NEW ZEALAND DATA SHEET

CERVIDIL® 10mg PESSARY

Dinoprostone (Prostaglandin E_2)

1 PRODUCT NAME

CERVIDIL® 10mg PESSARY

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pessary (vaginal insert) contains 10 mg of dinoprostone (prostaglandin E_2) and releases a mean dose of approximately 0.3 mg dinoprostone per hour over 24 hours. The dinoprostone is dispersed throughout a matrix consisting of 241 mg of hexanetriol/macrogol 8000/isocyanate cross-linked hydrogel copolymer, which is a semi-transparent, beige coloured, flat rectangular pessary (vaginal insert) measuring 29 mm by 9.5 mm and 0.8 mm in thickness. The pessary (vaginal insert) and its retrieval system, made of polyester yarn, are non-toxic and, when placed in a moist environment, absorb water, swell, and release dinoprostone.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

CERVIDIL® is a thin, flat, polymeric pessary (vaginal insert) which is rectangular in shape with rounded corners. The pessary (vaginal insert) is contained within the pouch of an off-white knitted polyester retrieval system designed to aid retrieval at the end of the dosing interval.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervical ripening in patients, at or near term, who have favourable induction features and in whom there is a medical or obstetrical indication for induction of labour.

4.2 Dose and method of administration

CERVIDIL® is used as a single dosage in a single application. Cervidil should only be administered by qualified healthcare personnel in hospitals and clinics with obstetric units with facilities for continuous fetal and uterine monitoring.

After insertion, uterine activity and fetal condition must be carefully and regularly monitored.

Paediatric population

The safety and efficacy of CERVIDIL® in pregnant woman aged less than 18 years has not been established. No data are available.

Administration

CERVIDIL® should be removed from the freezer immediately prior to the insertion. There is no need for prior warming of the product. To remove CERVIDIL® from the packaging, first tear the foil along the top of the sachet. Do not use scissors or sharp instruments to cut the foil as this may damage the product. Use the retrieval tape to gently pull the product out of the sachet.

The pessary (vaginal insert) should be inserted immediately after removal from the freezer and its foil package, however, controlled periods of time of up to one month at 2-8°C can be allowed within the shelf life of the product. CERVIDIL® must not be used without its retrieval system.

One pessary (vaginal insert) should be inserted high into the posterior vaginal fornix using only small amounts of water soluble lubricants to aid insertion. After CERVIDIL® has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside the vagina to allow removal. No attempt should be made to tuck the end of the tape into the vagina as this may make retrieval more difficult.

The patient should be recumbent for 30 minutes after insertion. As dinoprostone (PGE_2) will be released continuously over a period of 24 hours, it is important to monitor uterine contractions and fetal condition at frequent regular intervals.

Removal

The pessary (vaginal insert) can be removed quickly and easily by gentle traction on the retrieval tape. After removal ensure that the entire product, pessary (vaginal insert) and retrieval system, has been removed from the vagina.

It is necessary to remove the pessary (vaginal insert) to terminate drug administration when cervical ripening is judged to be complete or for any of the reasons listed below.

1. Onset of labour. For the purposes of induction of labour with CERVIDIL®, the onset of labour is defined as the presence of regular painful uterine contractions occurring every 3 minutes irrespective of any cervical change. There are two important points to note:
    (i) Once regular, painful contractions have been established with CERVIDIL®, they will not reduce in frequency or intensity as long as CERVIDIL® remains in situ because dinoprostone (PGE_2) is still being administered, nor will they reduce if CERVIDIL® is removed because the woman is in labour.
    (ii) Patients, particularly multigravidae, may develop regular painful contractions without any apparent cervical change. 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 CERVIDIL® in-situ, the pessary (vaginal insert) should be removed irrespective of cervical state to avoid the risk of uterine hyperstimulation.
2. Spontaneous rupture of the membranes or amniotomy.
3. Any suggestion of uterine hyperstimulation or hypertonic uterine contractions.
4. Evidence of fetal distress.
5. Evidence of maternal systemic adverse dinoprostone (PGE_2) effects such as nausea, vomiting, hypotension or tachycardia.
6. At least 30 minutes prior to starting an intravenous infusion of uterotonic drugs.
7. CERVIDIL® should be removed after 24 hours irrespective of whether cervical ripening has been achieved.

Upon removal of the product from the vagina, the pessary (vaginal insert) will have swollen

2-3 times its original size and be pliable. The whole product should be disposed of as clinical waste.

4.3 Contraindications

CERVIDIL® SHOULD NOT BE USED OR LEFT IN PLACE IN THE FOLLOWING CONDITIONS:

1. When there is known hypersensitivity to dinoprostone (Prostaglandin E_2) or any other constituent of the pessary (vaginal insert) (eg urethane).
2. When the patient is carrying more than one fetus.
3. When labour has started.
4. When uterotonic drugs and /or other labour induction agents are being given or if they are to be given intravenously within 30 minutes.
5. 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 (see sections 4.4 and 4.8)
    b. who have had previous major uterine cervix surgery (e.g. other than biopsies and cervical abrasion) or rupture of the uterine cervix
    c. with cephalopelvic disproportion
    d. with fetal malpresentation
    e. with suspicion or evidence of fetal distress (eg abnormal cardiotocography)
6. When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
7. Where vaginal delivery is not indicated, eg placenta praevia or active herpes genitalis
8. When there has been unexplained vaginal bleeding during the pregnancy.
9. When there is abnormal cardiotocography or suspected fetal compromise.
10. In the presence of any suggestion of uterine hyperstimulation or hypertonic uterine contractions.

4.4 Special warnings and precautions for use

For hospital use only

CERVIDIL® should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities for continuous fetal and uterine monitoring.

The condition of the cervix should be assessed carefully before CERVIDIL® is used.

Use with caution in patients with cervical (Bishop) scores of 8 or more.

CERVIDIL should be used with caution when the woman has had more than three full term deliveries. No studies in woman with more than three full term deliveries have been performed.

The experience of CERVIDIL® in patients with ruptured membranes is limited. Therefore, CERVIDIL® should be used with caution in those patients. Since the release of dinoprostone from the insert can

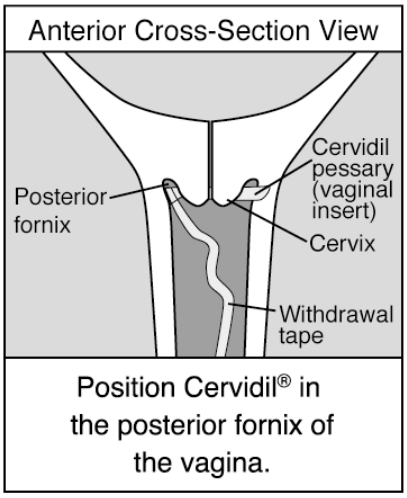
be affected in the presence of amniotic fluid, special attention should be given to uterine activity and fetal condition.

Uterine rupture has been reported in association with the use of CERVIDIL®, mainly in patients with contraindicated conditions (see section 4.3). Therefore, 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.

As with other uterotonics agents, the possibility of uterine hypertonus or rupture should be considered in the presence of prolonged or excessive uterine activity or unusual uterine pain. CERVIDIL® should be removed immediately in those cases.

After insertion, CERVIDIL® should be positioned transversely into the posterior fornix of the vagina (Figure 1). Incorrect positioning of the vaginal insert could lead to the loss of device from the vagina and consequent lack of efficacy, due to insufficient exposure of the cervix to the appropriate sustained concentrations of prostaglandin.

Figure 1



After insertion, uterine activity, fetal condition and the progression of cervical dilatation and effacement must be monitored carefully and regularly by qualified healthcare personnel. CERVIDIL® must only be used in hospitals and clinics with obstetric units with facilities for continuous fetal and uterine monitoring. If there is any suggestion of maternal or fetal complications or if adverse effects occur, the pessary (vaginal insert) should be removed.

CERVIDIL® should be removed after 24 hours irrespective of whether cervical ripening has been achieved.

Since prostaglandins potentiate the effect of oxytocin, CERVIDIL® must be removed before oxytocin administration is initiated (see section 4.5) and the patient's uterine activity carefully monitored for uterine hyperstimulation.

If uterine hyperstimulation is encountered or if labour commences, the pessary (vaginal insert) should be removed immediately. CERVIDIL® should also be removed prior to amniotomy.

CERVIDIL® should be used with caution in patients with compromised cardiovascular function.

CERVIDIL® should be used with caution when the membranes are ruptured.

CERVIDIL® should be used with caution in patients with a previous history of uterine hypertonus, glaucoma, epilepsy or asthma during the current pregnancy.

Medication with non-steroidal anti-inflammatory drugs, including aspirin, should be stopped before administration of PGE_2.

A second dose of CERVIDIL® is not recommended, as the effects of a second dose have not been studied.

The use of the product in patients with diseases which could affect the metabolism or excretion of dinoprostone, e.g. lung, liver or renal disease, has not been specifically studied. The use of the product in such patients is not recommended.

Women aged 35 and over, women with complications during pregnancy, such as gestational diabetes, arterial hypotension and hypothyroidism, and women at gestational age above 40 weeks have a higher post-partum risk of 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 and oxytocin should be used with caution in these women. In the immediate post-partum phase the physician should continue to monitor for early signs of a developing DIC (e.g. fibrinolysis).

The Clinician should be alert that, as with other labour induction methods, use of dinoprostone may result in inadvertent abruption of placenta and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

Renal, respiratory and hepatic impairment

The use of CERVIDIL® in patients with diseases which could affect the metabolism or excretion of dinoprostone / PGE_2, e.g. lung, liver or renal disease, has not been specifically studied. The use of CERVIDIL® in such patients is not recommended.

Paediatric population

The safety and efficacy of CERVIDIL® in pregnant woman aged less than 18 years has not been established. No data are available.

4.5 Interaction with other medicines and other forms of interaction

No dedicated interaction studies have been performed with CERVIDIL®. Prostaglandins potentiate the uterotonic effect of uterotonic drugs. Concurrent use of CERVIDIL® in patients receiving uterotonic drugs is not recommended. A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the dinoprostone pessary (vaginal insert) (see section 4.4). Medication with non-steroidal anti-inflammatory drugs, including acetylsalicyclic acid, should be stopped before administration of dinoprostone.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category C)

Prostaglandin E_2 has produced an increase in skeletal anomalies in rats and rabbits. No effect would be expected clinically, when used as indicated, since CERVIDIL® is administered after the period of organogenesis. Prostaglandin E_2 has been shown to be embryotoxic in rats and rabbits. Specific fetotoxicity studies of this dose form of PGE_2 have not been conducted. However, an increase in still births was noted when PGE_2 containing pessaries (vaginal inserts) were used in studies in pregnant rats. There has been idiosyncratic sensitivity of the uterus resulting in anoxia. Any dose that produces sustained increased uterine tone could put the embryo or fetus at risk.

CERVIDIL® is for the initiation of cervical ripening in pregnant patients at term (from 37 completed weeks) only where labour induction is indicated.

CERVIDIL® is not indicated for use in pregnancy prior to 37 completed weeks of gestation.

Breastfeeding

CERVIDIL® is not indicated for use during lactation.

No studies have been performed to investigate the amount of dinoprostone in colostrum or breast milk following the use of CERVIDIL®.

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 newborns have been observed in the clinical studies conducted.

Fertility

Fertility studies have not been conducted with CERVIDIL®.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Summary of safety profile:

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 %).

The table below displays the main ADRs distributed by system organ classes (SOC) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

Adverse reactions observed in clinical studies are presented according to their incidence, post authorisation reported adverse reactions are presented in the column frequency unknown.

System organ class	**Common** **(≥ 1/100 and < 1/10)**	**Uncommon** **(≥ 1/1000 and ≤ 1/100)**	**Frequency unknown**
Blood and lymphatic system disorders			Disseminated intravascular coagulation
Immune system disorders			Anaphylactic reaction Hypersensitivity
Nervous system disorders		Headache	
Cardiac disorders	Fetal heart rate disorder [1*]		
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions	
Gastrointestinal disorders			Abdominal pain Nausea, vomiting, diarrhoea
Hepatobiliary disorders		Neonatal hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting fetus [2*] Uterine contractions abnormal, uterine tachysystole, uterine hyperstimulation, uterine hypertonus Meconium in amniotic fluid	Postpartum haemorrhage Premature separation of placenta Apgar score low Arrested labour Chorioamnionitis Uterine atony	Anaphylactoid syndrome of pregnancy Fetal distress syndrome [3*] Fetal death, stillbirth, neonatal death [4*]
Reproductive system and breast disorders		Vulvovaginal burning sensation	Genital oedema
General disorders and administration site conditions		Febrile disorders	
Injury, poisoning and procedural complications			Uterine rupture

1* "Foetal heart rate disorder" was in clinical studies reported as "foetal heart rate abnormalities", "foetal bradycardia", "foetal tachycardia", "unexplained absence of normal variability", "foetal heart

rate decreased", "foetal heart rate deceleration", "early or late decelerations", "variable decelerations", "prolonged decelerations".

2* "Abnormal labour affecting foetus" as expression for hyperstimulation syndrome was in clinical studies reported as "uterine tachysystole" combined with "late decelerations", "foetal bradycardia", or "prolonged decelerations "

3* "Foetal distress syndrome" was also reported as "foetal acidosis" , "pathological CTG", "foetal heart rate abnormalities", "intrauterine hypoxia" or "threatening asphyxia". The term itself is unspecific, has a low positive predictive value and is often associated with an infant who is in good condition at birth.

4* Fetal death, stillbirth and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

CERVIDIL® is used as a single dosage in a single application. Overdosage may lead to hyperstimulation of the uterine muscle with or without foetal distress. If foetal distress occurs, remove CERVIDIL® immediately and manage in accordance with local protocol. Other treatment must be symptomatic since, to date, clinical experience with prostaglandin antagonists is insufficient.

The use of beta-adrenergic agents should be considered in the event of undesirable increased uterine activity, if removal does not diminish the undesirable uterine activity.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

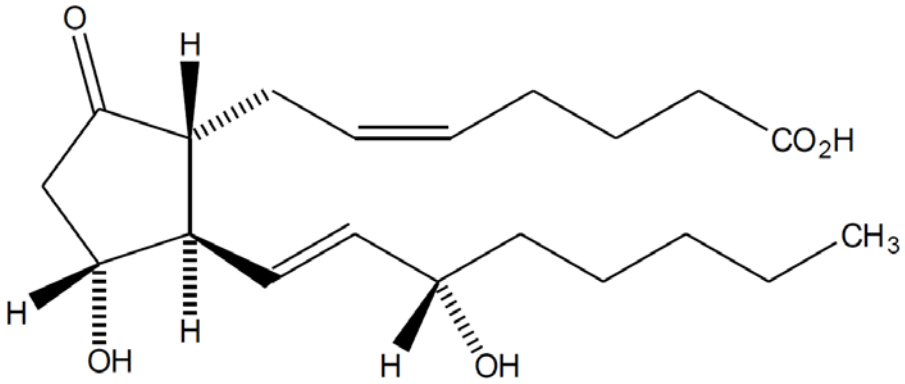
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: uterotonics, prostaglandins

ATC code: G02AD02

The chemical name for dinoprostone (commonly known as prostaglandin E_2 or PGE_2) is 11α-15S-dihydroxy-9-oxo-prosta-5Z, 13E-dien-1-oic acid. It is a white to off-white crystalline powder. It has a melting point within the range of 65°C to 69°C. Dinoprostone is soluble in ethanol and in 25% ethanol in water. The structural formula is represented below:



Molecular formula: $C_{20}H_{32}O_5$

Molecular weight: 352.5

CAS registry number: 363-24-6

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 complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a transformation of the uterine cervix which must be transformed from a rigid structure to a softened, yielding and dilated configuration to allow passage of the fetus through the birth canal. This process involves activation of the enzyme collagenase which is responsible for digestion of some of the structural collagen network of the cervix.

Clinical Trials

Three randomised, double-blind placebo controlled studies have been conducted. Studies 101-003 and 101-103 involved the pessary (vaginal insert) alone, whereas study 101-801 used the pessary (vaginal insert) fitted with retrieval system to facilitate rapid and reliable retrieval of the pessary (vaginal insert). Pharmacokinetic studies had demonstrated that there was no significant difference between the PGE_2 release characteristics of the "netted" and “unnetted" versions of the pessary (vaginal insert).

All three studies involved patients with singleton pregnancies and cephalic presentation, for whom there were medical or obstetrical grounds for the induction of labour, and who had a Bishop score of 4 or less. Patients had to be in at least the 37th week of gestation. On randomisation, patients were stratified according to whether they were primiparous or multiparous. The efficacy of CERVIDIL® as demonstrated in these studies is shown in Table 1:

Table 1 Efficacy of CERVIDIL® in Double Blind Studies

		Primip/Nulliparous		Multiparous		
Parameter	**Study**	**Cervidil**	**Placebo**	**Cervidil**	**Placebo**	**P-Value**
Treatment Success*	101-103 (n=81)	65%	28%	87%	29%	<0.001
	101-003 (n=371)	68%	24%	77%	24%	<0.001
	101-801 (n=206)	72%	48%	55%	41%	0.003
Time to Delivery (hrs)						
Average	101-103 (n=81)	33.7	48.6	14.0	28.6	
Median		25.7	34.5	12.3	24.6	0.001
Average	101-801 (n=206)	31.1	51.8	52.3	45.9	
Median		25.5	37.2	20.8	27.4	<0.001
Time to Onset of Labour (hrs)						
Average	101-103 (n=81)	19.9	39.4	6.8	22.4	
Median		12.0	19.2	6.9	18.3	<0.001

*Treatment success was defined as Bishop score increase at 12 hours of $\geq$ 3, vaginal delivery within 12 hours or Bishop score at 12 hours $\geq$ 6. These studies were not designed with the power to show differences in caesarean section rates between CERVIDIL® and placebo groups and none were noted.

5.2 Pharmacokinetic properties

CERVIDIL® releases PGE_2 to the cervical tissue continuously at a rate which allows cervical ripening to progress until complete (mean dose of approximately 0.3 mg per hour over 24 hours), and with the facility to remove the PGE_2 source when the clinician decides that cervical ripening is complete or labour has started, at which point no further PGE_2 is required. The reservoir of 10 mg dinoprostone serves to maintain a controlled and constant release. The release rate is approximately 0.3 mg per hour over 24 hours in women with intact membranes whereas release is higher and more variable in women with premature rupture of membranes.

Dinoprostone is established as a successful agent for cervical ripening and induction of labour. Dinoprostone initiates labour by a process which may be more akin to spontaneous labour than that produced by forewater amniotomy followed by oxytocin infusion. Local application of dinoprostone (endocervical and vaginal) has proved to be clinically superior to intravenous administration, avoiding gastrointestinal side effects.

Distribution

Using equilibrium dialysis, studies indicate that dinoprostone is approximately 73% bound to human plasma albumin.

Biotransformation

Dinoprostone is rapidly metabolised in the lungs, kidneys and liver. Approximately 90% of dinoprostone is metabolised in the first pass. In man, three metabolites of dinoprostone have been identified in plasma, 13, 14-dihydro-15-keto GE_2 (the primary metabolite), 11 alpha-hydroxy-9,15-diketoprost-5-enoic acid and 11 alpha-hydroxy-9,15-dioxyprost-5-13-dienoic acid.

Elimination

Dinoprostone is eliminated from the circulation very rapidly. Studies indicate that the half-life of dinoprostone is less than one minute.

The plasma concentration of dinoprostone and its metabolites is low after intravaginally administered PGE_2. The plasma half-life for dinoprostone is less than 1 minute and for its primary metabolite less than 10 minutes. Animal studies have shown that this metabolite (15-keto-13, 14-dihydro-PGE_2) is about half as active as the mother substance. Dinoprostone is metabolised in the lung and is excreted via the urine.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis

Long-term carcinogenicity and fertility studies have not been conducted with CERVIDIL®.

No evidence of mutagenicity has been observed with PGE_2 in the Micronucleus Test, or Ames Test. PGE_2 did induce chromosomal aberrations in Chinese hamster lung fibroblasts in culture but only at an unphysiologically high concentration.

Exposure to PGE_2 at the dosage and administration recommended for induction of labour is not considered to be of toxicological concern.

Long term clinical use of chemically related polymers such as those used in the hydrogel and retrieval system has not identified any concerns regarding genotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The hydrogel polymer of CERVIDIL® is prepared with Crosslinked macrogol (Hydrogel)/Polyethylene glycol 8000, Dicyclohexyl methane-4, 4'-diisocyanate and 1,2,6-Hexanetriol.

Polyester. The hydrogel polymer pessary is contained in a polyester retrieval system.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a freezer below -18°C. The pessary (vaginal insert) should be inserted immediately after removal from the freezer and its foil package, however, controlled periods of time of up to one month at 2-8°C can be allowed within the shelf life of the product.

Pessaries (vaginal inserts) exposed to high humidity will absorb moisture from the air and thereby alter the release characteristics of dinoprostone. Once used, the pessary (vaginal insert) should be discarded.

6.5 Nature and contents of container

CERVIDIL® is presented in an individual, sealed aluminium/polyethylene laminate sachet containing 1 pessary (vaginal insert).

6.6 Special precautions for disposal

After usage, the whole product should be disposed of as clinical waste

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

09/01/2003

10 DATE OF REVISION OF THE TEXT

October 2021

[CCDS 5971; ver. 3.0 01 Oct 2021]

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 4.2, 4.3, 4.4 and 4.8	Strengthening of wording in line with EU SmPC guideline
Section 4.8	Addition of uterine tachysystole, uterine hyperstimulation, uterine hypertonus, fetal death, stillbirth, neonatal death to side effects to side effects of "Pregnancy, puerperium and perinatal condition" and addition of
4.9	Deletion of "or hypersensitivity"
5.1	Update of pharmacotherapeutic group to align with CCDS – from oxytocic to uterotonic. Addition of prostaglandin.
6.1	Inclusion of Ph.Eur.term of excipient "Crosslinked macrogol (hydrogel)