LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Propess
(dinoprostone)

SE/H/129/01/E02

This module reflects the scientific discussion for the approval of Propess. The procedure was finalised on 2018-05-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Ferring Läkemedel AB has applied for a marketing authorisation for Propess, 10mg, vaginal delivery system. The active substance is dinoprostone (prostaglandin E_2; PGE_2), a naturally occurring compound found in low concentrations in most tissues of the body. Local administration of dinoprostone to the cervix results in cervical ripening, which then induces the subsequent events which complete labour.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

In the initial preclinical assessment of Propess by the MPA in 1996, no preclinical issues were raised. Furthermore, during the MR procedure in 1997, no potentially serious health concerns were identified in the preclinical documentation. In the MR procedure (2000), the Applicant updated the file with several new preclinical studies, both pharmacodynamic, pharmacokinetic and toxicity studies. The toxic effects observed were all related to an exaggerated pharmacodynamic effect of PGE2, observed at dosages/exposures several-folds higher than clinical exposure. At the proposed single administration of Propess vaginal insert, no preclinical safety issues were identified.

III.1 Ecotoxicity/environmental risk assessment

The Applicant has performed an adequate ERA in accordance with available guidance. It can be concluded that propess, in the proposed use, does not pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The national approval of Propess in Sweden took place many years ago (1996). Hence, new clinical data have become available over time, both from clinical studies as well as from post-marketing data.

IV.2 Pharmacokinetics

It was concluded from the initial pharmacokinetic studies that the extent of systemic absorption of PGE_2 from the pessary is not well characterized due to lack of placebo arms in the studies. The pharmacokinetic documentation for Propess is however considered to be sufficient since Propess is intended to act locally and the safety of this drug is assessed based on the clinical evaluation.

The release rate of PGE_2 from the pessary is approximately 0.3 mg/hour over 24 hours in vivo. The mean plasma concentration of the PGE_2 metabolites, PGE_m and PGF_m increases 3-4-fold, 4-8 hours after application. Since there was no placebo treated group included in the study, it is uncertain as to whether the measured concentrations reflect the natural progression of PGE_2 concentration in blood or to what extent the plasma concentration of PGE_m and PGF_m represent an increase over baseline levels.
Studies have also been performed, assessing the release of PGE_2 from different pessaries and comparing two Propess vaginal inserts of different thickness showed that the thinner pessary (the one to be marketed) releases PGE_2 at a higher rate than the thicker pessary (0.27 vs 0.20 mg/hour).

IV.3 Pharmacodynamics

Dinoprostone (prostaglandin E_2; PGE_2) is a naturally occurring compound found in low concentrations in most tissues of the body. It functions as a local hormone. PGE_2 plays an important role in the biochemical and structural alterations involved in cervical ripening. Local administration of dinoprostone to the cervix results in cervical ripening, which then induces the subsequent events which complete labour.

IV.4 Clinical efficacy

As mentioned above, the product was nationally approved in Sweden more than 20 years ago and further clinical studies have become available after the initial approval.

In the initial clinical evaluation, it was concluded that PGE_2 has been used for cervical ripening and induction of labour for many years and that Propess has the advantage of interruption of treatment as labour starts or if adverse events occur. The cervical ripening effect of Propess was convincingly shown in placebo-controlled studies. However, it was concluded that no studies vs. active comparator products (e.g. prostaglandin gels) were available.

Subsequently, new comparative efficacy data became available from three studies. One study compared Propess inserts of different thickness and two published studies included comparisons with other commercially available cervical ripening agents (intracervical gel containing dinoprostone). It was concluded that in all three studies, cervical ripening, expressed as increase in Bishop Score, ripening time or mean change in Bishop Score, was more pronounced in the Propess 0.8 mm groups than in the comparator groups. This more pronounced effect on cervical ripening is reflected in shorter times to active labour and to a certain extent also in shorter time to vaginal delivery. It was concluded that Propess 0.8 mm is at least not less effective than the comparators in inducing cervical ripening and active labour.

Further data from more recent studies were also available, e.g. data from studies Miso-Obs-004 and Miso-Obs-303, conducted in 2006-2007 and 2010-2012, respectively, in the US and partly in Canada. In studies Miso-Obs-004 and Miso-Obs-303, different doses of MVI were compared against Propess. In Study Miso-Obs-004, MVI 50 microgram and MVI 100 microgram were compared against Propess and in Study Miso-Obs-303, MVI 200 mcg was compared against Propess. Efficacy data are summarized briefly below:

The conclusion of study Miso-Obs-004 was that the MVI 100 and the comparator (Propess) had beneficial effects on the primary efficacy variable of time to vaginal delivery with almost identical results (MVI 100 median time to delivery 1596 min, Propess 1650 min; not significantly different), i.e. around 27 hours. Similar effects were also seen with MVI 100 compared to Cervidil 10 mg (Propess) for secondary efficacy variables. The study showed that MVI 50 was not as effective as Cervidil 10 mg for any of the primary (time to vaginal delivery; median time 2127 min) and secondary assessments.

In study Miso-Obs-303, time to vaginal delivery during first hospitalization was statistically significantly shorter for MVI 200 subjects (median 21.5 hours) compared with DVI (Propess) subjects (median 32.8 hours, $p<0.001$).

Thus, data from these two studies suggest that the efficacy of Propess is similar to the mid-dose of the tested Misoprostol Vaginal Inserts, i.e. MVI 100.

Assessor's overall conclusions on clinical efficacy

Clinical studies performed to support the initial approval of Propess as well as later studies have demonstrated that Propess has a cervical ripening effect which is reflected in shorter times to active labour and also in shorter time to vaginal delivery. Several comparative studies now exist, showing that Propess is at least as effective as the comparators (intracervical dinoprostone gel and Misoprostol Vaginal Inserts, expect for the highest dose MVI 200) in inducing cervical ripening and active labour. Thus, the efficacy of Propess in the applied indication is considered adequately supported.

IV.5 Clinical safety

As for safety, more extensive information has become available over the years since the first approval. Throughout the assessment, the main focus of the safety assessment has been on the risk for causing uterine hyperactivity, which constitutes a severe risk for the foetus and to some extent also for the mother.

The most commonly reported adverse drug reactions in placebo-controlled and active comparator efficacy clinical trials (N=1116) were “foetal heart rate disorder” (6.9%), “uterine contractions abnormal” (6.2%) and “abnormal labour affecting foetus” (2.6 %) (as reflected in section 4.8 of the SmPC).

Abnormal labour affecting the foetus and abnormal uterine contractions can be mitigated by removing the insert. Based on data from the comparative studies mentioned in the Efficacy section above, there was a similar rate of caesarean delivery in the DVI group as for the comparators. The need of precautions for use is reflected in the SmPC, including detailed instructions on when to remove the insert.

Assessor’s overall conclusions on clinical safety
The safety profile of Propess is adequately characterised and the approved product information adequately describes how risks related to uterine hyperactivity can be mitigated.

IV.6 Risk Management Plans

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, characterize, prevent or minimize risks relating to Propess.

Safety specification

Summary of safety concerns	
Important identified risks	Uterine hyperstimulation Uterine rupture Foetal distress Anaphylactoid syndrome of pregnancy Disseminated intravascular coagulation
Important potential risks	None
Important missing information	None

The safety concerns listed by the MAH are considered appropriate.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Uterine hyperstimulation	
Routine risk minimisation measures	**CCDS:** 4.2 Dosage and administration: Instructions to remove PROPESS in case of: *"any suggestion of uterine hyperstimulation or hypertonic uterine contractions"* *"Effacement and dilatation of the cervix may not occur until uterine activity is established. Because of this, once regular painful uterine activity is established with PROPESS in-situ, the vaginal delivery system should be removed irrespective of cervical state to avoid the risk of uterine hyperstimulation"* 4.4 Warnings and precautions: *"uterine activity and fetal condition must be monitored regularly"* and *"If uterine contractions are prolonged or excessive, there is a possibility of uterine hypertonus or rupture and the vaginal delivery system should be removed"* 4.8 Undesirable effects: Uterine hyperstimulation (PT: Uterine hypertonus) is listed as common ADR
	Ferring dinoprostone is prescription only medicine intended for use in facilities where uterine activity and foetal condition can be monitored frequently
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Uterine rupture	
Routine risk minimisation measures	**CCDS:** 4.3 Contraindications: *Ferring dinoprostone should not be used or left in place when strong prolonged uterine contractions would be inappropriate such as in patients:* *a. who have had previous major uterine surgery, e.g. caesarean section, myomectomy etc (see sections 4.4 and 4.8)* *b. with cephalopelvic disproportion* *c. with fetal malpresentation* *d. with suspicion or evidence of fetal distress* *e. who have had more than three full term deliveries* *f. who have had previous surgery or rupture of the cervix* 4.4 Warning and precautions: *"uterine activity and fetal condition must be monitored regularly"* *"If uterine contractions are prolonged or excessive, there is a possibility of uterine hypertonus or rupture and the vaginal delivery system should be removed"* *"Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contra-indicated conditions"* 4.8 Undesirable effects: Uterine rupture is listed as a rare ADR
	Ferring dinoprostone is prescription only medicine intended for use in facilities where uterine activity and foetal condition can be monitored frequently
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Foetal distress	
Routine risk minimisation measures	**CCDS:** 4.2 Dosage and administration: Instructions to remove Ferring dinoprostone in case of: *"evidence of foetal distress"* 4.3 Contraindications: *"when strong prolonged uterine contractions would be inappropriate such as in patients with suspicion or evidence of foetal distress"* 4.4 Warning and precautions: *"After insertion, uterine activity and fetal condition must be monitored regularly"* *"If there is any suggestion of maternal or fetal complications or if adverse effects occur, the vaginal delivery system should be removed from the vagina"* 4.8 Undesirable effects: 'Abnormal labour affecting foetus', 'Foetal heart rate disorder' and 'Foetal distress syndrome' are listed as common ADRs
	Ferring dinoprostone is prescription only medicine intended for use in facilities where uterine activity and foetal condition can be monitored frequently
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Anaphylactoid syndrome of pregnancy	
Routine risk minimisation measures	**CCDS:** 4.4 Warnings and precautions (to be added): *"The Clinician should be alert that, as with other labour induction methods, use of dinoprostone may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism)".* 4.8 Undesirable effects: Anaphylactoid syndrome of pregnancy will be added in the ADR table in the 'frequency unknown' column
	Ferring dinoprostone is prescription only medicine intended for use in facilities where uterine activity and foetal condition can be monitored frequently
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Disseminated intravascular coagulation	
Routine risk minimisation measures	**CCDS:** 4.4 Warning and precautions: *"Women aged 35 and over, women with complications during pregnancy, such as gestational diabetes, arterial hypertension and hypothyroidism, and women at gestational age above 40 weeks have a higher post partum risk for developing disseminated intravascular coagulation (DIC). These factors may additionally enhance the risk of disseminated intravascular coagulation in women with pharmacologically induced labour (see section 4.8). Therefore, dinoprostone should be used with caution in these women. In the immediate post-partum phase the physician should look out carefully for early signs of a developing DIC (e.g fibrinolysis)"* 4.8 Undesirable effects: *"An increased risk of postpartum disseminated intravascular coagulation has been reported in patients whose labour was induced by pharmacological means, (see section 4.4)"* DIC is listed as a rare ADR
	Ferring dinoprstone is prescription only medicine intended for use in facilities where uterine activity and foetal condition can be monitored frequently
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Summary of the RMP

The RMP was approved in the variation procedure SE/H/129/01/II/51.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimization) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Swedish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clinical studies performed to support the initial approval of Propess as well as later studies have demonstrated that Propess has a cervical ripening effect which is reflected in shorter times to active labour and also in shorter time to vaginal delivery. Several comparative studies now exist, showing that Propess is at least as effective as the comparators (intracervical dinoprostone gel and Misoprostol Vaginal Inserts, expect for the highest dose MVI 200) in inducing cervical ripening and active labour. Thus, the efficacy of Propess in the applied indication is considered adequately supported.

The safety profile of Propess is satisfactorily characterised and the approved product information adequately describes how risks related to uterine hyperactivity, the main safety concern, can be mitigated. Post-marketing experience data from more than 20 years of use have confirmed this view. The possibility to remove the insert is an advantage with this product compared with e.g. intracervical gels. An adequate Risk Management Plan is in place.

Therefore, the benefit-risk of Propess in the initiation of cervical ripening in patients, at term (from 37 completed weeks of gestation), is positive.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Propess, vaginal delivery system was positively finalised on 2018-05-01.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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