Dalacin Vaginal Ovules

1. NAME OF THE MEDICINAL PRODUCT

Dalacin Vaginal Ovules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clindamycin (as phosphate) 100 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal ovule.

Off-white, smooth solid ovule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dalacin vaginal ovules are indicated for 3-day treatment of bacterial vaginosis.

4.2 Posology and method of administration

Posology
The recommended dose is one clindamycin vaginal ovule intravaginally, preferably at bedtime, for three consecutive days.

Elderly population
The use of Dalacin Vaginal Ovule has not been studied in patients over 65 years of age.

Patients with renal impairment
The use of Dalacin Vaginal Ovule has not been studied in patients with impaired renal function.

4.3 Contraindications

Hypersensitivity to the active substance, to lincomycin, or to any of the excipients listed in section 6.1.

Dalacin Vaginal Ovules is also contraindicated in individuals with a history of antibiotic-associated colitis.

4.4 Special warnings and precautions for use

Before or after initiation of therapy with Dalacin, other infections including *Trichomonas vaginalis, Candida albicans, Chlamydia trachomatis* and gonococcal infections may need to be investigated by adequate laboratory tests.

The use of Dalacin may result in the overgrowth of nonsusceptible 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. It is therefore,

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 Vaginal Ovules to individuals with Inflammatory Bowel Disease such as Crohn's Disease or Ulcerative Colitis.

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 ovule base used in Dalacin Vaginal Ovules (see section 6.2). 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.

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

Safety and efficacy studies have not been performed with Dalacin Vaginal Ovule in the following populations: pregnant women, lactating women, patients with impaired hepatic function, immunodeficient or colitis.

Paediatric population

Safety and efficacy of Dalacin Vaginal Ovule in paediatric patients has not been established.

4.5 Interactions with other medicinal products and other forms of interaction

No information is available on the concomitant use of other vaginal medications with Dalacin Vaginal Ovule.

Systemic 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 (see sections 4.9 & 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Use of Dalacin 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 products in pregnant women during the second trimester and systemic use of clindamycin phosphate during the second and third trimester has not been associated with congenital abnormalities.

Dalacin 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.

Breast-feeding

It is unknown whether clindamycin is excreted in human breast milk following vaginal administration, but it is used in much lower doses than systemic clindamycin, and approximately 30% (range: 6% to 70%) is systemically absorbed. Following systemic administration, clindamycin has been reported to appear in human breast milk in ranges from < 0.5 to 3.8 µg/mL.

If clindamycin is administered systemically to a breastfeeding mother, there is a risk of adverse reactions on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. Use of Dalacin vaginal ovules in a breastfeeding woman can be considered if the expected benefit to the mother outweighs the risks for the child.

Fertility

Studies in animals revealed no effect on fertility.

4.7 Effects on ability to drive and use machines

Dalacin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of clindamycin vaginal ovules was evaluated in non-pregnant patients in clinical trials. Frequencies reported are as follows: Common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100).

System Organ Class	**Common** **≥ 1/100 to < 1/10**	**Uncommon** **≥ 1/1,000 to < 1/100**
Infections and infestations	Fungal infection, candida infection	
Nervous system disorders	Headache	
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea	Vomiting
Skin and subcutaneous tissue disorders	Pruritus (non-applicable site)	Rash
Musculoskeletal and connective tissue disorders		Flank pain
Renal and urinary disorders		Pyelonephritis, dysuria
Reproductive system and breast disorders	Vulvovaginal candidiasis, vulvovaginal pain, vulvovaginal disorder,	Vaginal infection, vaginal discharge, menstrual disorder
General disorders and administration site conditions		Application site pain, pruritus (topical applicable site), localized oedema, pain, pyrexia

Pseudomembranous colitis is a class event for antibacterials.

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 Dalacin Vaginal Ovule.

Vaginally applied clindamycin phosphate contained in Dalacin can be absorbed in sufficient amounts to produce systemic effects.

In the event of overdose, 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

Pharmacotherapeutic group: Antiinfectives and antiseptics, excl. combinations with corticosteroids, antibiotics, 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.

Clindamycin, like most protein synthesis inhibitors, is predominantly bacteriostatic and efficacy is associated with the length of time during which the concentration of active ingredient remains above the MIC of the infecting microorganism.

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.

In vitro 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.

Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis* and *Mobiluncus* spp. has not been defined. Clindamycin susceptibility breakpoints for Gram-negative and Gram-positive anaerobes bacteria have been published by EUCAST. Clinical isolates that test susceptible to clindamycin and resistant to erythromycin should

also be tested for inducible clindamycin resistance using the D-test. However, the breakpoints are intended to guide systemic, rather than localized, antibiotic treatment.

5.2 Pharmacokinetic properties

Absorption

Systemic absorption of clindamycin was estimated following a once-a-day intravaginal dose of one clindamycin phosphate vaginal ovule (equivalent to 100 mg clindamycin) administered to 11 healthy female volunteers for 3 days. Approximately 30% (range 6% to 70%) of the administered dose was absorbed systemically on day 3 of dosing based on area under the concentration-time curve (AUC). Systemic absorption was estimated using a sub-therapeutic 100 mg intravenous dose of clindamycin phosphate as a comparator in the same volunteers as well as a 100 mg dose of clindamycin phosphate vaginal cream. The mean AUC following day 3 of dosing with the ovule was 3.2 µg•hr/mL (range 0.42 to 11 µg•hr/mL). The C_{max} observed on day 3 of dosing with the ovule averaged 0.27 µg/mL (range 0.03 to 0.67 µg/mL) and was observed about 5 hours after dosing (range 1 to 10 hours). In contrast, the AUC and C_{max} after the single intravenous dose averaged 11 µg•hr/mL (range 5.1 to 26 µg•hr/mL) and 3.7 µg/mL (range 2.4 to 5.0 µg/mL), respectively. The mean apparent elimination half-life after dosing with the ovule was 11 hours (range 4 to 35 hours) and is considered to be limited by the absorption rate.

The results from this study showed that systemic exposure to clindamycin (based on AUC) from the ovule was, on average, three-fold lower than that from a single sub-therapeutic 100 mg intravenous dose of clindamycin. Relative to a comparable dose of clindamycin vaginal cream, systemic absorption of the ovule was approximately 7-fold greater than that following dosing of the vaginal cream with average values of AUC and Cmax of 0.4 µg.hr/mL (range 0.13 to 1.16 µg.hr/mL and 0.02 µg/mL (range 0.01 to 0.07 µg/mL) respectively for the clindamycin vaginal cream. In addition, the recommended daily and total doses of intravaginal clindamycin ovule are far lower than those typically administered in oral or parenteral clindamycin therapy (100 mg of clindamycin per day for 3 days equivalent to about 30 mg absorbed per day from the ovule relative to 600 to 2700 mg/day for up to 10 days or more, orally or parenterally). The overall systemic exposure to clindamycin from clindamycin vaginal ovules 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).

5.3 Preclinical safety data

Toxicology

Clindamycin phosphate (5 mg) suspended in a hard fat (an ovule base consisting of a mixture of glycerides of saturated fatty acids) ovule was tested in the ovariectomized rat model. The results indicated that the formulation caused mild vaginal irritation during treatment that quickly reversed after treatment was stopped.

Carcinogenicity/Mutagenicity

Long-term studies have not been performed in animals with clindamycin to evaluate carcinogenic potential. A rat micronucleus and an Ames genotoxicity test were negative.

Toxicity to reproduction

Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (31 times the human exposure based on mg/m²) revealed no effects on fertility or mating ability. No animal fertility studies have been performed using the vaginal route of administration.

In oral embryo-foetal development studies in rats and subcutaneous embryo-foetal development studies in rats and rabbits, embryo-foetal 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-foetal toxicity, including post-implantation loss and

decreased viability, occurred in rabbits at exposure margins of 120-fold. Clindamycin was not teratogenic in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard Fat Ph Eur.(Witepsol H-32)

6.2 Incompatibilities

No information is available on concomitant use with other intravaginal products. 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.

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 ºC.

6.5 Nature and contents of containers

Three ovules are supplied in individually sealed laminated foil pouches (strip) packed in a box.

6.6 Special precautions for disposal and other handling

Do not use this product if the foiled pouches containing vaginal ovules are torn, opened, or incompletely sealed.

Insertion:
- Remove the ovule from the foil pouch.
- Lie on your back with your knees drawn up to your chest.
- Insert the ovule into the vagina with the tip of your third (middle) finger as far as possible without causing discomfort.

7. LICENSE HOLDER

Pfizer PFE Pharmaceutical Israel Ltd, 9 Shenkar St., Herzeliya 46725.

8. LICENSE REGISTRATION NUMBER

122-32-30218

Revised in 07/2024