DALACIN® 2% VAGINAL CREAM

1. NAME OF THE MEDICINAL PRODUCT

Dalacin® 2% Vaginal Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains clindamycin phosphate equivalent to 20 mg or 2.0% w/w clindamycin. Each applicator full of 5 grams of vaginal cream contains approximately 100 mg of clindamycin phosphate.

Excipients of known effect
Dalacin Cream contains 160.5 mg cetostearyl alcohol in each 5 g applicator which is equivalent to 32.1 mg/g.
Dalacin Cream contains 250 mg propylene glycol in each 5 g applicator which is equivalent to 50 mg/g.
Dalacin Cream contains 50 mg benzyl alcohol in each 5 g applicator which is equivalent to 10 mg/g
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Vaginal Cream
White, semi-solid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of bacterial vaginosis only if bacteria susceptible to clindamycin were found.
DALACIN® 2% Vaginal Cream can be used to treat non-pregnant women and pregnant women during their second and third trimesters.

4.2 Posology and method of administration

The recommended dose is one applicatorful of clindamycin vaginal cream 2% intravaginally, preferably at bedtime, for three or seven consecutive days.

Paediatric population
Safety and efficacy in paediatric patients have not been established (see section 4.4).

Elderly
No clinical studies have been conducted in populations older than 60.

4.3 Contraindications

Dalacin® 2% Vaginal Cream is contra-indicated in patients with a history of hypersensitivity to clindamycin, lincomycin, or to any of the excipients listed in section 6.1.

Dalacin® 2% Vaginal Cream is also contraindicated in individuals with a history of inflammatory bowel disease or a history of antibiotic-associated colitis.

4.4 Special warnings and precautions for use

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.

The use of clindamycin may result in the overgrowth of non-susceptible organisms, particularly yeasts.

Onset of symptoms suggestive of pseudomembranous colitis may occur during or after antimicrobial treatment (see section 4.8). 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 contraindicated in this situation.

Caution is advised in patients when prescribing clindamycin to individuals with inflammatory bowel disease such as Crohn's disease or ulcerative colitis.

As with all vaginal infections, sexual intercourse during treatment with clindamycin vaginal cream is not recommended. Latex condoms and diaphragms may be weakened if exposed to the suppository base used in clindamycin vaginal cream. The use of such products within 72 hours following treatment with clindamycin vaginal cream is not recommended as such use could be associated with diminished contraceptive efficacy or protection against sexually transmitted disease.

The use of other vaginal products (such as tampons and douches) during the treatment with clindamycin vaginal cream is not recommended.

Paediatric population

Safety and efficacy in paediatric patients have not been established (see section 4.2).

Excipient information

Dalacin Cream contains propylene glycol, cetostearyl alcohol and benzyl alcohol (see section 2).
Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).
Benzyl alcohol may cause allergic reactions and mild local irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Systemic clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents (see section 4.9).

No information is available on the concomitant use of other vaginal medications with clindamycin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of clindamycin 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 clindamycin vaginal products 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.

Clindamycin may be used to treat pregnant women if clearly necessary during the second and third trimester of pregnancy.

Reproduction studies performed in rats and mice using oral and parenteral doses of clindamycin, ranging from 100 to 600 mg/kg/day, have revealed no evidence of harm to the fetus due to clindamycin (see section 5.3). In one mouse strain, cleft palates were observed in species treated fetuses; this response was not produced in other mouse strains or in other species, and is therefore considered to be a strain specific effect. Animal reproduction studies are not always predictive of human response.

In a clinical trial in pregnant women during the second trimester, Dalacin® 2% Vaginal Cream was effective in treating bacterial vaginosis, and no drug-related medical events were reported in the neonates. However, as with any drug used during pregnancy, a careful risk-benefit assessment should take place beforehand.

Breast-feeding
It is not known if clindamycin is excreted in human breast milk following the use of vaginally administered clindamycin vaginal cream. Clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8 µg/ml following systemic use. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. If oral or intravenous clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.

Fertility
Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability. No animal fertility studies have been performed using the vaginal route of administration.

4.7 Effects on ability to drive and use machines

The effect of clindamycin on the ability to drive or operate machinery has not been systematically evaluated.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The safety of clindamycin vaginal cream was evaluated in both non pregnant patients and patients during their second and third trimesters of pregnancy.

Adverse Drug Reactions Table for Clindamycin Vaginal Cream						
System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1 000 to <1/100**	**Rare ≥ 1/10, 000 to <1/1 000**	**Very Rare < 1/10, 000**	**Frequency not known (Cannot be estimated from available data)**
Infections and infestations		Fungal infection, candida infection	Bacterial infection			Skin candida
Immune System Disorders			Hypersensitivity			
Endocrine disorders						Hyperthyroidism
Nervous System Disorders		Headache Dizziness Dysgeusia				
Ear and labyrinth disorders			Vertigo			
Respiratory, thoracic and mediastinal disorders		Upper respiratory infection	Epistaxis			
Gastrointestinal Disorders		Abdominal pain constipation, diarrhea, nausea, vomiting	breath odour, Abdominal distension flatulence			Gastrointestinal disorder, *Pseudomembranous colitis** dyspepsia
Skin and Subcutaneous Tissue Disorders		Pruritus (non-applicable site), rash	Erythema, urticaria			Rash maculopapular
Musculoskeletal and connective tissue disorders		Back pain				
Renal and urinary disorders		Urinary tract infection, glycosuria, proteinuria	Dysuria,			
Pregnancy, puerperium and perinatal conditions		Abnormal labour				
Reproductive system and breast disorders	Vulvovaginal candidiasis	Vulvovaginitis, vulvovaginal disorder, Menstrual disorder, Vulvovaginal pain, Metrorrhagia, Vaginal discharge	Vulvovaginitis trichomonal, vaginal infection, pelvic pain			Endometriosis,
General disorders and administration site conditions						Pain, inflammation
Investigations			Microbiology test abnormal			

* ADRs identified post-marketing.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

There are no reports of overdose with clindamycin. Vaginally applied clindamycin phosphate vaginal cream 2% can be absorbed in sufficient amounts to produce systemic effects.

In the event of overdosage, general symptomatic and supportive measures are indicated as required.
Accidental oral intake can lead to effects comparable with those of therapeutic concentrations of orally administered clindamycin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties
Pharmacotherapeutic group: Gynaecological anti-infectives and antiseptics, ATC Code: G01AA10.

Mechanism of action
Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the translation process. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Similar to other protein synthesis inhibitors, efficacy is associated with the length of time the concentration of clindamycin remains above the MIC of the infecting organism.

Mechanism of resistance
Resistance to clindamycin is most often due to modification of the target site on the ribosome, usually by chemical modification of RNA bases or by point mutations in RNA or occasionally in proteins. Cross resistance has been demonstrated *in vitro* between lincosamides, macrolides and streptogramins B in some organisms. Cross resistance has been demonstrated between clindamycin and lincomycin.

Breakpoints
Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis*, and *Mobiluncus* spp has not been defined. Methods for determining the susceptibility of *Bacteroides* spp. and Gram-positive anaerobic cocci, as well as Mycoplasma spp. have been described by the Clinical and Laboratory Standards Institute (CLSI) and clindamycin susceptibility breakpoints for Gram-negative and Gram-positive anaerobes have been published by both EUCAST and CLSI. However the breakpoints are intended to guide systemic, rather than localized, antibiotic treatment.

Microbiological susceptibility
Clindamycin is active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

- *Bacteroides* spp.
- *Gardnerella vaginalis*
- *Mobiluncus* spp.
- *Mycoplasma hominis*
- *Peptostreptococcus* spp.

5.2 Pharmacokinetic properties

Following a once a day intravaginal dose of 100 mg of clindamycin phosphate vaginal cream 2%, administered to 6 healthy female volunteers for 7 days, approximately 4% (range 0.6% to 11%) of the administered dose was absorbed systemically. The peak serum clindamycin concentration observed on the first day averaged 18 ng/mL (range 4 to 47 ng/mL) and on day 7 it averaged 25 ng/mL (range 6 to 61 ng/mL). These peak concentrations were attained approximately 10 hours post-dosing (range 4–24 hours).

Following a once a day intravaginal dose of 100 mg of clindamycin phosphate vaginal cream 2%, administered for 7 consecutive days to 5 women with bacterial vaginosis, absorption was slower and less variable than that observed in healthy females. Approximately 4% (range 2% to 8%) of the dose was absorbed systemically. The peak serum clindamycin concentration observed on the first day averaged 13 ng/mL (range 6 to 34 ng/mL) and on day 7 it averaged 16 ng/mL (range 7 to 26 ng/mL). These peak concentrations were attained approximately 14 hours post-dosing (range 4–24 hours).

There was little or no systemic accumulation of clindamycin after repeated (7 day) vaginal dosing of clindamycin phosphate vaginal cream 2%. The systemic half-life was 1.5 to 2.6 hours.

Elderly
Clinical studies for clindamycin phosphate vaginal cream 2% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

5.3 Preclinical safety data

Impairment of fertility
Fertility studies in rats treated orally with up to 300 mg/kg/day (31 times the human exposure based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy
In oral embryo-foetal development studies in rats and subcutaneous embryo-foetal development studies in rats and rabbits, embryo-fetal toxicity was observed at doses that produced maternal toxicity. In rats, maternal death occurred with exposure margins of approximately 400-fold relative to patient exposure. In rabbits, maternal toxicity, including abortions, occurred at exposure margins of 50-fold relative to patient exposure. Embryo-fetal toxicity, including post-implantation loss and decreased viability, occurred in rabbits at exposure margins of 120-fold.

Mutagenesis
Clindamycin was not genotoxic when evaluated in the *in vivo* rat micronucleus test and the Ames test.

Carcinogenesis
Long-term studies in animals to evaluate carcinogenic potential have not been performed with clindamycin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mineral oil (liquid paraffin)
Polysorbate 60
Propylene glycol

Cetostearyl alcohol
Mixed fatty acids esters (cetyl palmitate)/ cutina CP
Stearic acid
Sorbitan monostearate
Benzyl alcohol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Laminate tube (consisting of LMDPE and aluminium foil) with polypropylene cap containing 40 g cream, packed in cardboard carton, together with 7 disposable LDPE applicators.

6.6 Special precautions for disposal and other handling

No special requirements.

7. LICENSE HOLDER:

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725

8. REGISRATION NUMBER:

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