraindication in the Core Data Sheet (CDS).	21 March 2011

Safety Concern 4			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries where clindamycin phosphate vaginal ovules are approved and marketed.	**4.3 Contraindications** *Text added:* Clindamycin vaginal cream and clindamycin vaginal ovules are contraindicated in patients with a history of hypersensitivity to clindamycin, lincomycin or any of the components of these products.	Added as a new contraindication in the CDS.	27 August 2007

Safety Concern 5			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries where clindamycin phosphate vaginal ovules are approved and marketed.	**4.4 Special warnings and precautions for use, Pediatric Use** *Text added:* Safety and efficacy in pediatric patients have not been established.	Added as a new warning in the CDS.	27 August 2007

Safety Concern 6			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries in the EEA where clindamycin phosphate vaginal ovules are approved and marketed.	**4.3 Contraindications** *Text added:* [Clindamycin is contraindicated in patients with a history of hypersensitivity to…] hard fat (a suppository base consisting of a mixture of glycerides of saturated fatty acid).	Added as a new warning in the RMS SmPC.	01 June 1999

Safety Concern 7			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries in the EEA where clindamycin phosphate vaginal ovules are approved and marketed.	**4.4 Special warnings and precautions for use** *Text added:* Before or after initiation of therapy with clindamycin, other infections including Trichomonas vaginalis, Candida albicans, Chlamydia trachomatis and gonococcal infections may need to be investigated by adequate laboratory tests.	Added as a new warning in the RMS SmPC.	01 June 1999

Safety Concern 8			
Countries	**Action taken**	**Comment**	**Date**
Please see Annex 3 for a list of countries in the EEA where clindamycin phosphate vaginal ovules are approved and marketed.	**4.4 Special warnings and precautions for use** *Text added:* Safety and efficacy studies have not been performed with clindamycin vaginal Ovule in the following populations: pregnant, lactating women, patients with impaired hepatic function, immunodeficient or colitis.	Added as a new warning in the RMS SmPC.	01 June 1999

5.2. NON-STUDY POST-AUTHORISATION EXPOSURE

The post-authorization usage volume (exposure as measured by standard units sold for the 2nd quarter of 2001 through the 1st quarter of 2013) for clindamycin ovules is summarized in Table 2 below.

5.2.1. Method Used to Calculate Exposure

Exposure for clindamycin ovules was calculated from Intercontinental Marketing Services (IMS) MIDAS standard unit data, which contains retail, hospital, and government channels from 63 major markets. Standard units are defined as the number of standard "dose" units sold. This number is determined by taking the number of counting units sold, divided by the standard unit factor, which is the smallest common dose of a product form, as defined by IMS Health. In the case of clindamycin ovules, a standard unit is defined as one ovule. Counting units are determined by multiplying the number of packages sold (units) by the size of the package. In this case, the pack size for clindamycin ovules is three. While data is reported in ovules, conversion to number of packs can be accomplished by dividing the standard units by the aforementioned pack size of three to approximate the treatment cycle.

The exposure distribution by age was approximated using written prescription data provided by IMS Medical Audits. Data by age group is available for 11 major markets over the past three years, through 1Q2013, and is summarized in Table 3.

Clindamycin ovule usage by indication is reported using ICD-10 codes from IMS Medical Audits. ICD-10 codes are created and maintained through the World Health Organization (WHO). Data is available for 24 markets over the past six years and is summarized in Table 4.

Note that data for clindamycin ovules is not available for all markets where the product is sold; standard unit data and age/indication distributions are approximated using information

where available. Distribution by gender is not applicable, as this product is limited to use in the female population.

5.2.2. Exposure

Table 2. Worldwide Clindamycin Ovule Usage – Standard Units in Thousands

	2001*	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013**
Europe	379.80	630.07	716.33	680.55	638.27	604.09	529.60	608.93	572.98	669.77	650.97	665.84	171.21
Spain	162.23	248.02	306.35	334.93	331.27	307.02	312.27	328.25	326.79	333.37	333.36	331.74	84.34
Sweden	45.81	76.22	84.52	79.66	78.00	80.56	85.98	87.77	94.43	111.96	105.91	117.87	33.63
Norway	9.62	27.75	35.21	37.20	40.22	39.17	40.73	43.00	48.25	69.64	70.69	73.69	19.16
Italy	162.14	278.08	290.24	228.66	188.62	176.37	86.06	142.17	93.99	145.45	129.22	128.99	30.44
Latvia	0.00	0.00	0.00	0.00	0.01	0.98	4.55	7.74	9.52	9.36	11.80	13.55	3.65
Slovenia	0.00	0.00	0.00	0.09	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW	1065.53	1563.88	1394.89	1443.43	1238.30	1263.72	1221.85	1257.61	1308.97	1210.40	968.95	932.45	230.70

Source: IMS MIDAS
*Contains data for Q2-Q4 only
**Contains data for Q1 only

Table 3. Usage of Clindamycin Ovules by Age Group

Age Group (in years)	% of Population
17 and below	1.8
18 - 30	41.4
31 - 50	48.4
51 - 64	7.0
65 - 74	0.8
75 and above	0.5
Age Unspecified	0.2

Source: IMS Medical Audit

Table 4. Usage of Clindamycin Ovules by Indication

Indication	% of Population
Other Specified Inflammation of Vagina and Vulva	31.7
Acute Vaginitis	25.0
Inflammatory Disease of Cervix Uteri	9.5
Other Bacterial Infections of Unspecified Site	8.9
Other Specified Noninflammatory Disorders of Vagina	8.5
Noninflammatory Disorder of Vagina, Unspecified	5.7
All Other*	10.7

Source: IMS Medical Audit

*Indications contributing to less than 2% of the population

5.3. POST-AUTHORISATION USE IN POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Review of relevant search results of the Pfizer safety database through 31 July 2013 did not reveal any variation in benefit/risk or any special risks with vaginal ovules in patients over 65 years of age, under 16 years of age, pregnant or breastfeeding women, or in patients who had either hepatic or renal impairment.

5.4. POST-AUTHORISATION OFF-LABEL USE

A comprehensive literature search was conducted through 31 July 2013, and there were no epidemiology studies found providing off-label exposure data. See Part II Module SVI.5 for information from the Pfizer safety database and the published literature regarding off-label use.

5.5. EPIDEMIOLOGICAL STUDY EXPOSURE

A comprehensive literature search was conducted through 31 July 2013, and no epidemiological exposure information for clindamycin ovules was found. There was also no epidemiological exposure information available from studies conducted either in-house or externally.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product concerned (brand names):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.1
Date of final sign off	30 April 2014		

6.1. POTENTIAL FOR HARM FROM OVERDOSE

Systemic overexposure following intravaginal overdosage is highly unlikely with clindamycin phosphate vaginal ovules. Results of a pharmacokinetic study showed that the overall systemic exposure to clindamycin from the ovule is considerably lower (3-fold less based on the area under the concentration-time curve [AUC] and 12-fold less based on the maximum concentration [Cmax]) than that from a single sub-therapeutic 100-mg intravenous dose of clindamycin.[1] Clindamycin vaginal ovules are supplied in individually sealed laminated foil pouches (strip) packed in a box.

The recommended dose in the SmPC and PIL is one ovule intravaginally at bedtime for three consecutive days. Administration of all three ovules in a pack at once (equivalent to 300 mg clindamycin total) could result in an absorbed dose of approximately 90 mg, assuming 30% absorption. This dosage is far lower than what is typically administered in oral (nearly complete [90%] absorption) or parenteral clindamycin therapy (600 to 2700 mg/day for up to 10 days or more).

There were no overdose cases reported in clinical trials. A search of the Marketing Authorization Holder's (MAH's) post-marketing safety database through 31 July 2013 identified no cases reporting overdose or accidental overdose with vaginal ovules. A comprehensive literature search (MEDLINE, BIOSIS, Derwent Drug File, EMBASE) through 31 July 2013 was performed, and no information regarding overdose was identified.

Review of the safety database did not identify any cases reporting accidental oral intake of clindamycin ovules. The proposed Summary of Product Characteristics (SmPC) states that there are no reports of overdose with clindamycin vaginal ovule, and that accidental oral intake of the ovule can lead to effects comparable with those of therapeutic concentrations of orally administered clindamycin.

Review of the cases associated with the use of clindamycin vaginal cream from the safety database did not identify any new overdose safety information relevant to clindamycin vaginal ovules. Given the pharmacokinetic properties of clindamycin vaginal ovules, the potential for clindamycin ovules overdose is negligible.

6.2. POTENTIAL FOR TRANSMISSION OF INFECTIOUS AGENTS

Investigations have been conducted to determine compliance of clindamycin ovules with guidance on minimizing risk of transmission of animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 – rev 3). The medicinal product was found to be compliant.

The bulk drug is packaged within two sealed, linear low-density polyethylene or low-density polyethylene bags in fiberboard drums. Clindamycin vaginal ovules are supplied in individually sealed laminated foil pouches (strip) packed in a carton box, with or without a plastic applicator.

All manufacturing operations are performed in accordance with current Good Manufacturing Practice (GMP) regulations.

6.3. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Given the underlying pharmacological mechanisms of clindamycin vaginal ovules, no potential for misuse for illegal purposes is anticipated. There have been no known reports of drug abuse or drug dependence associated with the use of clindamycin vaginal ovules in clinical trials or in the post-marketing safety database. In the literature, there are currently no reports of misuse for illegal purposes with clindamycin vaginal ovules. Review of the cases associated with the use of clindamycin vaginal cream from the safety database did not identify any significant new safety information relevant to clindamycin vaginal ovules.

6.4. POTENTIAL FOR MEDICATION ERRORS

Review of the literature (MEDLINE, BIOSIS, Derwent Drug File, EMBASE) through 31 July 2013 did not identify any significant new information with regard to clindamycin vaginal ovules and medication error.

Review of the cases from the safety database through 31 July 2013, did not identify any significant medication error information with the ovules.

6.4.1. Description of Medication Errors During the Clinical Trial Programme

There were no obvious medication errors observed in clinical trials.

6.4.2. Preventive Measures for the Final Product Being Marketed

Apart from detailed administration instructions in the product labeling, no preventative measures for the marketed final product are planned.

6.4.3. Effect of Device Failure

Review of the cases from the safety database identified three medication errors associated with applicator malfunction. Of these, one reported that the ovule dropped out, the second case reported that one ovule was stuck in the applicator and shredded into pieces, and the last case reported that the ovules melted in the applicator due to body temperature after repeated attempts at insertion. The patient can choose to insert the ovule into the vagina with the tip of third (middle) finger or with the applicator. Detailed and clear instructions regarding how to use the applicator are in the SmPC and PIL.

6.4.4. Reports of Medication Errors with the Marketed Product(s)

Cumulative data through 31 July 2013 from the safety database indicate that there have been 14 out of 125 clindamycin vaginal ovules cases in which 17 Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) involving medication error with clindamycin ovules were reported. All cases were non-serious. Six cases were medically confirmed.

MedDRA PT Decode (Event)	Total Number of Events
Circumstance or information capable of leading to medication error	1
Drug administration error	4
Drug dispensing error	1
Drug dose omission	2
Drug prescribing error	1
Incorrect dose administered	2
Medication error	1
Poor quality drug administered	2
Underdose	3
Total	**17**

Upon further review, the errors can be categorized as follows.

Product Name(s)				
Description of Error	**Number of Occurrences**	**Analysis of Cause**	**Steps Taken to Prevent**	**Comment**
Ovules crumbled / damaged	5	In four cases, it was reported that the crumbled/damaged ovules were administrated without any other adverse events. In one case, it was unclear whether the patient administered the damaged clindamycin ovule.	Clindamycin Vaginal Ovules are supplied in laminated foil pouches of 3 ovules packed in a box.	None
Drug dose omission / Underdose	6	Within these six cases, three reported drug ineffective or condition aggravated.	The proposed dosage regimen for 100 mg clindamycin phosphate vaginal ovules is one ovule per day, administered intravaginally at bedtime, for three consecutive days. Detailed and clear instructions regarding posology and method of administration are provided in the SmPC and PIL.	None
Physician prescribing/ Dispensing errors	2	Two cases described drug prescribing error or dispensing error (one case each). The drug prescribing error originated from Brazil. A physician prescribed clindamycin vaginal ovules, and the formulation did not exist in Brazil. The case of drug	Clindamycin hydrochloride is available in hard capsule formulation but not in tablet formulation. Clindamycin phosphate vaginal ovules and clindamycin hydrochloride hard capsules are adequately distinguishable. The current Dalacin	None

		dispensing error originated from Spain. The pharmacy dispensed "clindamycin hydrochloride tablets instead of intravaginal ovules to the patient."	Vaginal Ovules and Dalacin C Capsules appearance and package are described in PIL as below: *Dalacin Vaginal Ovules are white to off-white pessaries. They are supplied in laminated foil pouches of 3 ovules packed in a box with or without a plastic applicator.* *Dalacin C Capsules are hard gelatine capsules with an opaque white body and an opaque white cap containing a white to off-white powder. The capsule is imprinted with 'CLIN 150' and 'Pfizer'. Dalacin C Capsules 150mg are available in blister packs of 24 and 100 capsules.*	
Use of contaminated product	1	There was one case described a 53-year-old female who inserted the first and second doses after they fell to the floor. One month later, the patient experienced vaginal discharge and an odor (not further described). The narrative of this case suggested that, according to the consumer reporter, the possibly contaminated ovules could have caused a second infection.	Not applicable.	None
Other patient errors	3	Three errors involved incorrect route of drug administration, wrong drug administered and circumstance or information capable of leading to medication error (one case each). The first case described a patient who inadvertently administrated the ovule via rectal route. No adverse events were reported as a result of this administration. The second case reported that the patient applied clindamycin hydrochloride tablets instead of intravaginal ovules due to the dispensing error by the pharmacy (see drug dispensing error above) and experienced application site itching. The third case involved a patient reporting that the ovules fell out before she was able to lie down.	Detailed and clear instructions regarding posology and method of administration are provided in the SmPC and PIL. The SmPC and PIL instruct the patient to lie on the back with the knees drawn up to the chest and then insert the ovule into the vagina with the tip of third finger or a plastic applicator.	None

Review of the cases associated with the use of clindamycin vaginal cream from the safety database did not identify any significant new safety information relevant to clindamycin vaginal ovules.

Given the overall level of drug utilization, the event counts were low for each medication error category; thus, the potential for medication error with the ovule is also considered low.

6.5. POTENTIAL FOR OFF LABEL USE

Clindamycin vaginal ovule is indicated for the treatment of bacterial vaginosis only. Use in patients below 16 years of age or elderly patients (over 65 years of age), and during the first trimester of pregnancy would be considered off-label.

A search of the safety database through 31 July 2013 identified 18 cases reporting off-label use of clindamycin vaginal ovules.

Two of these 18 cases originated from the EU (i.e., Sweden and Estonia). The first case reported that clindamycin vaginal ovules were administrated to treat mucosal dryness in a 71-year-old patient. The second case reported that clindamycin vaginal ovules were administered to a 68-year-old patient.

Outside of the EU, a total of 16 cases (13 in the United States and three from Israel) reported off-label use. Within these cases, one case was serious (not medically confirmed) and 15 cases were non-serious (five of which were medically confirmed). In the five medically confirmed cases, clindamycin vaginal ovule was administrated for the unapproved indications of use in elderly patients (4), use during the first trimester of pregnancy (1), and cystocele (1). Within the 11 non-medically confirmed cases, clindamycin vaginal ovule was administrated for use in elderly patients (5), use during the first trimester of pregnancy (2), Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Cervix inflammation, Urinary tract infection, Hormone level abnormal (one case each). For the three pregnant patients who received clindamycin ovules in their first trimester, the first case described administration of clindamycin ovules to a pregnant woman at seven weeks who subsequently experienced a blood-colored vaginal secretion. The patient was referred to an emergency center, where a fetal heart rate was detected. The second case involved a pregnant woman who experienced discomfort with the applicator while inserting the ovule. The third case did not report any adverse event with clindamycin ovules administration. No information regarding the pregnancy outcomes were provided in these three cases.

It is unlikely that the clindamycin ovules would be used to treat conditions other than bacterial vaginosis, based solely on review of the safety database.

Literature review of databases (MEDLINE, BIOSIS, Derwent Drug File, EMBASE) through 31 July 2013 was performed, and no information specifically referencing off-label use was identified.

However, there is now a substantial body of evidence associating bacterial vaginosis in pregnancy with poor perinatal outcome, in particular, an increased risk of preterm birth.[2] With this in mind, a recent meta-analysis[3] could influence clinicians to prescribe clindamycin ovules during the first trimester of pregnancy for bacterial vaginosis, or, for that matter, for prophylaxis in general, even though compared with placebo/no treatment, there is, overall, no significant advantage for antibiotics in general to reduce the risk of premature birth.[2] This aforementioned meta-analysis[3] demonstrated that clindamycin administered prior to 22 weeks of gestation was associated with a significantly reduced risk of preterm birth at less than 37 weeks of gestation. However, subgroup analysis indicated that this beneficial effect was only statistically significant for clindamycin oral but not for clindamycin vaginal cream. No study included in this meta-analysis used vaginal ovules. The recent findings[4,5,6,7] suggesting a trend towards a lower incidence of preterm births in a clindamycin (oral, vaginal cream, or both) treatment group compared with placebo/no treatment group could also influence off-label use in pregnancy. It should also be noted that, among these four studies with positive results: 1) the studies by Larsson 2006[5] and Ugwumadu 2003[6] included patients in the first trimester of pregnancy. In Larsson's study, participants recruited were between 10 and 14 weeks of gestational age and treatment was initiated at a mean gestational age of 96 days (weeks 13 + 6, standard deviation [SD] 18 days). In Ugwumadu's study, some patients commenced clindamycin treatment at 12 weeks' gestation; and 2) only the study by Lamont 2003[4] showed a statistically significant reduction in the incidence of preterm birth with treatment with 2% clindamycin vaginal cream when compared with placebo to women with abnormal genital tract flora before 20 weeks' gestation. On the other hand, two earlier studies[8,9] did show a slightly non-statistically significant higher rate of preterm deliveries among women who received vaginal clindamycin than among women who received placebo. Even though the evidence to date seems to be conflicting, the positive findings could still prompt clinicians to prescribe ovules in the first trimester for vaginosis or prophylactically in any trimester.

As noted above, cumulative review of the safety database identified three patients who received vaginal clindamycin ovules in their first trimester of pregnancy. All three cases were reported after the publication of the Lamont study in 2003 and these three cases do not, in and of themselves, suggest that use in the first trimester was prompted by published studies but the potential, although negligible, does exist. Both the SmPC and PIL do not recommend the use of clindamycin vaginal ovules in the first trimester of pregnancy.

6.6. SPECIFIC PAEDIATRIC ISSUES

Use in pediatric patients is not approved.

6.7. CONCLUSIONS

No additional safety concerns have emerged based on the review of information in this module.

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PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

NON-ATMP VERSION

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.2
Date of final sign off	05 June 2014		

7.1. NEWLY IDENTIFIED SAFETY CONCERNS (SINCE THIS MODULE WAS LAST SUBMITTED)

No newly identified safety concerns were observed. However, the important potential risk "Pseudomembranous colitis" has been reclassified as an important identified risk.

7.2. RECENT STUDY REPORTS WITH IMPLICATIONS FOR SAFETY CONCERNS

There are no recent study reports with implications for safety.

7.3. DETAILS OF IMPORTANT IDENTIFIED AND POTENTIAL RISKS FROM CLINICAL DEVELOPMENT AND POST-AUTHORISATION EXPERIENCE (INCLUDING NEWLY IDENTIFIED)

Although this Risk Management Plan is specific for the vaginal ovules, in order to provide context and perspective, the known risks (identified and potential) for all three routes of administration (systemic, topical, vaginal) of clindamycin will be described, with focus on those specific for the ovules. With aspects not exclusively driven by the administration route, a broad overview will be provided.

- Risks relating to the active substance

  Pseudomembranous colitis (PMC) is an important identified risk for all three routes of administration and all finished drug forms. The risk of PMC is well characterized and will be further discussed in section 7.3.2 below, as applicable.

- Risks related to a specific formulation, indication or route of administration

  There are no additional important potential or identified risks for the oral formulation. For the injectable, there is a further potential risk of benzyl alcohol toxicity (as preservative) to premature babies and neonates. For the topical formulations (i.e., solution, lotion, gel), all of which are used to treat acne vulgaris, there are no additional important potential or identified risks. For the vaginal ovules and cream, there is the identified risk for vulvovaginal candidiasis, which is discussed in section 7.3.1 for the ovules. There is the potential risk for unintended pregnancy or sexually transmitted disease due to diminishing efficacy of latex condoms and diaphragms for vaginal ovules which is discussed in section 7.3.3

- Risks relating to a specific target population

  As noted above, benzyl alcohol toxicity is a potential risk with the intravenous formulation for neonates and premature babies.

7.3.1. Important Identified Risk of Vulvovaginal Candidiasis – Vaginal Ovules

Important Identified Risk – Vulvovaginal candidiasis	
Incidence	Incidence was derived primarily from integrated data from three prospective, randomized, comparator-controlled multicenter studies (Protocols M/1114/0001, M/1114/0002, and M/1100/0283), in which clindamycin vaginal ovules were administered once daily for three days in non-pregnant patients with bacterial vaginosis (BV). Vaginal moniliasis was the most frequently reported urogenital medical event, reported by 2.5% (15/589) of patients using ovules; 1.5% (9/589) of vaginal moniliasis cases were considered drug related. In the active comparative group, 0.9% (3/335) of patients receiving clindamycin vaginal cream reported vaginal moniliasis; 0.6% (2/335) of them were considered to be drug-related; 3.0% (6/197) of patients receiving oral metronidazole reported vaginal moniliasis, with 2.0% (4/197) of the cases considered to be drug related. No cases were reported in the placebo group.[1] "Vaginal moniliasis" has been updated to "vulvovaginal candidiasis" to reflect the current MedDRA dictionary (version 16.0) preferred term (PT). Based on the data above, the incidence rate of vulvovaginal candidiasis (VVC), irrespective drug-relatedness, following vaginal ovule administration is categorized as "Common" (≥1/100 and <1/10).
Seriousness/ outcomes	All VVC events reported during clinical trials were non-serious. Moreover, there were three non-serious cases of VVC that were identified via cumulative review of the safety database through 31 July 2013. No information is available on the event outcome.
Severity and nature of risk	Graded severity not available. By nature from a medical perspective, the symptoms of VVC are generally bothersome and rarely severe.
Background incidence/ prevalence	No epidemiologic data were identified for incidence of VVC among women with BV unexposed to clindamycin. Prevalence estimates for diagnosis of both VVC and BV vaginal infections have been reported to vary depending on the study population and presentation of symptoms at diagnosis. A descriptive study conducted among 338 women (mean age 25.8 years), who had not taken antibiotics in the four weeks prior to participation and presented with symptoms of vaginitis who were recruited from a sexually transmitted disease clinic in the southeastern US, observed a 4.4% prevalence of VVC and BV infections.[2] This percentage is based on the definition of VVC and BV infection as presence of patient-reported symptoms (such as odor, vaginal soreness, abnormal vaginal discharge, dyspareunia and dysuria), and of clinical signs (such as vulvar edema, fissures, excoriations, erythema, vaginal discharge, and vulvar pruritis), as well as confirmation of vaginal swab specimen. When the definition was extended to include either patient-reported symptoms or clinical signs, then the prevalence of VVC and BV infections increased to 12.4%. In Nigeria, a descriptive background study examined vaginal swab samples of 1,000 women aged 15 to 35 years at a medical center.[3] Participants were included in the study if they had had sex at least once. The prevalence of a mixed infection consisting of both VVC and BV was 11%.
Risk groups or risk factors	Risk factors or risk groups for VVC included condom use, underlying diabetes or diseases compromising the immune system, history of allergic phenomena, pregnancy, recent antibiotic use, young age, past gonococcal infection, or psychosocial stress.[4 5]
Potential mechanisms	Administration of clindamycin vaginal ovules may result in the overgrowth of nonsusceptible organisms, particularly yeasts.

Important Identified Risk – Vulvovaginal candidiasis	
Preventability	Physician supervision and care.
Impact on individual patient	Vulvovaginal candidiasis could have a significant impact on a patient's quality of life, given the social and physical discomfort that might results from vulvovaginal candidiasis.
Potential public health impact of safety concern	None identified.
Evidence source	Integrated Safety Summary in NDA filing documents, literature, Pfizer safety database.
MedDRA (Version 16.0) terms	System Organ Classes (SOCs): Infections and infestations

7.3.2. Important Identified Risk of Pseudomembranous Colitis – All Formulations

Clostridium difficile, a spore-forming, Gram-positive anaerobic bacillus, has been recognised as an important cause of antibiotic-associated colitis and diarrhea, *C. difficile*-associated diarrhea (CDAD) and PMC.[6,7,8] Antibiotic-associated PMC, the more serious variety of antibiotic-associated colitis, is defined by development of pseudomembranes (necrosis of the mucosa with production of a membranous appearance).[9] It is thought that antibiotic therapy may alter the enteric flora, enabling *C. difficile* to proliferate, which may be proven in about 95% of PMC cases, and produce toxins with cytopathic and hypersecretory effects on the mucosa. *C. difficile*-associated diarrhea and PMC have been reported with nearly all antimicrobial treatment, including clindamycin.

Pseudomembranous colitis is an important identified risk for systemic, topical, and vaginal formulations.

Important Identified Risk – Pseudomembranous colitis	
Incidence	A summary table of the post-marketing experience of PMC events is provided below. The cumulative review of the Pfizer safety database was conducted through 31 July 2013, using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0, with the suspect product generic name clindamycin, and the narrow Standardised MedDRA Query (SMQ) Pseudomembranous colitis, listing route of administration (Table 1).

Table 1. Pseudomembranous colitis SMQ events following systemic, topical, vaginal administration in the clindamycin adverse event reports in the safety database (through 31 July 2013)

MedDRA System Organ Class (SOC)	MedDRA Preferred Term (PT)	Number of events following systemic administration N = 659 (%)	Number of events following topical administration N = 14 (%)	Number of events following vaginal administration N = 19 (%)*
Infections and infestations	Clostridial infection	2 (0.3)	-	-
	Clostridium bacteraemia	-	-	-
	Clostridium colitis	4 (0.6)	-	1 (5.3)
	Clostridium difficile colitis	128 (19.4)	2 (14.3)	9 (47.4)
	Clostridium difficile infection	18 (2.7)	1 (7.1)	-
	Clostridium difficile sepsis	-	-	-
	Gastroenteritis clostridial	2 (0.3)	-	-
	Pseudomembranous colitis	503 (76.3)	11 (78.6)	9 (47.4)
Investigations	*Clostridium* test positive	2 (0.3)	-	-

* Cases followed use of vaginal cream. No clindamycin vaginal ovule cases were identified in the safety database.

Important Identified Risk – Pseudomembranous colitis	
Incidence	**Oral/injectable formulations** No cases of PMC were identified during registration trials in the 1960s. However, since introduction of clindamycin to the market, there was an increasing number of PMC patients in the 1970s, and studies were initiated to determine the incidence of this event. Six studies published in the 1970s and the 1980s[10,11,12,13,14,15] were identified from a literature review. The incidence rates of PMC among patients receiving clindamycin ranged from 0% to 10%, varying on study design, sample size, patient population, and follow-up (see Table 2 below). Therefore, the incidence rate of PMC, irrespective of drug-relatedness, following the systemic (oral/injectable) administration is categorized as "Common" (≥1/100 and <1/10).

Table 2. Summary of pseudomembranous colitis incidence rate in clinical studies

	Study design	**Incidence rate of pseudomembranous colitis among patients receiving clindamycin % (n/N)**
1[10]	From November 1974 through May 1975, adult medical and surgical patients hospitalized at the University of Michigan Medical Center University Hospital (US) who received clindamycin or ampicillin were identified from pharmacy records. The gastrointestinal side effects were collected for a period of up to 6 weeks after therapy was discontinued. Specific formulation information not provided.	1.9 (2/104)
2[11]	A prospective, cooperative study of the incidence of diarrhea and colitis associated with clindamycin therapy in patients at three hospitals in Toronto, Edmonton and Winnipeg (Canada) after May 1975 was conducted. Patients were admitted to the study in the ampicillin-treated group (control group) or the clindamycin-treated group in each institution. Specific formulation information not provided.	2 (7/343)
3[12]	All patients in the hospitals of the Wycombe Health District (UK) who were treated with parenteral clindamycin or lincomycin following oral administration during the period April 1975 to September 1976 were included in the study. All patients were recalled by letter for follow-up after the 18-month period of the study and were interviewed by the nurse. If this contact failed, a questionnaire was sent to the patient. Specific formulation information not provided.	0 (0/280)
4[13]	A prospective study in Barnes Hospital, St. Louis, Missouri (US), from November 1973 to April 1974 was performed in patients receiving oral or parenteral clindamcyin. The patients were interviewed, with special attention given to bowel disease.†	10 (20/200)†
5[14]	One-hundred consecutive adult patients treated with either lincomycin or clindamycin during the period January 1975 to April 1976 were monitored in St. Vincent's Hospital, Fitzroy (Australia). For each subject, a control patient receiving ampicillin was selected. Each patient was monitored for 6 weeks from the day of commencement of therapy. Specific formulation information not provided.	0 (0/4)

Table 2. Summary of pseudomembranous colitis incidence rate in clinical studies		
	Study design	**Incidence rate of pseudomembranous colitis among patients receiving clindamycin % (n/N)**
6[15]	All patients who received oral or parenteral clindamycin from the Surgical Service, Wood (Wis) Veterans Administration Center (US), between July 1975 and January 1977, were followed by a nurse-epidemiologist for at least 30 days or until death.	0 (0/145)

† Fourteen patients received clindamycin alone; six patients also received gentamicin, cloxacillin or ampicillin.

Important Identified Risk – Pseudomembranous colitis	
Incidence	In the Pfizer safety database, there were 658 cases reporting 659 events under the narrow SMQ Pseudomembranous colitis following systemic clindamycin use through 31 July 2013, representing 77% (658/855) of all narrow SMQ Pseudomembranous colitis cases. Approximately 76% (503/658) of the cases following systemic use involved diagnosed PMC. Among all the cases, there were 17 literature reports, including 15 reports of PMC, one report of *C. difficile* infection and one report of *C. difficile* colitis. **Topical formulations** The incidence rate of PMC following topical administration, is "Not known." No PMC cases were identified in the registration trials for the topical presentations. The event was identified based on post-marketing experience. Fourteen cases were retrieved from the Pfizer safety database through 31 July 2013, including three literature cases (two cases of PMC, and one case of *C. difficile* infection).
Incidence	**Vaginal formulations** The incidence rate of PMC is "Not known." No PMC cases were identified in the registration trials for vaginal presentations. The event was identified based on post-marketing experience. Nineteen cases were retrieved through 31 July 2013, including PMC (9), *C.difficile* colitis (9), and *Clostridium* colitis (1). All 19 vaginal cases, including nine cases of PMC, were reported following cream administration. No cases following clindamycin ovule administration were identified in a search using the narrow SMQ Pseudomembranous colitis. Studies were conducted to address the systemic absorption of clindamycin following intravaginal administration of clindamycin vaginal cream and vaginal ovules. These studies have indicated that the average absorption is approximately 4% for the cream and 30% for the ovule. This absorption was, on average, 7-fold greater than that for the 2% clindamycin phosphate vaginal cream. Thus, blood level data do not explain the different safety profile for PMC between the two formulations. It should be noted that systemic exposure to clindamycin from the ovule is still considerably lower (at least 3-fold) than that from a 300 mg oral dose of clindamycin, which is widely approved as a therapeutic dose and is known to be safe.
Seriousness/ Outcomes	PMC may range in severity from mild to life threatening. Table 3, Table 4, Table 5 display the outcome/seriousness of the cases in the safety database following systemic, topical, and vaginal administration, respectively, retrieved through 31 July 2013.

Table 3. Overview of outcome/seriousness of pseudomembranous colitis SMQ cases in the safety database following systemic administration (through 31 July 2013)

Case characteristic		Number of cases following systemic administration		
		All **N (%)** **Total = 658**	**Pseudomembranous colitis** **N (%)** **Total = 503**	**Other** **N(%)** **Total = 155**
Case outcome	Fatal*	129 (19.6)	120 (23.9)	9 (5.8)
	Not-recovered/not resolved	23 (3.5)	15 (3.0)	8 (5.2)
	Recovered/resolved	325 (49.4)	244 (48.5)	81 (52.2)
	Recovered/resolved with sequel	7 (1.1)	5 (1.0)	2 (1.3)
	Recovering/resolving	44 (6.7)	29 (5.8)	15 (9.7)
	No data	1 (0.2)	1 (0.2)	-
	Unknown	129 (19.6)	89 (17.7)	40 (25.8)
Case seriousness	Serious	315 (47.9)	223 (44.3)	92 (59.4)
	Non-serious	92 (14.0)	58 (11.5)	34 (21.9)
	Unknown	251 (38.1)	222 (44.1)	29 (18.7)

* Death was not necessarily a result of pseudomembranous colitis. There were cases with fatal outcome due to other events.

Table 4. Overview of outcome/seriousness of pseudomembranous colitis SMQ cases following topical administration (through 31 July 2013)

Case characteristic		Number of cases following topical administration		
		All **N (%)** **Total = 14**	**Pseudomembranous colitis** **N (%)** **Total = 11**	**Other** **N (%)** **Total = 3**
Case outcome	Not-recovered/not resolved	2 (14.3)	2 (18.2)	-
	Recovered/resolved	7 (50.0)	5 (45.5)	2 (66.7)
	Recovering/resolving	2 (14.3)	1 (9.1)	1(33.3)
	Unknown	3 (21.4)	3 (27.3)	-
Case seriousness	Serious	8 (57.1)	6 (54.5)	2 (66.7)
	Non-serious	4 (28.6)	4 (36.4)	-
	Unknown	2 (14.3)	1 (9.1)	1(33.3)

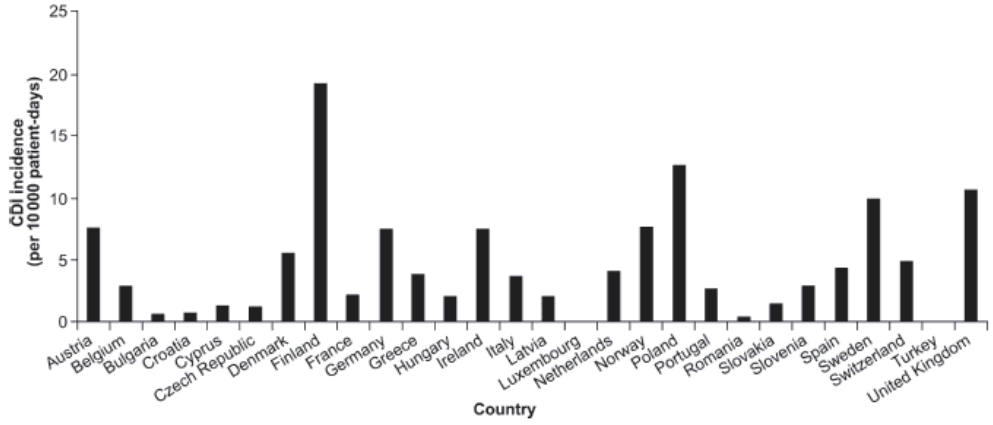
Table 5. Overview of outcome/seriousness of pseudomembranous colitis SMQ cases following vaginal administration (through 31 July 2013)

Case characteristic		Number of cases following vaginal administration		
		All events N (%) Total = 19	**Pseudomembranous colitis N (%) Total = 9**	**Other N (%) Total = 10**
Case outcome	Not-recovered/not resolved	1 (5.3)	-	1 (10.0)
	Recovered/resolved	13 (68.4)	6 (66.7)	7 (70.0)
	Recovering/resolving	1 (5.3)	-	1 (10.0)
	Unknown	4 (21.1)	3 (33.3)	1 (10.0)
Case seriousness	Serious	7 (36.8)	3 (33.3)	4 (40.0)
	Non-serious	7 (36.8)	1 (11.1)	6 (60.0)
	Unknown	5 (26.3)	5 (55.6)	-

Important Identified Risk – Pseudomembranous colitis	
Seriousness/ Outcomes	All fatal cases occurred following systemic administration, accounting for 24.4% (129/529) cases with known outcome of systemic pseudomembranous colitis SMQ cases. The majority of the fatal cases (93.0%, 120/129) reported the PT Pseudomembranous colitis. No fatal cases were reported following topical or vaginal administration. Based on data in the safety database, outcome following topical or vaginal use is more favorable than that following systemic clindamycin, possibly because the baseline status in patients receiving the drug systemically may be more compromised.
Severity and nature of risk	The clinical appearance of CDAD is highly variable, ranging from mild, self-limiting diarrhea, to severe, even fatal, PMC. Pseudomembranous colitis has the gastrointestinal features of diarrhea, abdominal pain, and abdominal distension. Common systemic manifestations include fever, nausea, anorexia, malaise, and dehydration. Sigmoidoscopy or colonoscopy reveals classic pseudomembranes on the colonic mucosa. Fulminant colitis, including fulminant PMC, has been broadly defined as C. difficile colitis, with significant systemic toxic effects and shock, resulting in the need for colectomy. According to a study published in 2009, fatal outcomes occur in approximately 3% to 8% of patients with C. difficile colitis, and there was a marked increase in mortality in the 10 years prior to publication.[16] A study showed that the mortality rate after colectomy for fulminant colitis was 34% to 57%.[17] Similarly, the overall surgical mortality of fulminant PMC was 47% in a retrospective study.[18]

Important Identified Risk – Pseudomembranous colitis	
Background Incidence/ Prevalence	The incidence of antibiotic-associated diarrhea (AAD) varies from 5% to 25%, irrespective of specific antibiotic. Broad-spectrum antibiotics, and those targeting anaerobic flora are more likely to cause diarrhea than other antibiotics. *C. difficile*-associated diarrhea and *C. difficile* colitis account for about 20% of AAD cases.[19] A retrospective, hospital-based, case-control study showed that some antibiotics were associated with a significantly increased risk of acquiring CDAD, notably clindamycin, third-generation cepholosporins and carbapenems.[20] Rates of *C. difficile* infection (CDI) have been increasing since 2000, especially for those elderly with a recent hospitalization or for those residing in a long-term care facility. In the US, carriage of *C. difficile* occurs in 5% to 15% of healthy adults, but may be as high as 84.4% in newborns and healthy infants, and up to 57 % in residents in long-term care facilities.[21] The incidence of CDI in Quebec increased from 35.6 cases per 100,000 in 1991, to 156.3 cases per 100,000 in 2003.[22] The number of cases in the US increased from 82,000 in 1996 to 178,000 in 2003.[23] Recently, it has been estimated that there are approximately 500,000 cases of CDI per year in the US. Moreover, CDI has a significant mortality impact 15,000 to 20,000 patients die annually from CDI in the US.[24, 25] Historically, rates of CDI in Europe have been broadly similar to those reported in the US, although surveillance for CDI has been more variable across Europe.[26] To address deficiencies in CDI reporting across Europe, a pan-European hospital-based survey of CDI was carried out in November 2008 to obtain a more complete overview of CDI in Europe and to build capacity for improved diagnosis and ongoing surveillance.[27] The survey, which covered up to six hospitals in each of the 34 countries surveyed and included data on 395 *C. difficile* isolates, showed that CDI remains a predominantly nosocomial infection in Europe, with 80% of cases being acquired in hospitalized patients as compared with 14% in the community, and 6% being of indeterminate origin. The incidence of CDI varied widely across Europe (as did rates of testing for CDI), with a mean incidence of nosocomial cases of 4.1 cases per 10,000 patient-days (range: 0.0–36.3). The measured incidence of CDI was relatively low in Spain, France, and Italy, but very much higher in Scandinavia, Ireland, and the UK (Figure 1). This survey showed that the overall mortality rate was 22%, with CDI being directly responsible for 2% of all hospital deaths and a contributor to death in an additional 7% of cases. As stated above, fulminant colitis, including fulminant PMC, is the most severe form of CDAD, with a mortality rate exceeding 40%.[17 18] No epidemiologic data were identified for the incidence or prevalence of PMC among women with BV who were not exposed to clindamycin.

Figure 1. The measured incidence of *Clostridium difficile* infection across Europe in 2008 (adapted from Bauer et al)



Risk Groups or Risk Factors	PMC/CDI/CDAD can occur after a single dose of antibiotics; the risk increases with longer duration of antibiotic therapy and/or continuous administration of antibiotics. The total number of antibiotics administered is also a risk factor. Hospitalization, especially the number of hospitalizations and duration thereof, is another important risk factor. A population-based study in Sweden showed that the incidence of positive assays for *C. difficile* toxin in people who were older than 60 years was 20 to 100 times higher than the incidence in those who were aged 10 to 20 years.[28] The increased incidence in the elderly may be related to increased length of stay and a greater likelihood of exposure to *C. difficile* if hospitalized as well as more severe underlying illnesses in this population.[29] The rate of *C. difficile* acquisition is also estimated to be 13% in patients with hospital stays of up to two weeks and 50% in those with hospital stays longer than four weeks.[30] A retrospective study of 150 consecutive patients admitted to the hospital from 2000 to 2004 was conducted in Korea to investigate the clinical risk factors for PMC among patients with presumed AAD.[31] Two clinical parameters that could be readily available to clinicians and were associated with an increased risk of PMC were: 1) advanced age, older than 70 years (adjusted odds ratio [OR]: 2.7; 95% confidence interval [CI]: 1.2-6.1), and 2) long hospital stay of more than 20 days (adjusted OR: 5.1; 95% CI: 2.1-12.3). When both risk factors were present, the positive predictive value for PMC was 0.86. Therefore, PMC should be first suspected in cases with presumed AAD having such risk factors.

Potential Mechanisms	*C. difficile* is a spore-forming, Gram-positive anaerobic bacillus acquired through the ingestion of spores, usually transmitted from other patients through the hands of healthcare personnel or from the environment. In general, as stated above, CDI is responsible for virtually all cases of PMC, and, as noted above, for up to 20% of cases of AAD.[19] Clindamycin is mainly excreted in bile leading to a very high concentrations in feces. The clinical significance of this excretion pathway, as it relates to overgrowth of non-susceptible organisms, was demonstrated in a study in healthy volunteers, where following the oral administration of clindamycin for seven days, *C. difficile* was isolated in seven of the 10 participants and three of the strains were toxin-positive following the oral administration of clindamycin for seven days.[32 33] Disruption of normal gut flora, typically by exposure to antimicrobials, allows *C. difficile* to proliferate, causing a broad spectrum of clinical manifestations that can range from asymptomatic carriage, to diarrhea of varying severity, to fulminant PMC and death. The virulence is conferred primarily by two large exotoxins, toxins A and B. In addition to these two toxins, some strains produce a third toxin known as binary toxin. Its role in the pathogenesis of *C. difficile* colitis remains unclear; however, the presence of this toxin in a previously rare and more virulent strain, BI/NAP1/027, has raised concerns about its synergism with toxins A and B in causing severe colitis.[34]
Preventability	The "Warnings and precautions for use" section in the clindamycin systemic (oral, injectable) Summary of Product Characteristics (SmPC) describes the risk of PMC and CDAD, including its etiology, clinical significance and manifestations, enteric precautions in patients with diarrhea, and management. The SmPC of clindamycin vaginal ovules provides the warning text for PMC clinical significance and management, as appropriate. It is important to consider the diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Control and prevention of antibiotic-associated CDAD and PMC in hospitals can be divided into two broad approaches: a restrictive approach to antimicrobial use (primary prevention) and preventing transmission of *C. difficile* to patients (secondary prevention).[35] It has been recommended that hospitals have clear and precise guidelines regarding antimicrobial use and restrict "high-risk" agents during outbreaks. It has been demonstrated that restricting the use of high-risk antimicrobials is an effective way of reducing the incidence of CDAD.[36] Suggested guidelines for hospitals to prevent the spread of CDI include education of all staff about *C. difficile*, hand hygiene, barrier precautions, and single-use disposable equipment.[21] Clindamycin topical (lotion, solution, gel) and vaginal (cream, ovule) presentations are contraindicated in individuals with history of antibiotic-associated colitis. It has been demonstrated that CDI has increased significantly in patients with inflammatory bowel disease (IBD).[37] The impact could be especially significant for the individual patient who is to be treated for a seemingly mild disorder such as BV, but who has an IBD history. Therefore, the SmPC of vaginal ovules states that caution is advised in patients when prescribing vaginal ovules to individuals with IBD, such as Crohn's disease or ulcerative colitis.
Impact on Individual Patient	CDAD can range from mild, self-limiting diarrhea, to severe, even fatal, PMC.

Potential Public Health Impact of Safety Concern	Antibiotic associated CDI, with subsequent CDAD and PMC, is a global problem. CDAD has increased in frequency and severity throughout North America and Europe over the last several years, largely due to the emergence of the NAP1 epidemic strain of *C. difficile*.[34] Institutions require accurate and rapid diagnostics for early detection of cases and possible outbreaks, in order to initiate specific therapy and implement early and effective infection control. However, it would be expected that PMC is infrequent with clindamycin vaginal ovule use, and that the potential public health impact with this clindamycin formulation would be minimal.
Evidence source	Literature and Pfizer safety database.
MedDRA (version 16.0) Terms	Narrow SMQ Pseudomembranous colitis, including Clostridial infection, *Clostridium* bacteraemia, *Clostridium* colitis, *Clostridium difficile* colitis, *Clostridium difficile* infection, *Clostridium difficile* sepsis, *Clostridium* test positive, Gastroenteritis clostridial, Pseudomembranous colitis.

7.3.3. Important Potential Risk of Weakening of Latex Condoms and Diaphragms – Vaginal Ovules

Important Potential Risk – Weakening of latex condoms and diaphragms	
Incidence	Not known.
Seriousness/ outcomes	No cases of sexually transmitted disease or unintended pregnancy because of diminished efficacy of latex condoms or diaphragms were identified via cumulative review of the safety database through 31 July 2013.
Severity and nature of risk	Potential for transmission of a sexually transmitted disease: Graded severity not available. By nature, this is a severe event. Potential for unintended pregnancy: Graded severity not available. By nature, this event has the potential to be severe, depending on individual patient circumstances.
Background incidence/ prevalence	No epidemiologic data were identified for incidence or prevalence of unintended pregnancy or sexually transmitted disease due to diminishing efficacy of latex condoms and diaphragms among women with BV unexposed to clindamycin.
Risk groups or risk factors	None identified.
Potential mechanisms	Latex condoms and diaphragms may be weakened if exposed to the suppository base used in clindamycin ovules. Given these circumstances, unintended pregnancy or transmission of a sexually transmitted disease may occur. *In vitro* testing indicated that latex condoms may be weakened if exposed to the suppository base used in clindamycin vaginal ovules. Negative effects on tensile strength were observed under extreme conditions: each condom tested was exposed to 16 to 20 ovules at 40°C for 4 days. Although the testing was extreme, a warning statement regarding use of condoms and diaphragms during clindamycin vaginal ovules treatment is included in the labeling.[38]

Important Potential Risk – Weakening of latex condoms and diaphragms	
Preventability	Section 4.4, "Special warnings and precautions for use" of the SmPC states that: "As with all vaginal infections, sexual intercourse during treatment with Dalacin Vaginal Ovule is not recommended. Latex condoms and diaphragms may be weakened if exposed to the suppository base used in Dalacin Vaginal Ovules. The use of such products within 72 hours following treatment with Dalacin Vaginal Ovules is not recommended, as such use could be associated with diminished contraceptive efficacy or protection against sexually transmitted disease." Section 6.2, "Incompatibilities" of the SmPC states that the use of latex condoms is not recommended during therapy with Dalacin Vaginal Ovules.
Impact on individual patient	Sexually transmitted disease could have a significant impact on a patient's quality of life, given the associated medical and pharmacological treatment required. An unintended pregnancy could have a situation-dependent impact.
Potential public health impact of safety concern	None identified.
Evidence source	Literature and Pfizer safety database.
MedDRA terms	System Organ Classes (SOCs): 1) Pregnancy, puerperium and perinatal conditions, and 2) Infections and infestations

7.4. IDENTIFIED AND POTENTIAL INTERACTIONS

7.4.1. Overview of Potential for Interactions

Studies were conducted to address the systemic absorption of clindamycin following intravaginal administration of clindamycin vaginal cream and vaginal ovules. These studies have indicated that the average absorption is approximately 4% for the cream and 30% for the ovule. Nevertheless, systemic exposure to clindamycin from the ovule is substantially lower than the systemic exposure from therapeutic doses of oral clindamycin hydrochloride (two-fold to 20-fold lower) or parenteral clindamycin phosphate (40-fold to 50-fold lower).

No drug-drug interaction studies were performed for vaginal formulations. No evidence of interactions was observed in any of the clinical studies of intravaginal clindamycin. No systemic drug interactions are known or anticipated with clindamycin vaginal cream or vaginal ovules. No information is available on the concomitant use of other vaginal medications with clindamycin vaginal formulations.

7.4.2. Important Identified and Potential Interactions

Interaction with neuromuscular blocking agents

When administered systemically during general anesthesia, clindamycin phosphate 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.[39,40]

This is not expected to be a concern with vaginal cream or vaginal ovule treatment due to the low systemic exposure from vaginal administration. There is a remote possibility that vaginal formulations could be administered during general anesthesia.

7.5. PHARMACOLOGICAL CLASS EFFECTS

Lincosamides (e.g., lincomycin, clindamycin), are a class of antibiotics which inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit and interfering with the process of peptide chain elongation. Lincosamides can inhibit the binding of aminoacyl-tRNA or inhibit the translocation reaction following amino acid binding on the ribosome.

Lincosamides are considered a bacteriostatic agent but they do exhibit bactericidal activity against a variety of organisms including staphylococci, streptococci, *Bacteroides fragilis* and some other anaerobes.

7.5.1. Pharmacological Class Risks Already Included as Important Identified or Potential Risks

See sections 7.3.1 and 7.3.2 above.

7.5.2. Important Pharmacological Class Effects Not Discussed Above

Not applicable.

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PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.1
Date of final sign off	30 April 2014		

Table 1. Summary of Safety Concerns for Clindamycin Ovules

Summary of Safety Concerns	
Important identified risks	Vulvovaginal candidiasis Pseudomembranous colitis
Important potential risks	Weakening of latex condoms and diaphragms
Missing information	Use in elderly patients over 65 years of age Use in pregnant and lactating women Use in pediatric patients under 16 years of age Use in immunodeficient patients Use in patients with colitis

PART III: PHARMACOVIGILANCE PLAN

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product concerned (brand names):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.1
Date of final sign off	30 April 2014		

3.1. SAFETY CONCERNS AND OVERVIEW OF PLANNED PHARMACOVIGILANCE ACTIONS

The following safety concerns and planned pharmacovigilance actions refer specifically to the clindamycin phosphate vaginal ovule formulation.

Important Identified Risks

Vulvovaginal candidiasis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to vulvovaginal candidiasis.

Pseudomembranous colitis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to pseudomembranous colitis.

Important Potential Risks

Weakening of latex condoms and diaphragms		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to weakening of latex condoms and diaphragms.

Missing Information

Use in elderly patients over 65 years of age		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to use in elderly patients over 65 years of age.

Use in pregnant and lactating women		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to use in pregnant and lactating women.

Use in pediatric patients under 16 years of age		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to use in pediatric patients under 16 years of age.

Use in immunodeficient patients		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to use in immunodeficient patients.

Use in patients with colitis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
None	Routine Pharmacovigilance. No additional pharmacovigilance activities are planned.	To collect and assess post-marketing data that may identify a change in the safety profile of clindamycin phosphate vaginal ovules related to patients with colitis.

3.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES TO ASSESS EFFECTIVENESS OF RISK MINIMISATION MEASURES

No additional pharmacovigilance activities are planned.

3.3. STUDIES AND OTHER ACTIVITIES COMPLETED SINCE LAST UPDATE OF PHARMACOVIGILANCE PLAN

No additional studies or activities are planned.

3.4. DETAILS OF OUTSTANDING ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

No additional pharmacovigilance activities are planned.

3.5. SUMMARY OF THE PHARMACOVIGILANCE PLAN

The pharmacovigilance plan for clindamycin phosphate ovules consists of routine pharmacovigilance. There are no ongoing or planned additional pharmacovigilance activities.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product concerned (brand names):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.0
Date of final sign off	26 November 2013		

4.1. TABLES OF POST-AUTHORISATION EFFICACY STUDIES

There are no ongoing or planned efficacy studies.

4.2. SUMMARY OF POST-AUTHORISATION EFFICACY DEVELOPMENT PLAN

There are no ongoing or planned efficacy studies.

4.3. SUMMARY OF COMPLETED POST-AUTHORISATION EFFICACY STUDIES

There are no completed post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES

Active substance(s) (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.1
Date of final sign off	30 April 2014		

5.1. RISK MINIMISATION MEASURES BY SAFETY CONCERN

5.1.1. Important Identified Risks

Safety Concern	Vulvovaginal candidiasis
Objective of the risk minimisation measure	To improve awareness of this identified risk and to foster early identification.
Routine risk minimisation measures	SmPC section 4.4 Special warnings and precautions for use The use of Dalacin Vaginal Ovule may result in the overgrowth of nonsusceptible organisms, particularly yeasts. SmPC section 4.8 Undesirable effects Infections and infestations: Vaginal candidiasis (frequency: common)
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is to foster early identification of and potential intervention for this identified risk.
Comment	None

Safety Concern	Pseudomembranous colitis
Objective(s) of the risk minimisation measures	To improve awareness of this identified risk and to decrease the identified risk through appropriate patient selection.
Routine risk minimisation measures	Summary of Product Characteristics (SmPC) section 4.3 Contraindications Dalacin Vaginal Ovules are also contraindicated in individuals with a history of antibiotic-associated colitis. SmPC section 4.4 Special warnings and precautions for use Onset of symptoms suggestive of pseudomembranous colitis may occur during or after antimicrobial treatment. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important that this is considered in patients who present with diarrhoea subsequent to the administration of antibacterial agents. Moderate cases may improve following withdrawal of the drug. Clindamycin treatment must be stopped if pseudomembranous diarrhoea occurs. An adequate antibacterial therapy should be prescribed. Drugs inhibiting peristalsis are contra-indicated in this situation.

	Caution is advised in patients when prescribing Dalacin 100mg Vaginal Ovules to individuals with Inflammatory Bowel Disease such as Crohn's Disease or Ulcerative Colitis.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new signals and monitor reporting trends.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is to decrease the potential for this risk, or complications from this risk, through appropriate patient selection and care.
Comment	None

5.1.2. Important Potential Risks

Safety Concern	**Weakening of latex condoms and diaphragms**
Objective(s) of the risk minimisation measures	To increase awareness of the incompatibility of the ovules with some contraceptive devices.
Routine risk minimisation measures	SmPC section 4.4 Special warnings and precautions for use As with all vaginal infections, sexual intercourse during treatment with Dalacin Vaginal Ovule is not recommended. Latex condoms and diaphragms may be weakened if exposed to the suppository base used in Dalacin Vaginal Ovules (for Incompatibilities see Section 6.2 [below]). The use of such products within 72 hours following treatment with Dalacin Vaginal Ovules is not recommended as such use could be associated with diminished contraceptive efficacy or protection against sexually transmitted disease. SmPC section 6.2 Incompatibilities The use of latex condoms is not recommended during therapy with Dalacin Vaginal Ovules. There are no data available regarding the effect of Dalacin Vaginal Ovule on latex diaphragms.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.

safety concern will be measured	
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is to improve awareness of an incompatibility of the product with latex rubber, which may diminish the efficacy of contraceptive devices that are made with latex rubber.
Comment	None

5.1.3. Missing Information

Safety Concern	**Use in elderly patients over 65 years of age**
Objective(s) of the risk minimisation measures	To increase awareness of the lack of clinical experience in patients over 65 years of age.
Routine risk minimisation measures	SmPC section 4.2 Posology and method of administration **Use in Elderly Patients:** The use of Dalacin Vaginal Ovule has not been studied in patients over 65 years of age.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify use in patients over 65 years of age, and evidence for safety signals that differ from use in younger patients.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is that the prescriber will be aware that the drug has not been studied in patients over 65 years of age, when considering using this product in this subpopulation.
Comment	None

Safety Concern	**Use in pregnant and lactating women**
Objective(s) of the risk minimisation measures	To raise awareness that use of this product in the first trimester of pregnancy is not recommended, as there are no adequate and well-controlled studies in pregnant women over this period. To raise awareness that it is not known whether the product is excreted in breast milk, therefore, a full benefit-risk assessment should be done when considering the use of this product in a nursing mother.
Routine risk minimisation measures	SmPC section 4.4 Special warnings and precautions for use Safety and efficacy studies have not been performed with Dalacin Vaginal Ovule in the following populations: pregnant, lactating women ….

	SmPC section 4.6 Pregnancy and Lactation PREGNANCY Use of Dalacin Vaginal Ovule is not recommended during the first trimester, as there are no adequate and well-controlled studies in pregnant women over this period. In clinical trials, intravaginal use of Dalacin Vaginal Cream in pregnant women during second trimester and systemic use of clindamycin phosphate during the second and third trimester has not been associated with congenital abnormalities. Dalacin Vaginal Ovule may be used to treat pregnant women if clearly necessary during the second and third trimester of pregnancy. Digital application of the vaginal ovule is recommended during pregnancy. LACTATION It is not known if clindamycin is excreted in breast milk following the use of vaginally administered clindamycin vaginal ovule. However, orally and parenterally administered clindamycin have been reported to appear in breast milk. Nevertheless, a full benefit-risk assessment should be done when considering the use of clindamycin vaginal ovule in a nursing mother.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends in pregnant women during the first trimester, breastfeeding mothers, newborns, and infants.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is that the prescriber will be aware that use of the product in women in the first trimester of pregnancy is not recommended, as there are no adequate and well-controlled studies in this subpopulation over this period. Also, the expected impact is that the prescriber will be aware that it is not known whether the product is excreted in breast milk, and that a full benefit-risk assessment should be done when considering the use of this drug in a nursing mother.
Comment	None

Safety Concern	Use in pediatric patients under 16 years of age
Objective(s) of the risk minimisation measures	To increase awareness of the lack of clinical experience in patients under 16 years of age.
Routine risk minimisation measures	SmPC section 4.2 Posology and method of administration **Use in Paediatric Patients:** The use of Dalacin Vaginal Ovule has not been studied in patients under 16 years of age.

	SmPC section 4.4 Special warnings and precautions for use **Pediatric Use** Safety and efficacy in pediatric patients have not been established.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is that the prescriber will be aware that the drug has not been studied in patients under 16 years of age, when considering using this product in this subpopulation.
Comment	None

Safety Concern	**Use in immunodeficient patients**
Objective(s) of the risk minimisation measures	To increase awareness of the lack of clinical experience in immunodeficient patients.
Routine risk minimisation measures	SmPC section 4.4 Special warnings and precautions for use Safety and efficacy studies have not been performed with Dalacin Vaginal Ovule in the following populations: … immunodeficient [patients] ….
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify safety signals in immunodeficient patients and to monitor reporting trends.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is that the prescriber will be aware that the drug has not been studied in immunodeficient patients.
Comment	None

Safety Concern	Use in patients with colitis
Objective(s) of the risk minimisation measures	To increase awareness of the lack of clinical experience in patients with colitis.
Routine risk minimisation measures	SmPC section 4.4 Special warnings and precautions for use Caution is advised in patients when prescribing Dalacin 100 mg Vaginal Ovules to individuals with Inflammatory Bowel Disease such as Crohn's Disease or Ulcerative Colitis. Safety and efficacy studies have not been performed with Dalacin Vaginal Ovule in the following populations: … patients with colitis.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends in this patient population.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified in this patient population.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is that the prescriber will be aware that the drug has not been studied in patients with colitis, when considering using this product in this subpopulation.
Comment	None

5.2. RISK MINIMISATION MEASURE FAILURE (IF APPLICABLE)

Not applicable at present.

5.2.1. Analysis of Risk Minimisation Measure(s) Failure

Not applicable at present.

5.2.2. Revised Proposal for Risk Minimisation

Not applicable at present.

5.3. SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Vulvovaginal candidiasis	Summary of Product Characteristics (SmPC) 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Pseudomembranous colitis	SmPC 4.3 Contraindications 4.4 Special warnings and precautions for use	None
Important Potential Risks		
Weakening of latex condoms and diaphragms	SmPC 4.4 Special warnings and precautions for use 6.2 Incompatibilities	None
Missing Information		
Use in elderly patients over 65 years of age	SmPC 4.2 Posology and method of administration	None
Use in pregnant and lactating women	SmPC 4.4 Special warnings and precautions for use 4.6 Pregnancy and lactation	None
Use in pediatric patients under 16 years of age	SmPC 4.2 Posology and method of administration 4.4 Special warnings and precautions for use.	None
Use in immunodeficient patients	SmPC 4.4 Special warnings and precautions for use	None
Use in patients with colitis	SmPC 4.4 Special warnings and precautions for use.	None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Active substance (INN or common name):	clindamycin phosphate
Pharmaco-therapeutic group (ATC Code):	Lincosamide antibiotic (J01FF01)
Name of Marketing Authorisation Holder or Applicant:	Pharmacia Limited Ramsgate Road Sandwich Kent CT13 9NJ
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	Cleocin Dalacin Dalacin V

Data lock point for current RMP	31 July 2013	Version number	1.1
Date of final sign off	30 April 2014		

6.1. ELEMENTS FOR SUMMARY TABLES IN THE EPAR

6.1.1. Summary Table of Safety Concerns for Clindamycin Ovules

Summary of Safety Concerns	
Important identified risks	Vulvovaginal candidiasis Pseudomembranous colitis
Important potential risks	Weakening of latex condoms and diaphragms
Missing information	Use in elderly patients over 65 years of age Use in pregnant and lactating women Use in pediatric patients under 16 years of age Use in immunodeficient patients Use in patients with colitis

6.1.2. Table of On-going and Planned Studies in the Post-authorisation Pharmacovigilance Development Plan

There are no ongoing or planned studies.

6.1.3. Summary of Post-Authorisation Efficacy Development Plan

There are no ongoing or planned studies.

6.1.4. Summary Table of Risk Minimisation Measures

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimization Measures**
Important Identified Risk		
Vulvovaginal candidiasis	Summary of Product Characteristics (SmPC) 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Pseudomembranous colitis	SmPC 4.3 Contraindications 4.4 Special warnings and precautions for use	None
Important Potential Risks		
Weakening of latex condoms and diaphragms	SmPC 4.4 Special warnings and precautions for use 6.2 Incompatibilities	None

Missing Information		
Use in elderly patients over 65 years of age	SmPC 4.2 Posology and method of administration	None
Use in pregnant and lactating women	SmPC 4.4 Special warnings and precautions for use 4.6 Pregnancy and lactation	None
Use in pediatric patients under 16 years of age	SmPC 4.2 Posology and method of administration 4.4 Special warnings and precautions for use	None
Use in immunodeficient patients	SmPC 4.4 Special warnings and precautions for use	None
Use in patients with colitis	SmPC 4.4 Special warnings and precautions for use	None

6.2. ELEMENTS FOR A PUBLIC SUMMARY

6.2.1. Overview of Disease Epidemiology

Bacterial vaginosis is the most common vaginal infection in women of childbearing age. It occurs when the normal bacterial balance in the vagina becomes disrupted, causing an overgrowth of certain "bad" types of bacteria and infection. This can result in symptoms such as bad odor, itching, burning, increase in vaginal discharge (fluid coming out of the vagina) or pain after intercourse. However, most women do not show any symptoms at all. Since the symptoms described can also be caused by other conditions, patients must always inform their doctor of their situation.

6.2.2. Summary of Treatment Benefits

Clindamycin phosphate vaginal ovules are pessaries for use in the vagina. They contain clindamycin phosphate, which is an antibiotic used in the treatment of a bacterial infection of the vagina called bacterial vaginosis.

These antibiotics work by stopping bacterial growth. The treatment should be completed as prescribed by a healthcare professional.

6.2.3. Unknowns Relating to Treatment Benefits

None.

6.2.4. Summary of Safety Concerns

Important Identified Risk

Risk	What is Known	Preventability
Fungal (yeast) infection; inflammation of the vagina (Vulvovaginal candidiasis)	Vaginal yeast infection is characterized by vaginal itching, soreness, and irritation; pain or discomfort during sexual intercourse; pain or discomfort during urination; and vaginal discharge. It is caused by an overgrowth of microscopic organisms that clindamycin does not affect.	Patient supervision and care.

Risk	What is Known	Preventability
Inflammation of the colon (Pseudomembranous colitis)	Pseudomembranous colitis is characterized by diarrhea, abdominal pain, and fever and can occur with mostly all antibiotics. Complications from this disorder can be life-threatening. It is caused by an overgrowth of microscopic organisms that clindamycin does not affect. This condition usually occurs when antibiotics are taken by mouth or by injection, although there is the potential for it to occur with vaginal administration.	Patient supervision and care.

Important Potential Risks

Risk	What is Known
Breakdown of latex condoms or latex diaphragms if used with ovules (Weakening of latex condoms and diaphragms)	The fat covering of the ovule may weaken condoms or diaphragms that are made of latex. Thus, there is the potential for an unplanned pregnancy or transfer of a sexually transmitted disease. Because of this, use of these contraceptives is not recommended for three days after completion of therapy with clindamycin.

Missing Information

Risk	What is Known
Use in elderly patients over 65 years of age	The use of the ovules has not been studied in patients over 65 years of age.
Use in pregnant and breastfeeding (lactating) women	The use of the ovules has not been studied in pregnant women, but the use of the cream form of vaginal clindamycin has been studied. The cream form has not been studied in the first trimester. Therefore, the use of the clindamycin ovules, just like the cream, is only recommended in the second or third trimester. When clindamycin is administered via the ovule, it is not known whether it is excreted in human milk. However, it is excreted in human milk when the drug is taken by mouth. The decision to use the ovules while breastfeeding should be made after careful consideration of the benefits and the risks.
Use in pediatric patients under 16 years of age	The use of the ovules has not been studied in patients under 16 years of age.
Use in patients with weak immune systems (immunodeficient)	The use of the ovules has not been studied in patients with weak immune systems.
Use in patients with large bowel (colon) inflammation	The use of the ovules has not been studied in patients with inflammation of the large bowel.

6.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks, and the recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimisation measures.

6.2.6. Planned Post-Authorisation Development Plan

There a no studies planned.

6.2.7. Summary of Changes to the Risk Management Plan Over Time

As this is an initial RMP for this product, there are no changes to report at this time.