IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dalacin 100 mg Vaginal Ovule
CLINDAMYCIN PHOSPHATE
PA0822/119/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Dalacin 100mg Vaginal Ovules, from Pfizer Healthcare Ireland on 21st December 1998 for the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis).

This application relates to a line extension using the repeat-use mutual recognition procedure with France and Denmark as concerned member states. The original applciation was a full application according to Article 9 Directive 79/319/EEC for Dalacin Ovules (Clindamycin). Pfizer Healthcare Ireland, a wholly owned subsidiary of Pfizer Limited, is the current Marketing Authorisation Holder (MAH) for Dalacin Ovules which were first approved nationally in Ireland in October 1993. A mutual recognition procedure (MRP) application, with Ireland as the reference member state (RMS), was first approved in 1998 (IE/H/119/001).
The licence is for prescription only.
The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Dalacin 100 mg Vaginal Ovule
Name(s) of the active substance(s) (INN)	CLINDAMYCIN PHOSPHATE
Pharmacotherapeutic classification (ATC code)	J01FF01
Pharmaceutical form and strength(s)	Pessary 100 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0822/119/001
Marketing Authorisation Holder	Pfizer Healthcare Ireland
MRP/DCP No.	IE/H/119/001/E/001/MR
Reference Member State	IE
Concerned Member State	DE, FI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Dalacin 100 mg Vaginal Ovules.

II.2 Drug substance

The active substance is Clindamycin (which is in the form of Clindamycin Phosphate) an established active substance described in the European Pharmacopoeia (Ph. Eur.), and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).
The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition
Each vaginal ovule contains 100 mg of Clindamycin.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.
The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)
All ingredients comply with the requirements of the Ph. Eur.

P.5 Control of Finished Product
The Finished Product Specification is based on European guidelines, and the tests and control limits are considered appropriate for this type of product.
The analytical methods used are described in sufficient detail and are supported by validation data.
Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.
Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Dalacin 100 mg Vaginal Ovules.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This application is a line extension for Dalacin Ovules (Clindamycin) using the repeat-use mutual recognition procedure in accordance with Article 9 Directive 79/319/EEC. Pharmacia Limited, a wholly owned subsidiary of Pfizer Limited, is the current Marketing Authorisation Holder (MAH) for Dalacin Ovules which were first approved nationally in Ireland in October 1993. A mutual recognition procedure (MRP) application, with Ireland as the reference member state (RMS), was approved in 1998 (IE/H/119/001). As part of that submission, an expert report on the pharmaco-toxicological documentation of Dalacin Vaginal Ovule (clindamycin phosphate vaginal ovule) signed by Gerald J. Kolaja, DVM, PhD (Dated 31 Jul 1997) was submitted.

Since the submission of the expert report (Kolaja, 1997), a number of additional pharmacokinetic/toxicokinetic studies as well as confirmatory studies with respect to reproduction and development toxicity have been performed or have been reported within the scientific literature.
The HPRA has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology
No new pharmacology studies were conducted for the current application. The overview was based on the previously submitted Pharmaco-toxicological expert report (Kolaja, 1997) that was used to support the original MRP application (approved in 1998 (IE/H/119/001)).

III.3 Pharmacokinetics
Several additional pharmacokinetic studies were reported/conducted to support the Pharmaco-toxicological expert report (Kolaja, 1997) that was used for the original MRP application (approved in 1998 (IE/H/119/001)). These data confirmed that Clindamycin rapidly absorbed (Tmax ~ 2 hours) and was extensively distributed and measureable at 6 hours post-dose but was below the limit of quantitation by 24 hours. Highest tissue-to-serum AUCs (0-6) were found in the lung and kidney. Clindamycin is primarily oxidized to clindamycin sulfoxide primarily by CYP3A. Clindamycin also inhibited CYP3A4, however, based on [I]/Ki ratio for clindamycin with respect to CYP3A4, it is considered that clindamycin should not substantially alter a second drug whose clearance is primarily medicated by CYP3A4.

III.4 Toxicology
Four additional reproductive and developmental toxicity studies have been performed since the previously submitted Pharmaco-toxicological expert report (Kolaja, 1997) that was used to support the original MRP application (approved in 1998 (IE/H/119/001)). From these studies malformations were not observed in either rat or rabbit and clindamycin phosphate was not a teratogen. The Embryo-foetal toxicity observed in rabbits was considered related to maternal toxicity and secondary to decreased food consumption during gestation, which is consistent with other studies with antibiotics. Safety margins from rat

and rabbit developmental NOAELs (250 and 5 mg/kg/day, respectively) were at doses 39 times and 5 times the mean AUC (3.2 g•h/mL) of clindamycin in healthy female volunteers administered clindamycin phosphate vaginal suppository (equivalent to 100 mg clindamycin) once daily for 3 days. Overall, these data support the original conclusions described in the Pharmaco-toxicological Expert Report which suggested that clindamycin phosphate and clindamycin HCl are not teratogenic and do not affect reproductive function.

III.5 Ecotoxicity/environmental risk assessment

This new formulation would be available to existing patients as an alternative to the vaginal cream currently on the market in the EU. Approval of the new formation is not expected to result in an increase in the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The new data submitted supports the original conclusions of the expert report on the pharmaco-toxicological documentation of Dalacin Vaginal Ovule (clindamycin phosphate vaginal ovule).

IV. CLINICAL ASPECTS

IV.1 Introduction

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted. An updated expert report was provided but most of the data provided in support of the original MR application were still the bases for the assessment.

IV.2 Pharmacokinetics

A pharmacokinetic study was conducted to evaluate the absolute bioavailability of clindamycin phosphate vaginal ovule and to assess relative bioavailability of the ovule compared to cream. This study sought to investigate the systemic absorption of Clindamycin following intravaginal administration of the ovule or 2% Clindamycin phosphate vaginal cream in normal subjects and non-pregnant patients with bacterial vaginosis. On two separate occasions, each subject received 100mg clindamycin phoshate as an ovule or 5mL of 2% clindamycin cream once daily in the evening for 3 consecutive days. During a third treatment period, subjects received a 4 minute intravenous infusion of the equivalent Clindamycin phosphate solution as a reference for the determination of absolute bioavailability of vaginal cream and ovule.

Results from the 12 evaluable healthy women showed that following intravaginal administration in healthy women, systemic absorption of Clindamycin averaged 30% (range 6.5 to 70%) and this was about 7 times greater than that following doses of the vaginal cream. Although it was suggested that vaginal or vulvar pruritus or burning associated with use of the ovule may have had associated inflammation which caused increased absorption, it is noted that there was no apparent trend toward higher absorption observed in 4 subjects reporting vaginal or vulvar pruritus, relative to other subjects.

The differences in absorption were considered to be related to differences in the drug or dose form effects on vaginal membranes

Based on comparison of the AUC values (with oral doses), the systemic absorption from a 100mg intra-vaginal ovule dose is 3 fold lower than that following the 150 or 300mg oral doses.

The results suggest that the clindamycin ovule is associated with greater absorption than with the vaginal cream with approximately 30% of the dose absorbed systemically after administration of the ovule.

The use of Dalacin Vaginal Ovule has not been studied in patients with impaired renal function and this is also stated in the SmPC and this is acceptable.
The use of Dalacin Vaginal Ovule has not been studied in patients under 16 years of age and this is stated in the SmPC.

IV.3 Pharmacodynamics

In a placebo controlled, randomised, double blind, dose duration pilot study 100mg Clindamycin ovules were administered at bed time for 3 or 5 consecutive days in patients with bacterial vaginosis diagnose using the standard criteria of vaginal fluid pH.4.5,amine odour after addition of 10% KOH and presence of clue cells. The five day enrolment treatment part of the study was stopped when the 3 day regimen was shown to be effective and based on results from 85 (43 placebo and 42 clindamycin) evaluable patients (cure of 52.4% of clindamycin patients versus 14.0% placebo patients) the 3 day regimen was considered to be superior to placebo and comparable to that previously seen with 3 and 7 day courses of clindamycin vaginal cream. This regimen was adopted for future studies.

This product has been available for many years. The rationale for the 3 day regimen is provided

IV.4 Clinical Efficacy

Efficacy results from the studies conducted to support the original submission for the vaginal formulations of clindamycin continue to support the use of the dalacin vaginal ovule as a suitable treatment for bacterial vaginosis. These results are further supported by the efficacy results from Study M/1114/0001 (TR-9150-98-002), which was completed after the original submission.

A current (2011) European guideline written by the International Union against Sexually Transmitted Infections cites clindamycin as a treatment option for bacterial vaginosis as follows:
Alternative regimens for bacterial vaginosis ONLY:

- Intravaginal metronidazole gel (0.75%) once daily for 5 days or
- Intravaginal clindamycin cream (2%) once daily for 7 days or
- Clindamycin 300 mg orally twice daily for 7 days.

The lack of general availability in the EU at present may account for the lack of inclusion of the ovules in the current European guideline, unlike in the USA, where they are available.
Two large clinical studies were performed using the vaginal ovule. Both studies were multi-centre, prospective, randomised, double-blind with administration of a control in the form of placebo or active comparator.

Study 0283 was a placebo controlled dose duration pilot study using a parallel design with sequential analysis. After an initial enrolment for a 3 day regimen was complete, enrolment for the 5 day regimen started with the 5 day enrolment ceasing as soon as analyses were performed showing the 3 day regimen to be effective.
Study 002 was an active controlled double dummy study comparing clindamycin vaginal ovules to oral metronidazole with patients receiving either clindamycin ovules for three days and oral placebo for 7 days or oral metronidazole for 7 days and placebo ovules for 3 days.
Similar criteria for determining efficacy were used in studies.
Study M/1114/0001 (TR- 9150-98-002) was an active-controlled, randomised, observer-blind study conducted in the US, Canada, and Mexico, comparing clindamycin vaginal ovules (CVO) for 3 days to clindamycin vaginal cream (CVC) for 7 days.
A total of 662 patients participated, 589 treated with clindamycin vaginal ovules, 196 with metronidazole and 57 with placebo.

The three clinical trials demonstrate the efficacy of 100-mg CVO, administered once daily for 3 days, in the treatment of bacterial vaginosis (BV). In the placebo-controlled pilot study (Study 0283), cure rates for evaluable patients (42 CVC, 43 placebo) were 52.4% for CVO patients and 14.0% for placebo patients, a statistically significant difference. In the pivotal active-controlled study (Protocol 0002) comparing CVO with oral metronidazole, cure rates for evaluable patients (113 CVC, 120 metronidazole) were 50.4% for CVC patients and 58.3% for metronidazole, a difference that was not statistically significant. The cure rates for CVO patients are comparable to those reported in previous submissions for patients receiving 3-day and 7-day regiments of CVC (ranging approximately 54% to 63%).
The third active controlled study (M/1114/0001 (TR-9150-98-002) comparing CVC with CVO cure rates for evaluable patients (203 CVC, 178 CVO) were 56.3% for the CVO patients and 50.4% for the CVC patients, a difference that was not statistically significant.

The use of Dalacin Vaginal Ovule has not been studied in patients under 16 years of age and this is stated in the SmPC.
The use of Dalacin Vaginal Ovule has not been studied in patients over 65 years of age and this is stated in the SmPC.
The use of Dalacin Vaginal Ovule has not been studied in patients with impaired renal function and this is also stated in the SmPC.

IV.5 Clinical Safety

The studies provided suggest that a 3 day regimen with 100mg of clindamycin vaginal ovule is effective and safe. The clinical trials have shown that 100mg of clindamycin administered once daily for 3 days in the treatment of bacterial vaginosis is superior to placebo and suggested that it is equivalent to metronidazole.
Vaginal moniliasis was the most frequently reported urogenital medical event in clinical trials reported in 3.8% of clindamycin vaginal ovule patients. It is important to note that the overall frequency of vaginal moniliasis may be estimated at up to 6.1% if events coded as moniliasis are included. Most cases were mild and none were serious. Vulvovaginal disorder was infrequent (2.3%), mild to moderate in intensity and non-serious.
The risk of antibiotic associated colitis in patients using clindamycin vaginal ovule therapy is likely to be minimal relative to systemic clindamycin therapy due to be far lower systemic exposure.

Whilst it is unclear why the absorption of clindamycin is greater with the ovule than with the cream, the levels attained are still significantly lower than with oral dosing.

The benefits of clindamycin vaginal ovules given at the recommended dosage of one 100-mg ovule daily for 3 consecutive days, in the treatment of BV outweigh any risks associated with its use.
Controlled clinical studies of clindamycin vaginal ovules have demonstrated safety and efficacy comparable to that of the most widely used antibiotic therapy for bacterial vaginitis, oral metronidazole. Patient compliance with the 3-day clindamycin vaginal ovules was shown to be slightly better than that observed for the 7-day metronidazole regimen studied. The observed adverse events were acceptable and analysis of post-marketing safety data (21 December 1998 to 01 September 2011) identified no new safety issues that alter the benefit/risk profile of the clindamycin phosphate vaginal formulations for the treatment of bacterial vaginitis.

In summary, safety and efficacy of this product in the vaginal ovule formulation has been adequately demonstrated.

The marketing authorisation holder (MAH) submitted documentation describing the Pharmacovigilance System in place, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dalacin 100mg Vaginal Ovules. The summary of safety concerns is as follows and it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Missing information

Important identified risks.	Vulvovaginal candidiasis. Pseudomembranous colitis.
Important potential risks.	Weakening of latex condoms and diaphragms.
Use in elderly patients over 65 years of age. Use in pregnant and lactating women. Use in paediatric patients under 16 years of age. Use in immunodeficient patients. Use in patients with colitis.	

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

V. OVERALL CONCLUSIONS

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The applicant has performed a number of studies which confirm the benefit and demonstrate an acceptable safety profile. Benefit risk of use of the vaginal ovules in the proposed indication is considered positive.