Risk Management Plan

Active substance (INN or common name):	Dinoprostone
Pharmaco-therapeutic group (ATC Code):	G02AD02
Name of Marketing Authorisation Holder:	Ferring Pharmaceuticals A/S Kay Fiskers Plads 11, 2300 Copenhagen S Denmark
Product concerned (brand name(s)):	PROPESS/CERVIDIL

Data lock point for RMP:	30 June 2020	Version number:	3.0

Date of final sign off:	11 Nov 2020

Rationale for submitting an updated RMP:	Based on the PSUR single assessment (PSUSA/00001104/201909) the safety concerns were recommended to be removed from the RMP. All safety concerns have been re-assessed in light of revision 2 of GVP Module V and important identified risks are removed: - Foetal distress - Anaphylactoid syndrome of pregnancy - Disseminated intravascular coagulation
Summary of significant changes in this EU-RMP:	Safety concerns: Important identified risks removed from RMP: - Foetal distress - Anaphylactoid syndrome of pregnancy - Disseminated intravascular coagulation Please see Annex 8 for an overview of changes made to the risk management plan over time.

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

RMP Version number	Approved with procedure	Date of Approval
2.0	SE/H/129/001/II/051	26 April 2017

QPPV name: Lene Holdrup

QPPV oversight declaration:

The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV.

The electronic signature is available on file.

Part I: Product(s) Overview

Table 1 Part I – Product Overview

Active substance (INN or common name)	Dinoprostone
Pharmacotherapeutic group (ATC Code)	Oxytocics (G02AD02)
Marketing Authorisation Holder	Ferring Pharmaceuticals A/S Kay Fiskers Plads 11, 2300 Copenhagen S Denmark
Medicinal product to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	PROPESS
Marketing authorisation procedure	Mutual recognition
Brief description of the product	Chemical class: Oxytocics
	<u>Summary of mode of action:</u> Ferring dinoprostone is prostaglandin E2 (PGE2) that is a naturally occurring compound found in low concentrations in most tissues of the body. It functions as a local hormone. Local administration of dinoprostone to the cervix results in cervical ripening which then induces the subsequent events which complete labour.
	<u>Important information about its composition:</u> Ferring dinoprostone consists of a synthetic polymer slice containing10 mg dinoprostone. The slice is contained within the pouch of a knitted polyester retrieval system, which has been irradiated prior to insertion of the polymer slice. No materials used in the synthesis of Ferring dinoprostone are of animal or human origin.
Hyperlink to the Product Information	1.3.1 SmPC
Indication in the EEA	Initiation of cervical ripening in patients, at term (from 37 completed weeks of gestation).
Dosage in the EEA	Ferring dinoprostone is available as a vaginal delivery system containing 10 mg dinoprostone. A single administration of Ferring dinoprostone is recommended.

	Posology One vaginal delivery system administered high into the posterior vaginal fornix.
Pharmaceutical form and strength	Vaginal delivery system, containing 10 mg dinoprostone
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Ferring dinoprostone vaginal delivery system is registered under the trade names PROPESS and CERVIDIL and in this report, the term dinoprostone refers to these two names collectively.

Part II: Module SI - Epidemiology of the indication and target population

Indication

In the EEA Ferring dinoprostone has the following indication approved: Initiation of cervical ripening in patients, at term (from 37 completed weeks of gestation).

Incidence and prevalence:

There is a wide variation in the rate of induced labour between European countries. In 2013, rates of induced labour among nulliparous women varied from 13.8% in Sweden to 35.9% in Ireland and from 8.2% in Sweden to 28.1% in Malta among multiparous women[1]. The latest birth data from the United States for 2018 show that 27.1% of all pregnant women required medical intervention to induce labour[2], an increase compared to birth data for 2017 (25.7%)[3]. In England, in 2004–05, one in every five deliveries was induced compared to 33% in 2018–19 suggesting that the proportion of labour induction has been steadily increasing[4,5]. It is estimated that about 50% of women who require labour induction also require cervical ripening. For rates per country see Table 2.

Note: The countries presented in Table 2 is the data available.

Table 2 Rates of labour induction in European countries[1]

Country	Induction of Labour (% of respective nulliparous or multiparous births)	
	Nulliparous	Multiparous
Belgium	29.7	26.3
Denmark	31.9	24.5
Finland	23.0	19.3
Germany, State of Hesse	23.7	17.3
Ireland	35.9	23.0
Malta	33.0	28.1
Netherlands	33.3	25.3
Norway	19.7	15.2
Sweden	13.8	8.2
United Kingdom, England	27.2	21.2

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Women undergoing induction of labour tend to be older, primarily as the incidence of pre-existing comorbidities increases with age and, as a consequence, the risks related to expectant management of delivery at term pregnancies[6,7]. Common reasons for induction include postdate pregnancy, hypertension, pre-eclampsia, maternal diabetes, premature rupture of membranes and foetal growth restriction. Prolonged pregnancy (47%) and maternal hypertensive disorders (19%) are the major

indications in the UK. In a clinical study conducted in Italy, 24% of inductions were classified as elective and 24% as due to prolonged pregnancy[8]. In a US study in women with unfavourable cervix who required cervical ripening, prolonged pregnancy accounted for 32% of the subjects and elective and gestational hypertension for about 12% each[9]. In this randomised controlled trial mean age was 26 years at induction, however, women aged <18 years were excluded.

The main existing treatment options:

Pharmacological and mechanical methods are used for cervical ripening. The latter can be an inflatable balloon catheter inserted in the cervix, such as a Foley catheter or a device specifically developed and approved for the purpose of cervical ripening, the Cock catheter. The pharmacological methods in use are various preparations of prostaglandins, misoprostol (PGE1) and dinoprostone (PGE2). Non-Ferring dinoprostone is marketed as vaginal tablets, vaginal gel and intracervical gel.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

As a pregnancy continues beyond the term, the risk of both adverse events in the mother and the risk of foetal or perinatal death increases. A national register-based study in Denmark between 1978 and 1993 involving 77,956 post-term and 34,140 term singleton spontaneous deliveries showed an overall risk of perinatal death of 0.4% in the post-term group compared to 0.3% in the term group[10]. In a Cochrane review of 19 trials with a total of 7,984 women, excluding deaths due to congenital anomalies, there were no perinatal deaths in the labour induction group compared to nine deaths in the expectant management group[11]. A multicenter randomised controlled trial conducted in the Netherlands showed that induction of labour was associated with a lower risk of poor maternal outcome, which was mainly related to progression to severe disease, than was expectant monitoring[12].

Important co-morbidities:

Ferring dinoprostone is not indicated for a disease per se. It facilitates induction of labour where cervical ripening for unfavourable cervix is required. The need for induction can be due to a medical condition of the pregnant woman such as diabetes, preeclampsia, hypertension, deep vein thrombosis or a condition related to the foetus including oligohydramnios, reduced foetal movement and intrauterine growth restriction[13,14]. Prolonged pregnancy in such cases poses different risks dependent on the type of condition.

In general, induction of labour is sought to prevent a worsening of the condition or the occurrence of an event, such as eclampsia in women with preeclampsia or pulmonary embolus in women with deep vein thrombosis. Other indications for induction of labour include the conditions, which are at increased risk of intra-uterine foetal death, such as intra-uterine growth retardation, oligohydramnios or reduced foetal movement.

The frequencies of the most common medical conditions, maternal or foetal, expressed as primary reason for induction, in a US study[9] (n=1,358) in women with unfavourable cervix who required cervical ripening are presented in Table 3.

Table 3 Incidence of co-morbidities expressed as primary reason for induction, Miso-Obs 303[15]

Hypertension incl. pregnancy induced hypertension	12.2%
Preeclampsia	9.6%
Diabetes	6.7%
Prolonged pregnancy (more than 40 weeks)	32.2%
IUGR	5.2%
Non-reassuring CTG	-
Decreased foetal movement	0.7%
PROM	3.5%
Foetal macrosomia	0.3%
Oligohydramniosis	8.9%
Maternal haematological factor	0.4%
Cholestasis	1.3%

Part II: Module SII - Non-clinical part of the safety specification

Most of the available toxicological data on PGE2 are based on the experience of the former Upjohn Company products PROSTIN E2 and PREPIDIL for cervical ripening.

Table 4 Key safety findings from non-clinical studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single-dose toxicity	
Several of the exaggerated pharmacological effects of PGE2 that may be expected at high exposure levels were demonstrated. However, all findings were in line with the expected biological activity of the active component. The single dose toxicity studies did not reveal any new toxicological findings that may be of concern in the clinical use of Ferring dinoprostone.	The safety pharmacology and single dose toxicity data have shown a good safety profile for single administration of Ferring dinoprostone, which is confirmed by the clinical experience with only few signs of PGE2-related systemic adverse events.
Repeated-dose toxicity	
A wide range of treatment-related effects were seen in these studies however, all of the findings were in line with the expected biological activity of the active component of Ferring dinoprostone and were in agreement with previously reported data for the active substance.	No concerned raised.
Reproductive toxicity	
The perinatal development toxicity study was designed with a perinatal treatment schedule and subsequent effects hereof on pre- and post-natal development. Only minor effects were seen on parent females during the dosing period at a release rate 16 times that of humans. No effects on litters or development of offspring were seen at the same release rate (16 times that of humans).	The reproductive toxicity study has not revealed any new data that may impact the clinical use of Ferring dinoprostone, also it demonstrates that a reasonable safety margin is achievable through the use of a controlled release PGE2 formulation.
Nephrotoxicity	
No signs of nephrotoxicity were observed in any study.	No concerns raised.
Hepatotoxicity	
No signs of hepatotoxicity were observed in any study.	No concerns raised.
Carcinogenicity	
No carcinogenicity studies have been performed.	No concerns expected.
Genotoxicity	

No genotoxicity studies have been performed.	No concerns expected.
Mechanism for drug interactions and systemic exposure	
The non-clinical studies performed via the vaginal route at clinically relevant dose level demonstrated minimal transfer of radioactivity to the uterus, foetus and placenta indicating that the Ferring dinoprostone formulation does not possess a high risk of precipitating uterine overstimulation or foetal distress, which are well known adverse effects of PGE2 preparations. Furthermore, tissue distribution studies performed also appear to indicate that any PGE2 absorbed into the systemic circulation from the Ferring dinoprostone vaginal delivery system will be rapidly inactivated and excreted in the manner expected for this prostaglandin. Since dinoprostone is rapidly metabolised primarily in the local tissues and does not interact with cytochrome P450 enzyme systems, the potential for drug-drug interactions is considered to be low.	A low systemic exposure of dinoprostone should be expected with the recommended treatment. No drug-drug interactions should be expected.
General safety pharmacology	
Safety pharmacology revealed effects like diarrhoea, body temperature changes, increased heart rate and respiration, contractions in isolated ileum and slight diuretic effects. Most of the changes seen in the studies can be attributed to primary pharmacology of this PGE2 prostaglandin.	Safety pharmacology investigations have not revealed any previously unknown effects of PGE2 of which clinicians who use this substance are not already aware.
High exposure rates were used in many of the pre-clinical studies without adverse effects, these often being large multiples of the exposure rates that are encountered in human use.	The short period of exposure in the clinical setting (up to 24 hours), the controlled release characteristics of the formulation and the ability to retrieve the dosage form rapidly should an adverse event occur, all give reassurance that ‘over-dosing’ is very unlikely to occur. It is therefore concluded that there is a very low risk of any of the effects described in the nonclinical studies occurring in routine clinical use of Ferring dinoprostone.
A local tolerance study in rabbits reveal a slight exacerbation of the spontaneous findings of oedema and cellular infiltration in the vaginal mucosa by Ferring dinoprostone at a PGE2 exposure rate (mg/kg/hour) about twice that in human. These changes may be related to local pharmacological	Local tolerance investigations of the active component and the carrier-system have not revealed clinically significant signs of a local irritation potential of Ferring dinoprostone on the vaginal mucosa.

effects of the prostaglandin, and being slight in degree, are not considered to be of any major toxicological importance.	
The non-clinical studies performed with the hydrogel polymer, and the polyester polymer have not demonstrated any toxicological or local tolerance effects of concern. The novel retrieval system is made from polyester of medical grade. The results of the standard tests presented and its long established use in vascular grafts, for example, lead to the conclusion that there is nothing of concern with regard to safety.	No adverse effects should be expected from the hydrogel polymer and the polyester polymer retrieval system.

Conclusion on non-clinical data:

The safety profile of dinoprostone is well-established. The non-clinical data and the safety profile of Ferring dinoprostone and the polyester retrieval system presented, support the short and controlled exposure of women at term to PGE2 using this vaginal delivery system. No data have been generated that raise any significant concerns from a pharmacological or toxicological view point, and the available non-clinical data support the use of Ferring dinoprostone in the approved indication. In view of the considerable clinical experience with PGE2 over many years, further preclinical experimentation is not warranted to define the toxicity profile of the PGE2-impregnated vaginal delivery system. The toxicology studies with Ferring dinoprostone indicate a safe product at the intended human dosages as confirmed by its clinical use.

Part II: Module SIII - Clinical trial exposure

The cumulative exposure to Ferring dinoprostone in completed clinical trials during the clinical development programme up to 30 June 2020, is estimated to 2,424 subjects (see Table 5).

Table 5 Estimated cumulative subject exposure from clinical trials

Treatment	Number of Subjects
Ferring IMP	2,424
Comparator	1,861
Placebo	394

	Clinical trials								
	101-003	101-103	101-801	000262	PRO-002/-003/-004/-005	Miso-Obs-004	Miso-Obs-303	SOFTNES (FE999901 CS01)	Open uncontrolled trials (incl. 000261)
Treatment	Number of subjects								
Ferring IMP	176	42	102	57	243	436	680	89	599
Comparator 1	-	-	-	-	233	443	678	79	-
Comparator 2	-	-	-	-	-	428	-	-	-
Placebo	195	39	104	56	-	-	-	-	-
Total	**371**	**81**	**206**	**113**	**476**	**1,307**	**1,358**	**168**	**599**

There are no ongoing clinical trials for Ferring dinoprostone at the time of this report. Table 6 and Table 7 present pooled clinical trial data from the two most recently completed studies (000261 and 000262) for Ferring dinoprostone completed by Ferring.

Table 6 Cumulative subject exposure to investigational drug from most recently completed studies (000261 and 000262) by age and sex

Number of subjects			
Age range	**Male**	**Female**	**Total**
<25	N/A	13	**13**
>=35	N/A	66	**66**
25-<30	N/A	41	**41**
30-<35	N/A	61	**61**

Table 7 Cumulative subject exposure to investigational drug from most recently completed studies (000261 and 000262) by racial/ethnic group

Racial/ethnic group	Number of subjects
Asian	181
Black	N/A
Caucasian	N/A
Other	N/A
Unknown	N/A
Total	**181**

Tabulated summary of completed pharmacovigilance study programme is presented in Annex 2.

Part II: Module SIV - Populations not studied in clinical trials

Ferring dinoprostone has neither been studied in the children or elderly, however the use in these populations is not relevant as Ferring dinoprostone is only indicated for use in pregnant women.

Patients with multiple pregnancy were not included in the clinical development programme and Ferring dinoprostone should therefore be used with caution in these patients (see Table 8).

Safety, efficacy, and pharmacokinetics of Ferring dinoprostone in patients with renal or hepatic impairment have not been specifically studied in clinical trials and use in these patients is therefore not recommended (see Table 8).

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria which will remain as contraindications	
Criteria	**Implications for target population**
Previous major uterine surgery or rupture of the uterine cervix	Ferring dinoprostone should not be used in women with previous major uterine surgery, including caesarean section, as this increases the risk of uterine rupture in combination with strong prolonged uterine contractions that can occur with Ferring dinoprostone.
Cephalopelvic disproportion	Ferring dinoprostone should not be used in women with cephalopelvic disproportion as this increases the risk of uterine rupture in combination with strong prolonged uterine contractions that can occur with Ferring dinoprostone.
Foetal malpresentation	Ferring dinoprostone should not be used in women with foetal malpresentation as this, including abnormal lie, increases the risk of dystocia and therefore uterine rupture in combination with strong prolonged uterine contractions that can occur with Ferring dinoprostone.
Suspicion or evidence of foetal distress	Ferring dinoprostone should not be used in women with foetal distress as this can be aggravated by strong prolonged uterine contractions that can occur with Ferring dinoprostone.
Onset of labour	When labour has been established, whether it is spontaneous labour or labour induced by Ferring dinoprostone, (continued) administration of Ferring dinoprostone may cause uterine hypercontractility. Ferring dinoprostone is indicated for cervical ripening and the need for further ripening after onset of labour is rarely justified in clinical practice.

Patients already receiving intravenous oxytocic drugs/ or other labour induction agents	A pharmacodynamic interaction may occur between Ferring dinoprostone and administration of other drugs with uterotonic properties leading to uterine hypercontractility. There should be at least a 30 minutes waiting period after removal of Ferring dinoprostone until intravenous administration of oxytocin is started.
Current pelvic inflammatory disease	Ferring dinoprostone should not be used in women with current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
Placenta previa or unexplained vaginal bleeding	Ferring dinoprostone should not be used in women with vaginal bleeding as this can be due to placenta previa or partial placenta abruption. In the former case, vaginal delivery is contraindicated and, in the latter, vaginal delivery may be contraindicated or carries an increased risk of uterine hypercontractility.
Hypersensitivity to Prostaglandin E_2 or to any of the components of the drug	Ferring dinoprostone should not be used in women, who are allergic to Prostaglandin E_2.

Exclusion criteria which are not proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
Patients with cardiac lesions or cardiovascular conditions which may put them at undue risk of the hypotensive effect of PGE_2	The hypotensive effect of PGE_2 was considered to be sufficiently pronounced in order to be a risk to this patient category.	The hypotensive effect was re-evaluated and considered to be negligible.
Medication with aspirin or NSAIDs within four hours	These medications would potentially interact pharmacodynamically with dinoprostone and limit its efficacy.	The criteria is not a safety concern since Ferring dinoprostone is not indicated for a life threatening condition.
Drug or alcohol abuse	Risk of low compliance with study procedures	The criteria is not a safety concern.
More than three previous full term pregnancies	Ferring dinoprostone should not be used in women with more than three previous full	According to the EU SmPC guideline, a patient population not studied in the clinical trial

	term pregnancies as this increases the risk of uterine rupture in combination with strong prolonged uterine contractions that can occur with Ferring dinoprostone.	program should be mentioned in section 4.4 and not in section 4.3 unless the patients has been excluded due to a contraindication on grounds of safety. According to Ofir et al., 2003[16], parity was not showed to be a significant risk factor and Ferring has not experienced any safety issue related to parity.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency. Further, the clinical programme was not of an adequate size to allow quantification of the risk of rare reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 8 SIV.2: Special populations not included in clinical trial development programmes

Type of special population	
Pregnant women/ Breastfeeding women	No studies have been performed to investigate the amount of dinoprostone in colostrum of breast milk following the use of Ferring dinoprostone. Dinoprostone may be excreted in colostrum and breast milk, but the level and duration is expected to be very limited and should not hinder breastfeeding. No effects on the breastfed neonates have been observed in the clinical studies conducted[17].
Patients with multiple pregnancy	Patients with multiple pregnancy were not included in the clinical development programme.
Patients with renal or hepatic impairment	There is no experience with Ferring dinoprostone treatment in patients with impaired kidney or liver function.
Population with relevant different ethnic origin	The populations studied in the clinical trials were predominantly Caucasian. There is no data indicating a difference in efficacy or safety in different ethnicities.
Subpopulations carrying relevant genetic polymorphisms	There is no experience with Ferring dinoprostone treatment in patients carrying known and relevant polymorphisms.

Patients with a disease severity different from the inclusion criteria in the clinical trial population	The experience of Ferring dinoprostone in patients with ruptured membranes is limited.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

As of 30 June 2020 Ferring dinoprostone has been approved in 74 countries.

SV.1.1 Method used to calculate exposure

Since January 1999, Ferring has captured sales data in its current sales database. Prior to January 1999, detailed data was not captured in a systematic manner and is therefore not used. This information is used for estimating cumulative patient exposure presented in Table 9.

Calculation of patient exposure to Ferring dinoprostone is based on sales up to 30 June 2020. It is assumed that 100 percent of sales were consumed by patients. All calculations concerning patient exposure are based upon a single administration of the 10 mg dinoprostone vaginal delivery system.

SV.1.2 Exposure

The cumulative exposure to Ferring dinoprostone from marketing experience calculated up to 30 June 2020 is estimated to 9,902,133 patients. The estimated cumulative exposure to Ferring dinoprostone (expressed as number of patients exposed) is presented in Table 9.

Table 9 Cumulative exposure since January 1999 by region and number of patients

Region	Africa	Asia	Europe	N. America	S. America	Oceania	Total
No. of patients	150,385	1,894,809	4,704,561	2,870,169	121,581	160,628	**9,902,133**

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the pharmacological properties of Ferring dinoprostone misuse for illegal purposes is considered unlikely.

Part II: Module SVII - Identified and potential risks

Current safety concerns are listed in Table 14.

SVII.1 Identification of safety concerns in the initial RMP submission

Safety concerns in the initial RMP submission are listed in Table 10.

Table 10 Safety concerns in the initial RMP submission

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

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable as this is not the initial RMP for Ferring dinoprostone.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable as this is not the initial RMP for Ferring dinoprostone.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

'Foetal distress', 'Anaphylactoid syndrome of pregnancy' and 'Disseminated intravascular coagulation', all previously classified as important identified risks, are removed from the list of safety concerns since these risks are considered sufficiently well characterised and are adequately addressed in the SmPC. This is also in line with recommendations in the PSUSA/00001104/201909 assessment report. The safety concerns of 'Foetal distress', 'Anaphylactoid syndrome of pregnancy' and 'Disseminated intravascular coagulation' have been re-examined against the criteria for important identified risks in revision 2 of GVP module V as well as the clinical experience with dinoprostone and post-marketing safety surveillance.

Foetal distress (previously an important identified risk)

Transient and repetitive episodes of foetal hypoxemia and hypoxia manifested as foetal heart rate changes, even at the level of the central nervous system are common during normal labour and are generally well tolerated by the foetus[18]. The potential mechanism for the foetal distress (defined as need for prompt caesarean delivery) are excessive or prolonged uterine contractions that result in decreases in foetal oxygenation and umbilical cord or head compression. Some degree of maternal

hypotension occurs in 5 to 25 % epidural blocks[24]. Maternal hypotension can cause interruption of oxygen pathway to the foetus (hypoxia) that may manifest as late decelerations during fetal heart rate monitoring. Maternal position (supine) can also affect placental perfusion. Other risk factors of foetal distress include placental insufficiency, intrauterine growth retardation, maternal hypertension, pre-eclampsia, oligohydramnios, gestational diabetes, multiple pregnancy and maternal drug abuse, which are all indication for induction of labour and therefore also confounding factors.

'Foetal distress' type adverse events were reported differently throughout the development of Ferring dinoprostone. Generally, two main types of foetal distress adverse events were reported, 1) events that occurred independently (without an accompanying abnormal uterine contraction pattern) or 2) events that were in close temporal relation to abnormal uterine contraction patterns. The terms used to report the umbrella term 'Foetal distress' are non-specific, have low positive predictive value and are often associated with an infant who is in good condition at birth.
In the pivotal clinical trials 'Foetal distress' was reported as 'Foetal acidosis', 'Pathological CTG', 'Foetal heart rate abnormalities', 'Intrauterine hypoxia' or 'Threatening asphyxia'. For the Miso-Obs trials, 'Foetal distress' was reported as the PT 'Foetal heart rate disorder'. In pivotal clinical trials 'Abnormal labour affecting foetus' as expression for hyperstimulation syndrome was in clinical studies reported as 'Uterine tachysystole' combined with 'Late decelerations', Fetal bradycardia', or 'Prolonged decelerations'.

In pivotal clinical trials, the frequency of adverse drug reactions (ADRs) considered as 'Foetal distress' without an associated uterine hyperstimulation event was 3.8%. In pooled analysis of Miso-Obs-004 and 303 the frequency of 'Foetal heart rate disorder' ADRs was 6.9%. In the Japanese phase III clinical trials (000261 and 000262), there was one serious adverse reaction of 'Nonreassuring foetal heart rate pattern'. In pooled results of Miso-Obs-004 and 303 the frequency of 'Abnormal labour affecting foetus' ADR in the dinoprostone vaginal delivery system (DVDS) safety population (reported as 'Uterine tachysystole' or 'Hypertonus with foetal heart rate disorder') was 2.3%. Frequency of 'Abnormal labour affecting foetus' ADR (reported as 'Uterine hyperstimulation with foetal distress') in pivotal clinical trials was 2.8%.

Cumulatively until 30 June 2020, a search within Ferring safety database, with MedDRA HLT (high level term) 'Foetal complications', Foetal conditions due to maternal conditions' and 'Foetal and neonatal diagnostic procedures' yielded 333 ADRs (234 serious and 99 non-serious) in 298 cases from post-marketing sources for Ferring dinoprostone, distributed as per Table 11.

Table 11 Distribution of post-marketing 'Foetal distress' ADRs cumulatively

Preferred Term	Cumulative	
	Serious	Non-Serious
HLT 'Foetal complications NEC'		
Foetal distress syndrome	62	5

Preferred Term	Cumulative	
	Serious	Non-Serious
Bradycardia foetal	36	7
Foetal heart rate deceleration abnormality	28	12
Tachycardia foetal	19	13
Foetal heart rate disorder	18	2
Foetal arrhythmia	2	0
Nonreassuring foetal heart rate pattern	2	0
Foetal acidosis	1	0
Baseline foetal heart rate variability disorder	1	1
Foetal disorder	0	1
HLT 'Foetal conditions due to maternal conditions'		
Abnormal labour affecting foetus	27	27
HLT 'Foetal and neonatal diagnostic procedures'		
Foetal heart rate abnormal	17	16
Foetal monitoring abnormal	11	9
Foetal heart rate increased	5	3
Foetal heart rate decreased	4	3
Foetal heart rate	1	0
Grand Total	**234**	**99**

The outcome for the 333 ADRs of 'Foetal distress' was: recovered/recovering/recovered with sequelae (201), unknown (109), fatal (21) and not recovered (2). The fatal ADRs were: 'Foetal distress syndrome' (10) 'Foetal heart disorder' (4), 'Bradycardia foetal' (4), 'Foetal heart rate abnormal' (2) and 'Foetal heart rate decreased' (1).

Regarding the 21 fatal ADRs of 'Foetal distress' maternal fatality was reported for all. In addition for 3 of the 21 fatal 'Foetal distress' foetus/neonate fatality was co-reported. For 15 of the 21 fatal 'Foetal distress' maternal risk factors and obstetric complications that may have contributed to the foetal/neonatal/maternal outcomes were co-reported: maternal hypertension, amniotic fluid embolism, strong uterine contractions, premature separation of placenta, and uterine rupture. For 2 of the 21 fatal 'Foetal distress' dinoprostone was contraindicated due to the previous caesarean section and multiparity. For the remaining 4 fatal 'Foetal distress' there was limited or no information on the clinical course, maternal medical history, co-morbidities and concomitant medication.

Foetal distress often leads to emergency caesarean section, which can be associated with risks for both the mother or the neonate and Ferring dinoprostone should not be administered when there is suspicion or evidence of foetal distress. Only when hypoxia and resultant metabolic acidemia reach extreme levels is the foetus at risk of long-term neurologic impairment[19].

In an unselected population the overall risk of foetal distress was 3.1%. The risk exceeded 20% in patients with moderate/severe asthma, severe hypothyroidism, severe preeclampsia, and post-term or foetal growth restricted foetuses with abnormal Doppler studies[20]. The incidence of the 'Foetal distress' in women treated with Ferring dinoprostone appears to be low, and in the last five years the annual reporting rates of 'Foetal distress' have been estimated between 0.02 and 0.04 events per 1,000 patient exposures.

Conclusively, Ferring's assessment is that 'Foetal distress' neither requires risk minimisation measures nor further evaluation as part of pharmacovigilance plan but is appropriately managed by continued routine pharmacovigilance. It is further considered to be appropriately managed by the contraindication and precaution in the product information and to be well known by health care professionals. 'Foetal distress' is not considered to have an impact on the benefit-risk profile for Ferring dinoprostone and keeping it as an important identified risk is not expected to result in further characterisation. This is also in line with PRAC's assessment as presented in the assessment report for procedure PSUSA/00001104/201909. Therefore, the important identified risk of 'Foetal distress' is removed from the list of safety concerns.

Anaphylactoid syndrome of pregnancy (previously an important identified risk):
Anaphylactoid syndrome of pregnancy (ASP, previously known as amniotic fluid embolism) is a rare but serious condition with a high fatality for both mother and foetus/neonate. Although ASP is a rare event, the fatality rate is very high and reported as 20 to 90%. The estimated incidence of ASP is 1:15,200 (0.06 in 1,000) deliveries in the USA and 1:53,800 (0.19 in 1,000) deliveries in Europe[21]. Risk factors of ASP vary and include multiple pregnancy, advanced maternal age, multiparity, surgical and medical inductions of labour, Caesarean section, tetanic contractions, precipitous labour, placental abnormalities, eclampsia, polyhydramnios, and uterine rupture[22]. The pathophysiology of ASP is not completely understood but postulated to be caused by amniotic fluid, foetal cells, hair or other debris entering the maternal circulation via the placental bed of the uterus causing an allergic reaction. Anaphylactoid syndrome of pregnancy is considered class risk seen with other cervical ripening and labour induction products.

No case reports of ASP with Ferring dinoprostone have been reported from the clinical trials.

Cumulatively until 30 June 2020, a search within Ferring safety database, by MedDRA PT 'Anaphylactoid syndrome of pregnancy' (ASP) yielded a total of 25 ADRs (all serious) in 25 cases from post-marketing sources for Ferring dinoprostone. The outcomes for the 25 ADRs of ASP were: fatal (15), unknown (7), and recovered (3).

Regarding the 15 fatal ADRs of ASP, maternal fatality was reported for all, in addition for 3 of the 15 fatal ASP foetus/neonate fatality was co-reported. For 6 of the15 fatal ASP maternal risk factors and obstetric complications that may have contributed to the maternal/foetal/neonatal outcomes were co-reported: maternal age (≥ 35), gestational age (≥ 40 weeks), pre-eclampsia, and disseminated intravascular coagulation (DIC). For the remaining 9 fatal ASP limited/no information

on the clinical course, maternal medical history, co-morbidities and concomitant medication was reported.

ASP is diagnosed when sudden severe signs and symptoms progressing rapidly to coma and death occur during labour or postpartum[21]. Survival depends on early recognition and immediate intensive treatment. Also, overall neonatal outcomes have improved with prompt delivery[22]. The occurrence of ASP cannot be predicted or prevented. The clinician should be alert that, as with other labour induction methods, use of Ferring dinoprostone may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of anaphylactoid syndrome of pregnancy.

The incidence of ASP in women exposed to Ferring dinoprostone appears to be low and in the last five years the annual reporting rates of ASP have been estimated between zero reported events and 0.002 events per 1,000 patient exposures. Based on this reporting rate, even taking into account the common under-reporting of post-marketing ADRs, the incidence of ASP in connection with treatment with Ferring dinoprostone is very rare (<1/10,000 and not higher than (or similar to) the observed incidence in the USA and Europe).

Conclusively, Ferring's assessment is that anaphylactoid syndrome of pregnancy neither requires risk minimisation measures nor further evaluation as part of pharmacovigilance plan but is appropriately managed by continued routine pharmacovigilance. It is further considered to be appropriately managed by the contraindication and precaution in the product information, and to be well known by health care professionals. Anaphylactoid syndrome of pregnancy is not considered to have an impact on the benefit-risk profile for Ferring dinoprostone and keeping anaphylactoid syndrome of pregnancy as an important identified risk is not expected to result in further characterisation. This is also in line with PRAC's assessment as presented in the assessment report for procedure PSUSA/00001104/201909. Therefore, the important identified risk of 'Anaphylactoid syndrome of pregnancy' (ASP) is removed from the list of safety concerns.

Disseminated intravascular coagulation (previously identified as important identified risk)
Postpartum disseminated intravascular coagulation (DIC) is a rare condition with high fatality rate, for both the mother and foetus/neonate. DIC is an acquired syndrome characterised by formation of microthrombi and fibrin deposition in the microvasculature. In some cases DIC may be preceded by symptoms suggesting ASP. The precise mechanism inducing DIC from ASP remains unclear but is probably multifactorial. DIC is a syndrome characterized by a massive, widespread, and ongoing activation of the coagulation system, secondary to a variety of clinical conditions. In modern obstetric practice the most common cause is haemorrhagic shock with delay in resuscitation leading to endothelial damage. Risk factors include pre-eclampsia, sepsis, septic abortion, intrauterine infection, retained dead foetus, hydatidiform mole, placenta accrete, abruptio placentae and amniotic fluid embolism[23]. Likewise, an increased risk of postpartum DIC has been described in patients whose labour has been induced by any physiological or pharmacological method[24].

Disseminated intravascular coagulation is considered class risk seen with other cervical ripening and labour induction products.

No case reports of DIC with Ferring dinoprostone have been reported from the clinical trials. The literature describes postpartum DIC occurring in 6 in 10,000 (0.06%) of induced women[24].

Cumulatively until 30 June 2020, a search within Ferring safety database, by MedDRA PT 'Disseminated intravascular coagulation' (DIC), yielded a total of 19 ADRs (all serious) in 19 cases from post-marketing sources for Ferring dinoprostone. The outcome for the 19 ADRs of DIC, per number of occurrences, was: recovered/recovered with sequelae (8), fatal (7), and unknown (4).

Regarding the 7 fatal ADRs of DIC, maternal fatality was reported for all. In addition for 1 of the 7 fatal DIC foetus/neonate fatality was co-reported. For 5 of the 7 fatal DIC maternal risk factors that may have contributed to the maternal/foetal/neonatal outcome were co-reported: maternal age (≥35), gestational age (≤40 weeks), gestational diabetes, mild pre-eclampsia, hypothyroidism, arterial hypertension and ASP. Also, in connection with 2 of the 7 fatal DIC Ferring dinoprostone was administered multiple times (off-label use).

As previously mentioned, risk factors of postpartum DIC include advanced maternal age (≥35), complications during pregnancy and high gestational age (≥40 weeks)[24]. These factors may additionally enhance the risk of DIC in women with pharmacologically induced labour, therefore dinoprostone should be used with caution in these women[17]. The literature describes postpartum DIC occurring in 0.6 in 1,000 (0.06%) for induced woman[24]. Further, a single administration of Ferring dinoprostone is recommended as the effects of a second dose have not been studied. Many obstetric complications, such as abruptio placentae, amniotic fluid embolism, endotoxin sepsis, retained dead foetus, post-haemorrhagic shock, hydatidiform mole, and gynaecologic malignancies, might trigger DIC. In these gynaecologic and obstetric settings, DIC is usually associated with high fatality rates and severe morbidity[25]. However, the incidence of the Ferring dinoprostone associated DIC appears to be low compared to incidence reported in literature, and in the last five years the annual reporting rates of DIC have been estimated between 0.001 and 0.004 events per 1,000 patient exposures.

Conclusively, Ferring's assessment is that disseminated intravascular coagulation neither requires risk minimisation measures nor further evaluation as part of pharmacovigilance plan but is appropriately managed by continued routine pharmacovigilance. It is further considered to be appropriately managed by the contraindication and precaution in the product information and to be well known by health care professionals. Disseminated intravascular coagulation is not considered to have an impact on the benefit-risk profile for Ferring dinoprostone. Keeping disseminated intravascular coagulation as an important identified risk is not expected to result in further characterisation. This is also in line with PRAC's assessment as presented in the assessment report for procedure PSUSA/00001104/201909. Therefore, the important identified risk of 'Disseminated intravascular coagulation' (DIC) is removed from the list of safety concerns.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk 1: Uterine hyperstimulation

Table 12 Distribution of 'Uterine hyperstimulation' ADRs cumulatively

Preferred Term	Cumulative	
	Serious	Non-Serious
Uterine hyperstimulation	89	141
Uterine hypertonus	71	54
Uterine tachysystole	8	27
Uterine contractions abnormal	3	16
Uterine spasm	2	0
Grand Total	**173**	**238**

Characterisation of the important identified risk of uterine hyperstimulation is presented below.

Important identified risk: Uterine hyperstimulation	
Frequency	Clinical: The overall frequency of uterine hyperstimulation (uterine tachysystole and uterine hypertonus) in integrated results of pivotal clinical trials was 7.3% (based on pooled data from the pivotal efficacy clinical trials 101-801, 101-003 and 101-103 (n=320) and Miso-Obs-004 and 303 (n=1,116)), and the majority of ADRs from these trials were mild or moderate in severity. One case (0.8%) of Uterine contractions abnormal was observed in Japanese phase III clinical trials (000261 and 000262 studies). Note: The terms reported in the pivotal clinical trials (101-801, -003, -103) versus the Miso-Obs clinical studies varied but were consistent with the MedDRA PT terms used to code adverse events representative of the important identified risk 'Uterine hyperstimulation' (see row 'MedDRA terms').

Important identified risk: Uterine hyperstimulation	
Seriousness/outcomes	Clinical: In pivotal clinical trials dinoprostone vaginal insert (DVI) was removed in all but three cases resulting in normal uterine activity. There was no adverse effect on the neonatal outcome in any of the cases. In Miso-Obs-004 and 303 the majority of uterine contractions abnormal (uterine tachysystole) did not lead to removal of the insert. Incidence of uterine contractions abnormal leading to study drug removal was 1.5% (17 of 1116 subjects). No events were regarded as serious.
Severity and nature of risk	The majority of the ADRs concerning uterine hyperstimulation, uterine tachysystole and uterine hypertonus from clinical trials were mild or moderate in severity.
Background incidence/prevalence	Uterine tachysystole occurs in more than 10% of spontaneous labours and is associated with non-reassuring FHR, increased rate of caesarean deliveries and NICU admissions. It is not associated with low Apgar scores or meconium-stained amniotic fluid.
Risk groups or risk factors	The risk increases with labour induction or labour augmentation, such as the use of prostaglandins and/or oxytocin for stimulation of uterine contractility. Epidural anaesthesia and hypertension have also been shown as increasing the risk of tachysystole.
Potential mechanisms	Excessive pharmacological effect of an exogenously applied uterotonic.
Preventability	After insertion of Ferring dinoprostone uterine activity and foetal condition must be regularly monitored. Also, Ferring dinoprostone should be removed if uterine contractions are excessive or prolonged and as soon as active labour is established (Section 4.4. CCDS/SmPC). If excessive uterine contractions continue after drug removal tocolytic treatments should be considered.
Impact on individual patient	Severe uterine hyperstimulation can result in placental abruption, foetal distress and uterine rupture. The consequences of a uterine rupture can range from uterine repair, to hysterectomy and in some circumstances to maternal or foetal death.

Important identified risk: Uterine hyperstimulation	
Potential public health impact of safety concern	Potential negative effects on the foetus (foetal distress) or the mother (uterine rupture).
Evidence source	Ferring Global Safety Database, summary of clinical safety data, literature.
MedDRA terms	PTs: 'Uterine hypertonus', 'Uterine contractions abnormal', 'Uterine hyperstimulation', 'Uterine tachysystole', 'Uterine spasm'.
Regulatory Actions	The risk minimisation activities for uterine rupture are addressed in the current SmPC sections 4.2, 4.3 and 4.4. An update of the SmPC has been proposed in accordance with the PRAC endorsed recommendations made in procedure PSUSA/00001104/201909 to strengthen the warnings and contraindications to further minimise the risk of uterine rupture. The correct use and handling of the product as well as contraindications, warnings and precautions to minimize risks attributable to incorrect product use are clarified and further reinforced in the proposed updates to the previously mentioned SmPC sections.

Impact on the risk-benefit balance of the product:

Uterine tachysystole occurs in more than 10% of spontaneous labours and is associated with non-reassuring foetal heart rate, increased rate of caesarean deliveries and neonatal intensive care unit admissions[26]. It is not associated with low Apgar scores or meconium-stained amniotic fluid[26].

Ferring dinoprostone vaginal insert has been designed to control the release of dinoprostone by removing it when adverse event that can compromise the safety of the mother or the foetus occurs. After withdrawal, due to the short half-life of dinoprostone, the median time to resolution of uterine hyperstimulation (tachysystole or hypertonus) with foetal heart rate involvement is 8.5 minutes[27].

The achievement of a vaginal delivery in over 70% of the women with an unripe cervix is of great clinical relevance since the alternative to cervical ripening for these women would in most cases be either an uncertain and risk-filled expectancy or a caesarean delivery. In many institutions, women who once had a caesarean section would not be candidates for vaginal delivery in subsequent pregnancies. The reduction of the incidence of caesarean deliveries with Ferring dinoprostone therefore has far-reaching implications.

Important Identified Risk 2: Uterine rupture

Table 13 Distribution of 'Uterine rupture' ADRs cumulatively

Preferred Term	Cumulative	
	Serious	Non-Serious
Uterine rupture	76	1
Uterine perforation	1	0
Uterine dehiscence	0	1
Grand Total	**77**	**2**

Characterisation of the important identified risk of uterine rupture is presented below.

Important identified risk: Uterine rupture	
Frequency	Clinical: No case reports of uterine rupture were received from clinical trials.
Seriousness/outcomes	Uterine rupture is always a serious event with implications for both the mother and the foetus. It can lead to foetal disorders, foetal death, hysterectomy and in some cases – fatal outcome for the mother.
Severity and nature of risk	In general, uterine rupture may range from incomplete rupture, where the visceral peritoneum is still intact, to complete rupture, where the contents of the uterus may enter the peritoneal cavity or broad ligament. Complete uterine rupture is potentially life-threatening for both the mother and the foetus.
Background incidence/prevalence	Published rates of uterine rupture in industrialised nations range between 1:200 (0.5 %) in Norway[28] to 1:3314 (0.03 %) in the United States of America[29].
Risk groups or risk factors	The risk increases with labour induction or labour augmentation, such as the use of prostaglandins and/or oxytocin for stimulation of uterine contractility. Risk factors include uterine scars (previous uterine surgery e.g. caesarean section), multiparity, high maternal age, high gestational age (GA) (≥42 weeks) and high birth weight (≥4000g).[30]
Potential mechanisms	Excessive pharmacological effect of an exogenously applied uterotonic causing the uterine muscle to tear.

Important identified risk: Uterine rupture	
Preventability	Ferring dinoprostone is contraindicated when oxytocic drugs and/or other labour induction agents are being given, when there is suspicion or evidence of uterine scar resulting from previous uterine surgery (e.g. caesarean delivery), when there is uterine abnormality and when there is placenta previa or unexplained vaginal bleeding. In accordance with SmPC section 4.4 'Special warning and precautions for use', Ferring dinoprostone is to be removed if uterine contractions are excessive or prolonged, or there is a clinical concern for the mother or baby. If excessive uterine contractions continue after drug removal, tocolytic treatments should be considered.
Impact on individual patient	The consequences of a uterine rupture can range from uterine repair, to hysterectomy and in some circumstances to maternal or foetal death.
Potential public health impact of safety concern	Uterine rupture is a rare complication of labour, which can result in serious outcomes for the mother and the foetus. However, labour induction may be required to prevent other unfavourable outcomes.
Evidence source	Ferring Global Safety Database, summary of clinical safety data, literature.
MedDRA terms	Preferred terms (PTs): 'Uterine dehiscence', 'Uterine perforation', 'Uterine rupture'.
Regulatory actions	The risk minimisation activities for uterine rupture are addressed in the current SmPC sections 4.2, 4.3 and 4.4. An update of the SmPC has been proposed in accordance with the PRAC endorsed recommendations made in procedure PSUSA/00001104/201909 to strengthen the warnings and contraindications to further minimise the risk of uterine rupture. The correct use and handling of the product as well as contraindications, warnings and precautions to minimize risks attributable to incorrect product use are clarified and further reinforced in the proposed updates to the previously mentioned SmPC sections.

Impact on the risk-benefit balance of the product:

Having multiple risk factors likely compounds the risk of uterine rupture. The Ferring dinoprostone SmPC recommends using Ferring dinoprostone with caution in women aged 35 and over, or with hypertension, gestational diabetes or hypothyroidism because of the risk of delivery complications[31,32,33,34,35].

Women aged 35 or over, or with hypertension, gestational diabetes or hypothyroidism, together with other described risk factors for uterine rupture such as high parity, foetal macrosomia, or polyhydramnios, are often the indications for labour induction because expectant management until spontaneous labour is considered at higher risk for foetal demise than termination of pregnancy[36, 37].

A recently updated Cochrane Systematic Review found evidence that a policy of induction of labour at 37 weeks of gestation or beyond compared to expectant management is associated with fewer neonatal deaths, stillbirths and caesarean sections[38].

SVII.3.2. Presentation of the missing information

No missing information is classified as a safety concern.

Part II: Module SVIII - Summary of the safety concerns

A summary of the safety concerns is presented in Table 14.

Table 14 SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Uterine hyperstimulation Uterine rupture
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Cumulative and interval review of adverse events of interest for the safety concerns are included in the periodic safety update reports (PBRERs). Routine pharmacovigilance activities beyond adverse reactions reporting, post-marketing safety surveillance and signal detection are not planned for Ferring dinoprostone.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies have been proposed by Ferring pharmaceuticals and none have been performed as specific obligation and/or as a condition of the MA.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

Note: In the PSUR single assessment (PSUSA/00001104/201909) issued on 14 May 2020, and with data lock point of 30 September 2019, Ferring was invited to discuss ways to further minimise the risk of uterine hyperstimulation including serious complications such as uterine rupture, foetal and neonatal death, and uterine haemorrhage. Ferring considers that the product information (SmPC) already includes wording to prevent uterine hyperstimulation including serious complications such as uterine rupture, foetal and neonatal death, and uterine haemorrhage therefore, Ferring has proposed to strengthen the wording of the current SmPC in the sections 4.2, 4.3, and 4.4. The proposed wording has been submitted in the follow-up (SE/H/PSUFU/00001104/201909), on 19 August 2020, and at the time of this report Ferring is awaiting PRAC's assessment and recommendation.

Effectiveness of the above mentioned routine risk minimisation measure will be monitored via routine pharmacovigilance and described in succeeding PSURs.

No additional risk minimisation measures are proposed besides routine pharmacovigilance activities including routine risk minimisation measures addressed in the product labelling (see below).

V.1. Routine Risk Minimisation Measures

Note: Routine risk minimisation activities for safety concerns presented in Table 15 are in accordance with the current version of the SmPC (version 2.0, effective 29 February 2016).

Table 15 Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern:	Routine risk minimisation activities
Important identified risk 1: Uterine hyperstimulation	Routine risk communication: CCDS/SmPC: - Section 4.2. states that it is necessary to remove PROPESS/CERVIDIL in case of any suggestion of uterine hyperstimulation or hypertonic uterine contractions. Also, that 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. - In section 4.8, 'uterine contractions abnormal' (reported as 'uterine hyperstimulation' and 'uterine hypertonus') is listed as a common ADR.

	In the PIL this information and orientation to avoid this condition is emphasized.
	Routine risk minimisation activities recommending specific clinical measures (beyond standard care) to address the risk: - Section 4.4 of the CCDS/SmPC states that uterine activity and foetal 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.
	Other routine risk minimisation measures: Prescription only medicine.
Safety concern:	**Routine risk minimisation activities**
Important identified risk 2: Uterine rupture	Routine risk communication: CCDS/SmPC: - Section 4.3, states that strong prolonged uterine contractions are contraindicated. - Section 4.4. states that PROPESS/CERVIDIL should not be administered to patients with a history of previous caesarean section or uterine surgery given the potential risk for uterine rupture and associated obstetrical complications. Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contra-indicated conditions. - Section 4.8, 'uterine rupture' is listed as a rare ADR. In the PIL this information and orientation to avoid this condition is emphasized.
	Routine risk minimisation activities recommending specific clinical measures (beyond standard care) to address the risk: - CCDS/SmPC, section 4.4. states that uterine activity and foetal 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.
	Other routine risk minimisation measures: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Removal of additional risk minimisation activities

Not applicable.

V.3 Summary of risk minimisation measures

Note: Summary of risk minimisation measures for safety concerns presented in Table 16 are in accordance with the current version of the SmPC (version 2.0, effective 29 February 2016).

Table 16 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Uterine hyperstimulation	Routine risk minimisation measures: - CCDS/SmPC section 4.2. states that it is necessary to remove the PROPESS/CERVIDIL in case of any suggestion of uterine hyperstimulation or hypertonic uterine contractions. Further, 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. - CCDS/SmPC section 4.4 states that 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. - CCDS/SmPC section 4.8, 'uterine contractions abnormal' is listed as a common ADR. - In the PIL this information and orientation to avoid this condition is emphasized.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None.	Additional pharmacovigilance activities: None.
Uterine rupture	Routine risk minimisation measures: - CCDS/SmPC section 4.3 states that strong prolonged uterine contractions are contraindicated. - CCDS/SmPC section 4.4 states that PROPESS/CERVIDIL should not be administered to patients with a history of previous caesarean section or uterine surgery given the potential risk for uterine rupture and associated obstetrical complications. Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contra-indicated conditions. - CCDS/SmPC section 4.4 states that uterine activity and foetal 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. - CCDS/SmPC section 4.8 ‘uterine rupture’ is listed as a rare ADR. - In the PIL this information and orientation to avoid this condition is emphasized.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.
	Additional risk minimisation measures: None.	Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for PROPESS/CERVIDIL. The RMP details important risks of PROPESS/CERVIDIL, how these risks can be minimised, and how more information will be obtained about PROPESS/CERVIDIL's risks.

PROPESS/CERVIDIL's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PROPESS/CERVIDIL should be used.

Important new concerns or changes to the current ones will be included in updates of PROPESS/CERVIDIL's RMP.

I. The medicine and what it is used for

PROPESS/CERVIDIL is authorised for initiation of cervical ripening in patients, at term (from 37 completed weeks of gestation) (see SmPC for the full indication). It contains dinoprostone as the active substance and it is given by vaginal delivery system, containing 10 mg dinoprostone.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PROPESS/CERVIDIL together with measures to minimise such risks and the proposed studies for learning more about PROPESS/CERVIDIL 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Ferring dinoprostone are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which

there is sufficient proof of a link with the use of Ferring dinoprostone. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Uterine hyperstimulation Uterine rupture
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Uterine hyperstimulation	
Evidence for linking the risk to the medicine	Ferring Global Safety Database, summary of clinical safety data, literature.
Risk factors and risk groups	The risk increases with labour induction or labour augmentation, such as the use of prostaglandins and/or oxytocin for stimulation of uterine contractility. Epidural anaesthesia and hypertension have also been shown as increasing the risk of tachysystole.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> - CCDS/SmPC section 4.2 states that it is necessary to remove the PROPESS/CERVIDIL in case of any suggestion of uterine hyperstimulation or hypertonic uterine contractions. Further, 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. - CCDS/SmPC section 4.8 ‘uterine contractions abnormal’ is listed as a common ADR. - In the PIL this information and orientation to avoid this condition is emphasized. <u>Routine risk minimisation activities recommending specific clinical measures (beyond standard care) to address the risk:</u> - CCDS/SmPC section 4.4 states that 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.

	Additional risk minimisation measures: None.

Important identified risk: Uterine rupture	
Evidence for linking the risk to the medicine	Ferring Global Safety Database, summary of clinical safety data, literature.
Risk factors and risk groups	The risk increases with labour induction or labour augmentation, such as the use of prostaglandins and/or oxytocin for stimulation of uterine contractility. Risk factors include uterine scars (previous uterine surgery e.g. caesarean section), multiparity, high maternal age, high gestational age (GA) (≥42 weeks) and high birth weight (≥4000g).[39]
Risk minimisation measures	Routine risk minimisation measures: - CCDS/SmPC section 4.3 states that strong prolonged uterine contractions are contraindicated. - CCDS/SmPC section 4.4 states that PROPESS/CERVIDIL should not be administered to patients with a history of previous caesarean section or uterine surgery given the potential risk for uterine rupture and associated obstetrical complications. Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contra-indicated conditions. - CCDS/SmPC section 4.8 'uterine rupture' is listed as a rare ADR. - In the PIL this information and orientation to avoid this condition is emphasized. Routine risk minimisation activities recommending specific clinical measures (beyond standard care) to address the risk: - CCDS/SmPC section 4.4 states that uterine activity and foetal 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. Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ferring dinoprostone.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ferring dinoprostone.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Only applicable for medicinal products approved by centralised procedure.

Annex 2 – Tabulated summary of completed pharmacovigilance study programme

Table 17 Annex II: Completed studies

Study	Description (Phase, short description of study including comparator name(s)/placebo)	Countries	Study design	Number of patients	Completion date/ Link to report
Main studies					
101-801	Phase III study versus placebo in pregnant women at or near term (at least 37 weeks gestation) with a medical or obstetrical indication for the induction of labour and Bishops score ≤4	US (10 centres)	Randomised double-blind	206 102 DVI (active) 104 Placebo	1992/1993 E-Clinical Study Report Body-21507
101-003	Phase III study versus placebo in pregnant women at or near term (at least 37 weeks gestation) with a medical or obstetrical indication for the induction of labour and Bishops score ≤4	US (6 centres)	Randomised double-blind	371 176 DVI (active) 195 Placebo	1991 Study Report: December 1993 E-Clinical Study Report Body-21508
101-103	Phase III study versus placebo in pregnant women at or near term (at least 37 weeks gestation) with a medical or obstetrical indication for the induction of labour and Bishops score ≤4	US (1 centre)	Randomised double-blind	81 42 DVI 39 Placebo	September 1993 E-Clinical Study Report Body-21509
Further safety/efficacy studies					
000261	Phase III Trial Investigating the Efficacy and Safety of FE 999901 Vaginal Insert in Pregnant Women at Term (≥ 37 weeks and < 41 weeks of gestation) Requiring Cervical Ripening. Indication: pregnant women at term requiring cervical ripening	Japan	Multicentre, open-label	68	LPLV: 25 February 2018 E-Clinical Study Report Body-22974
000262	Phase III Trial Investigating the Efficacy and Safety of FE 999901 Vaginal Insert in Pregnant Women at Term (41 weeks of gestation) Requiring Cervical Ripening	Japan	Multicentre, Randomized, Double-blind, Placebo controlled	114 57 DVI 57 Placebo	LPLV: 30 August 2018 E-Clinical Study Report Body-23242
000228 (PK)	Phase 1 trial, investigating pharmacokinetics, safety and tolerability of controlled release FE 999901 (dinoprostone) vaginal insert (DVI) in healthy pre-menopausal Japanese and non-Japanese women	Japan, (single centre)	Open-label	20 10 Japanese 10 Non-Japanese	LPLV: 18 May 2016 E-Clinical Study Report Body-20906
MISO-OBS-004	Phase III study comparing the efficacy and safety of misoprostol vaginal insert (MVI) to CERVIDIL for women requiring cervical ripening and induction of labour	US Canada (52 centres)	Randomised double-blind	1307 436 DVI 428 MVI 100 443 MVI 50	LPLV: 07 August 2007 Study report: 28 November 2007 (CT.gov July 2009) E-Clinical Study Report Body-14352
MISO-OBS-303	Phase III study comparing the efficacy and safety of misoprostol vaginal insert (MVI) 200mcg to dinoprostone vaginal insert (DVI) for reducing time to	US (34 centres)	Randomised double-blind	1358 680 DVI	LPLV: 15 March 2012 Study report: 5 July 2012 E-Clinical Study Report Body-21190

Study	Description (Phase, short description of study including comparator name(s)/placebo)	Countries	Study design	Number of patients	Completion date/ Link to report
	vaginal delivery in pregnant women				
CS01 SOFTNES	Phase IV study comparing the efficacy and safety of DVI plus/minus Oxytocin to Oxytocin alone for women requiring cervical ripening prior to induction of labour	Brazil (5 centres)	Randomised, open-label	200 planned/ 168 completed 89 DVI	January 2012 (Study was terminated early due to problems enrolling adequate number of patients
PRO-002/003/004/005	Phase III/IV study Comparing the efficacy and safety of PROPESS (DVI) and dinoprostone gel for cervical ripening and initiation of labour	France, Sweden, Netherlands, Germany (12 centres)	Randomised, open-label	476 243 DVI 233 Gel	LPLV: July 1999 Study report: 03 July 2001 E-Clinical Study Report Body-21511
101-003 Open	Phase III Included subjects from pivotal trial 101-003 (described above) who did not meet the criterion of a Bishop Score≤ 4, but had a score 5 or 6	US (6 centres)	Uncontrolled open-label	67	1991 Study report: December 1993 E-Clinical Study Report Body-21512
	Phase III Included placebo-treated subjects from pivotal trial 101-003 (described above)	US (6 centres)	Uncontrolled open-label	142	1991 Study report: E-Clinical Study Report Body-21512
	Phase III An open label evaluation of PGE_2 in a controlled release vaginal pessary as a ripening agent for the unfavourable cervix in the medically or obstetrically indicated induction of labour	US (1 centre)	Uncontrolled, open-label	67	1991 Study report: E-Clinical Study Report Body-21512
101-105	Phase II study of the safety and efficacy of a controlled release PGE_2 vaginal infusette™ as a ripening agent for the unfavourable cervix in the induction of labour	UK (1 centre)	Uncontrolled, open-label	6	1989 Study report: March 1993 E-Clinical Study Report Body-21514
101-550	Phase II study assessing the ease and reliability of removal of a controlled release pessary from the posterior fornix of the vagina when fitted in a retrieval device and the efficacy of the pessary when enclosed in the retrieval system.	UK (1 centre)	Uncontrolled, open-label	111	Study report: October 1993 E-Clinical Study Report Body-21515
101-100 (Safety)	Phase II study comparing the safety and efficacy of controlled release PGE_2 pessary and Witepsol based PGE_2 pessary	UK (1 centre)	Open, randomised parallel group	195	Not stated E-Clinical Study Report Body-21516
101-100 Follow-up (Safety)	A retrospective study of the long-term effects of PGE_2 on children born of mothers treated with PGE_2 (in study 101-100) compared to control patients not recieving PGE_2	UK (1 centre)	Open	313 infants 51 infants of mothers who received controlled release PGE_2 (Propess)	Study report: June 1990 E-Clinical Study Report Body-21517
101-101 (Safety)	Phase II study investigating the in vivo (and in vitro) release rate, safety and efficacy of controlled release PGE_2	UK (1 centre)	Open, non-randomised	33	Study report: November 1993 E-Clinical Study Report Body-21518

Study	Description (Phase, short description of study including comparator name(s)/placebo)	Countries	Study design	Number of patients	Completion date/ Link to report
101-104 (Safety)	Phase I study evaluating the ease of removal and feasibility of the use of an attached cord in the removal of a blank placebo pessary from the posterior fornix of the vagina and to study PGE_m blood levels	UK (1 centre)	Open, non-randomised	5	Study report: March 1993 E-Clinical Study Report Body-21519
101-109 (Safety)	Phase II study investigating the efficacy of Propess to ripen cervix of primiparae with Bishops score ≤ 6 and to compare safety and efficacy of a second pessary v. oxytocin in patients with a Bishops score < 8 after the first pessary.	UK (1 centre)	Open, randomised	27	Study report: March 1993 E-Clinical Study Report Body-21520
101-401 (Safety)	Phase II study investigating the in vivo and in vitro release, safety and efficacy of a controlled release pessary containing 10 mg PGE_2	UK (1 centre)	Open, non-randomised	27	Study report: November 1993 E-Clinical Study Report Body-21521
101-501 (Safety)	Phase II study investigating the in vivo and in vitro release, safety and efficacy of a controlled release pessary containing 10 mg PGE_2	UK (1 centre)	Open, non-randomised	24	Study report: October 1993 E-Clinical Study Report Body-21522
101-107 (Safety)	Phase II study with the objective to determine effect (or lack of effect) of Propess on patients undergoing elective surgical termination of a first trimester pregnancy	UK (1 centre)	Double blind randomised, placebo-controlled	21 10 DV 11 Placebo	Study report: May 1989 E-Clinical Study Report Body-21523
101-201 (PD)	Phase II study with the objective to determine the in vivo and in vitro release rate characteristics as well as efficacy and safety of Propess in the target population	UK (1 centre)	Open	24	Study report: October 1993 E-Clinical Study Report Body-21501
101-601 (PD)	Phase II study with the objective to determine the in vivo and in vitro release rate, efficacy and safety of Propess in the target population	US (1 centre)	Open	31	Study report: April 1993 E-Clinical Study Report Body-21502
101-701 (PD)	Phase II study determining the *in vivo* (and *in vitro* release), safety and efficacy of Propess in the target population using pessaries contained within the retrieval device and pessaries not contained in a retrieval device.	US (1 centre)	Open, randomized, comparative	63	Study report: April 1993 E-Clinical Study Report Body-21503
PRO-001 (PD)	Phase IIb *in vivo* controlled release of PGE from Propess (0.8mm) 10 mg ripening of the unfavourable cervix during induction of labour.	Sweden (1 centre)	Open	68	Study report: June 1998 E-Clinical Study Report Body-21504
L004ZPI/001 (PD)	Phase IV study comparing the *in vivo* dissolution rates over a maximum of 24 hours of two formulations of a dinoprostone vaginal pessary (1.1 mm vs 0.8	UK (4 centres)	Double-blind, randomised, parallel group	184	Study report: June 1998 E-Clinical Study Report Body-21504

Study	Description (Phase, short description of study including comparator name(s)/placebo)	Countries	Study design	Number of patients	Completion date/ Link to report
	mm) in medically or obstetrically indicated induction of labour				

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

None (not applicable).

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

None (not applicable).

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Approved protocols:
None (not applicable).

Final protocols not reviewed or not approved:
None (not applicable).

Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up forms

Not applicable (no specific adverse drug reaction follow-up forms).

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable (no planned and on-going imposed post authorisation studies).

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable (no proposed additional risk minimisation activities).

Annex 7 - Other supporting data (including referenced material)

Literature references

[1] Seijmonsbergen-Schermers AE, et al. Variations in use of childbirth interventions in 13 high-income countries: A multinational cross-sectional study. PLoS Med 2020;17(5): e1003103.

[2] Martin JA, et al. Births: Final Data for 2018. National Vital Statistics Reports. 2019;68(13):1–47.

[3] Osterman MJK, Martin JA. Recent declines in induction of labor by gestational age. NCHS data brief, no 155. Hyattsville, MD: National Center for Health Statistics. 2014.

[4] NHS Maternity Statistics, England: 2004-05. Available at: https://files.digital.nhs.uk/publicationimport/pub01xxx/pub01674/nhs-mater-eng-2004-2005-rep.pdf. (Last accessed 5 September 2020)

[5] The NHS Maternity Statistics, England: 2018-19. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2018-19, Last accessed 5 September 2020)

[6] Sarah J Stock, Evelyn Ferguson, Andrew Duffy Ian Ford, James Chalmers, Jane E. Outcomes of elective induction of labour compared with expectant management: population based study. BMJ 2012; 344

[7] Mary N. ZAKI, Judith U. HIBBARD, and Michelle A. KOMINIAREK, Contemporary Labor Patterns and Maternal Age. Obstet Gynecol. 2013 November; 122(5): 1018–1024.

[8] Gerli S, Favilli A, Giordano C, Bini V and Di Renzo GC. Single indications of induction of labor with prostaglandins and risk of caesarean delivery: A retrospective cohort study. J. Obstet. Gynaecol. Res. 2013.

[9] Clinical study report Miso-Obs-303. The EXPEDITE Study: a phase III, double-blind randomized, multicentre study of exogenous prostaglandin comparing the efficacy and safety of the misoprostol vaginal insert (MVI) 200 mcg to the dinoprostone vaginal insert for reducing time to vaginal delivery in pregnant women at term.

[10] Olsen AW, Wetergaard JG, Olsen J. Perinatal and maternal complications related to postterm delivery: a national register-based study, 1978-1993. Am J Obstet Gynecol. 2003;189;222-7.

[11] Begley CM, Gyte GML, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour (Review). In: The Cochrane Library 2011;11.

[12] Koopmans, Corine M et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial). The Lancet, Volume 374, Issue 9694, 979 – 988

[13] Gülmezoglu, A Metin et al. "Induction of Labour for Improving Birth Outcomes for Women at or beyond Term." The Cochrane database of systematic reviews 6 (2012): CD004945. PMC. Web. 6 Jan. 2017

[14] Mozurkewich, E., Chilimigras, J., Koepke, E., Keeton, K. and King, V. (2009), Indications for induction of labour: a best-evidence review. BJOG: An International Journal of Obstetrics & - Gynaecology, 116: 626–636. doi:10.1111/j.1471-0528.2008. 02065.x

[15] Clinical study report Miso-Obs-303. The EXPEDITE Study: a phase III, double-blind randomized, multicentre study of exogenous prostaglandin comparing the efficacy and safety of the misoprostol vaginal insert (MVI) 200 mcg to the dinoprostone vaginal insert for reducing time to vaginal delivery in pregnant women at term, Table 14.

[16] Ofir K, Sheiner E, Levy A, Katz M, Mazor M. Uterine rupture: Risk factors and pregnancy outcome. *Am J Obstet Gynecol*. 2003;189: 1042-6

[17] Company Core Data Sheet (CCDS) PROPESS/CERVIDIL vaginal delivery system 10 mg, Company Core Data Sheet-5971, ver. 2.0. effective 29 February 2016.

[18] American College of obstetricians and Gynecologists (ACOG), Technical Bulletin 207: Fetal Heart Rate Patterns: Monitoring, interpretation and Management. July 1995.

[19] American College of Obstetricians and Gynecologists (ACOG), Practice Bulletin 106: Intrapartum Fetal Heart Rate Monitoring: Nomenclature, Interpretation, and General Management Principles. July 2009.

[20] Chauhan SP., Magann EF. and Scott JR. Caesarean delivery for fetal distress: rate and risk factors. Obstet Gynecol 2003 May; 58(5):337-350.

[21] Conde-Agudelo A et al. Amniotic Fluid Embolism: an evidence-based review. Am J Obstet Gynecol, 2009 Nov; 201(5):445 e1-e13.

[22] Clark SL. Amniotic fluid embolism. Clin Obstet Gynecol. 2010 Jun;53(2):322-8

[23] Letsky EA. Disseminated intravascular coagulation. Best Practice & Research Clinical Obstetrics and Gynaecology 2001 Aug;15(4):623-44.

[24] De Abajo FJ et al. Labour Induction with Dinoprostone or Oxytocin and Postpartum Disseminated Intravascular Coagulation: a hospital-based case-control study. Am J Obstet Gynaecol 2004 Nov; 191(5):1637-1643.

[25] Montagnana M., Franchi M., Danese E et al. Disseminated Intravascular Coagulation in Obstetric and Gynaecologic Disorders. Semin Thromb Hemost 2010 Jun; 36(4): 404-418.

[26] Ahmed I. Ahmed et al. Uterine tachysystole in spontaneous labour at term (2016). The Journal of Maternal-Fetal & Neonatal Medicine. doi: 10.3109/14767058.2015.1125463

[27] Rugarn, O., Tipping, D., Powers, B., & Wing, D. (2017). Rugarn, O., Tipping, D., Powers, B., & Wing, D. A. (2017). Induction of labour with retrievable prostaglandin vaginal inserts: outcomes following retrieval due to an intrapartum adverse event. BJOG: an international journal of obstetrics and gynaecology, 124(5), 796-803. doi:10.1111/1471-0528.14147

[28] Al-Zirqi I., Stray-Pedersen B., Forse L. and Vangen S. Uterine rupture after previous caesarean section. BJOG 2010 Jun; 117(7):809-820

[29] Yap OW S., Kim ES. and Laros RK. Maternal and neonatal outcomes after uterine rupture I labor. Am J Obstet Gynecol 2001 Jun; 184(7):1576-1581

[30] Kaczmarczyk M et al. Risk factors for uterine rupture and the neonatal consequences: a population-based study of successive pregnancies in Sweden. BJOG 2007 Oct; 114(10):1208-1214.

[31] Lydon-Rochelle, M., Holt, V., Easterling, T., & Martin, D. (2001). Risk of uterine rupture during labor among women with a prior caesarean delivery. N Engl J Med, 345(1), 3-8.doi:10.1056/NEJM200107053450101

[32] Lean, S. C., Derricott, H., Jones, R. L., & Heazell, A. P. (2017). Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. PLoS One, 12(10), e0186287. doi: 10.1371/journal.pone.0186287

[33] Elbers, L., Fliers, E., & Cannegieter, S. (2018). The influence of thyroid function on the coagulation system and its clinical consequences. J of Thromb Haemost, 16, 634-45.
[34] Dennedy, M., & Dunne, F. (2010). The maternal and fetal impacts of obesity and gestational diabetes on pregnancy outcome. Best Practice & Research Clinical Endocrinology & Metabolism, 24(4), 573-589. doi: https://doi.org/10.1016/j.beem.2010.06.001

[35] Hutcheon, J., Lisonkova, S., & Joseph, K. (2011). Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol, 25(4), 391-403. doi: 10.1016/j.bpobgyn.2011.01.006

[36] Pierce, S., Bakker, R., Myers, D. A., & Edwards, R. K. (2018). Clinical Insights for Cervical Ripening and Labor Induction Using Prostaglandins. AJP reports, 8(4), e307-e314. doi: https://doi.org/10.1055/s-0038-1675351

[37] Magro-Malosso, E., Saccone, G., Chen, M., Navathe, R., Di Tomaso, M., & Berghella, V.(2017). Induction of labour for suspected macrosomia at term in non-diabetic women: a systematic review and meta-analysis of randomized controlled trials. BJOG: an international journal of obstetrics and gynaecology, 124(3), 414-421. doi: https://doi.org/10.1111/1471-0528.14435

[38] Middleton, P., Shepherd, E., Morris, J., Crowther, C. A., & Gomersall, J. C. (2020). Induction of labour at or beyond 37 weeks' gestation. Cochrane Database of Systematic Reviews (7), Art. No.: CD004945. doi: 10.1002/14651858.CD004945.pub5.

[39] Kaczmarczyk M et al. Risk factors for uterine rupture and the neonatal consequences: a population-based study of successive pregnancies in Sweden. BJOG 2007 Oct; 114(10):1208-1214.

Annex 8 - Summary of changes to the risk management plan over time

Version	Approval date/ Procedure	Change
3.0	Format: EU GVP Module V revision 2	The RMP was updated based on the PSUR single assessment (PSUSA/00001104/201909) for the PSUR submitted to EMA in December 2019. Part II: Module SI, 'Incidence and prevalence' updated. <u>Safety Concerns</u> Removal of Important Identified Risks in line with recommendations in the PSUSA/00001104/201909 assessment report and in line with EU GVP module V, revision 2: - Foetal distress - Anaphylactoid syndrome of pregnancy - Disseminated intravascular coagulation <u>Pharmacovigilance Plan</u> No changes. <u>Post-authorisation Efficacy Plan</u> No changes. <u>Risk Minimisation Measures</u> No changes.
2.0	18 January 2017 Format: EU Vol 9A	<u>Safety concerns</u> No changes. <u>Missing information:</u> None.
1.0	05 December 2014 Format: EU Vol 9A	Initial RMP.