DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION
AGREED WITH EUROPEAN MEDICINES AGENGY (EMA)
AND
ITALIAN MEDICINES AGENCY (AIFA)

15th July 2021

PREPIDIL AND PROPESS (DINOPROSTONE) STRENGTHENING OF PRODUCT INFORMATION ABOUT THE RISKS OF UTERINE HYPERSTIMULATION, UTERINE RUPTURE AND FOETAL/NEONATAL DEATH AND RESTRICTION OF USAGE TO QUALIFIED HEALTH CARE PROFESSIONALS, TO HOSPITALS AND CLINICS.

Dear Healthcare Professional,

Pfizer Italia S.r.l. and **Ferring S.p.A.**, in agreement with the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA), would like to inform you about dinoprostone medicinal products **PREPIDIL** (Pfizer Italia S.r.l.) and **PROPESS** (Ferring S.p.A), as it follows:

Summary

The product information[1], Summary of Product Characteristics (SmPC) and Package Leaflet (PIL), of the two medicinal products PREPIDIL and PROPESS have been updated with the following safety information agreed at European level and reported below:

- **risks of uterine hyperstimulation and uterine rupture and their serious complications, including foetal and neonatal death.**
- **restriction of usage to qualified health care professionals and to hospitals and clinics with specialized obstetric units with facilities for continuous monitoring.**
- **strengthening of the warning and recommendations regarding the maximum dose (<u>PREPIDIL and PROPESS</u>) and the dosing interval (<u>PREPIDIL only</u>).**
- **strengthening of the contraindications (<u>PROPESS only</u>) and warnings and precautions for use, including those for concomitant and/or sequential use of dinoprostone and oxytocin.**

[1] Changes to product information are under evaluation

Background on the safety concern

Following the conclusion, on 27th April 2021, of the procedure PSUFU - PSUR Follow-Up assessment report n.SE/H/PSUFU/00001104/201909 for Dinoprostone, the Pharmacovigilance Risk Assessment Committee (PRAC) has made the recommendations to be included in the Product Information of PREPIDIL and PROPESS, as confirmed by the CMDh (Coordination Group for Mutual Recognition and Decentralized Procedures):

PREPIDIL (Pfizer Italia s.r.l.) is indicated for the treatment of:

PREPIDIL 0.5 mg/3 g of endocervical gel: Induction of cervical ripening (softening and dilation) in pregnant women at term or near term and in long-lasting pregnancy when, due to a medical or obstetrical indication, it is necessary to induce the labor.

PREPIDIL 1 mg/3 g and 2 mg/3 g vaginal gel: Induction of labor in pregnant women at term or near term and in long-lasting pregnancy, in conditions favorable to induction and with singleton in cephalic presentation.

The SmPC and the PIL will be updated with the following safety recommendations:

SmPC

PREPIDIL 0.5 mg/3 g of endocervical gel

Section 4.2 - Posology and method of administration

The dose of PREPIDIL endocervical gel is of 0.5 mg.
The whole content of the syringe should be administered by slow extrusion into the cervical canal a little before the internal uterine orifice, using the properly enclosed applicator. After the gel administration, the patient should remain in supine position for 10 to 15 minutes in order to prevent it flowing out of the cervical canal.

When the therapeutic response is satisfactory, wait for a time interval of 6 to 12 hours prior to any intravenous administration of oxytocin. In the absence of signs of cervical ripening and/uterine response, a second dose of PREPIDIL endocervical gel 0.5 mg should be administered after a 6-h interval.

The opportunity of further administrations and the relevant time intervals will be established by the treating physician basing on the evolution of the clinical events.

We recommend of not going over the maximum total dose of 1.5 mg of PREPIDIL endocervical gel in the 24-h period.

Usage is restricted to qualified health care professionals and to hospitals and clinics with specialised obstetric units with facilities for continuous monitoring.

The recommended dose should not be exceeded, and the dosing interval should not be shortened as this increases the risk of uterine hyperstimulation, uterine rupture, uterine haemorrhage, foetal and neonatal death.

Section 4.3 – Contraindications

Deletion of the contraindications for the use of PREPIDIL in case of multiple gestation and in presence of rupture of the membranes.

The administration of PREPIDIL gel is not indicated in patients for whom the oxytocic drugs are generally contraindicated and when long lasting uterine contractions are considered to be inappropriate, as in the following cases:

- previous surgeries on the uterus such as cesarean section or hysterotomy
- cephalo-pelvic disproportion;

- previous difficult labors and/or traumatic deliveries;
- large multiparous women (6 or more previous term pregnancies)

Moreover, the product is contraindicated in the following situations:

- non-cephalic presentation of the fetus;
- presence of vaginal blood losses of unknown etiology during the present pregnancy;
- fetal heart rate pattern suggests incipient fetal compromise
- obstetric conditions where either maternal or fetal benefit/risk ratio favors surgical intervention
- hypersensitivity to the active substance, prostaglandins or any other component of the product listed in the section 6.1.

Section 4.4 - Special warnings and precautions for use

Prostaglandins are capable of potentiating the effect of oxytocin.

We warn against the simultaneous use with oxytocin. Whenever it is established to administer the two drugs in sequence, a minimum interval of 6-12 hours should elapse.

Before and during the administration of PREPIDIL gel, a continuous monitoring of the uterine activity, fetal heart rate and conditions of the cervix (dilation and flattening) should be performed.

As it occurs with any oxytocic agent, the risk of uterine rupture should be considered in the presence of an exceeding activity of the myometrium or unusual uterine pain. The response to oxytocin may be enhanced during therapy with exogenous prostaglandins.
Concomitant medication, maternal and foetal status should be taken into consideration in order to minimise the risk of uterine hyperstimulation, uterine rupture, uterine haemorrhage, foetal and neonatal death. Continuous electronic monitoring of uterine activity and foetal heart rate should be conducted during use of dinoprostone. Patients who develop uterine hypertonus or hypercontractility, or in whom unusual foetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the foetus and mother.

PREPIDIL gel should be administered carefully to patients with impaired cardiovascular, hepatic, renal function or in patients with asthma, glaucoma **or ruptured chorioamniotic membranes. Dinoprostone should be used with caution in patients with multiple pregnancy.**

The cephalopelvic ratio should be carefully assessed before using the drug.

PREPIDIL endocervical gel should not be introduced beyond the level of the internal uterine orifice. Its administration into the extra-amniotic space was associated with a uterine hyperstimulation.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labour induction (see section 4.8 Undesirable Effects). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

The Clinician should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

Section 4.5 - Interactions with other medicinal products and other forms of interaction

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. Concurrent use with other oxytocic agents is not recommended. A dosing interval of at least 6 hours is recommended in case of oxytocin use is considered necessary following dinoprostone administration.
Beta-mimetic drugs are capable of antagonizing the effects induced by PGE_2.

Section 4.8 - Undesirable effects

Fetal Adverse Events

Pregnancy, puerperium and perinatal conditions: foetal death*, stillbirths*, neonatal death*

*Foetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture (see sections 4.2, 4.3 and 4.4).

PREPIDIL 1 mg/3 g and 2 mg/3 g vaginal gel

Section 4.2 - Posology and method of administration
The initial dose of PREPIDIL vaginal gel is of 1 mg, administered into the posterior vaginal fornix. After 6 hours, a second dose of PREPIDIL vaginal gel of 1 mg or 2 mg, should be administered according to the need and on the basis of the following criteria: in the absence of response to the initial dose of 1 mg, a dose of 2 mg should be administered; to enhance the response to the initial dose, a dose of 1 mg should be administered.

Usage is restricted to qualified health care professionals and to hospitals and clinics with specialised obstetric units with facilities for continuous monitoring.

The recommended dose should not be exceeded, and the dosing interval should not be shortened as this increases the risk of uterine hyperstimulation, uterine rupture, uterine haemorrhage, foetal and neonatal death.

Section 4.3 – Contraindications

Deletion of the contraindications for the use of PREPIDIL in case of multiple gestation and in presence of rupture of the membranes.

The administration of PREPIDIL gel is not indicated in patients for whom the oxytocic drugs are generally contraindicated and when long lasting uterine contractions are considered to be inappropriate, as in the following cases:

- previous surgeries on the uterus such As cesarean section or hysterotomy
- cephalo-pelvic disproportion;
- previous difficult labors and/or traumatic deliveries;
- large multiparous women (6 or more previous term pregnancies)

Moreover, the product is contraindicated in the following situations:

- non-cephalic presentation of the fetus;
- presence of vaginal blood losses of unknown etiology during the present pregnancy;
- fetal heart rate pattern suggests incipient fetal compromise
- obstetric conditions where either maternal or fetal benefit/risk ratio favors surgical intervention
- hypersensitivity to the active substance, prostaglandins or any other component of the product listed in the section 6.1

Section 4.4 - Special warnings and precautions for use

Prostaglandins are capable of potentiating the effect of oxytocin.
We warn against the simultaneous use with oxytocin. Whenever it is established to administer the two drugs in sequence, a minimum interval of 6-12 hours should elapse.
During the induction of labor with intravaginal PGE2, a continuous monitoring of the uterine activity and fetal heart rate should be performed.
As it occurs with any oxytocic agent, the risk of uterine rupture should be considered in the presence of an exceeding activity of the myometrium or unusual uterine pain.

The response to oxytocin may be enhanced during therapy with exogenous prostaglandins.
Concomitant medication, maternal and foetal status should be taken into consideration in order to minimise the risk of uterine hyperstimulation, uterine rupture, uterine haemorrhage, foetal and neonatal death. Continuous electronic monitoring of uterine activity and foetal heart rate should be conducted during use of dinoprostone. Patients who develop uterine hypertonus or hypercontractility, or in whom unusual foetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the foetus and mother.

PREPIDIL gel should be administered carefully to patients with impaired cardiovascular, hepatic, renal function or in patients with asthma, glaucoma **or ruptured chorioamniotic membranes. Dinoprostone should be used with caution in patients with multiple pregnancy.**

The cephalopelvic ratio should be carefully assessed before using the drug.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labour induction (see section 4.8 Undesirable Effects). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

The Clinician should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

Section 4.5 - Interactions with other medicinal products and other forms of interaction

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. Concurrent use with other oxytocic agents is not recommended. A dosing interval of at least 6 hours is recommended in case of oxytocin use is considered necessary following dinoprostone administration.

Beta-mimetic drugs are capable of antagonizing the effects induced by PGE_2.

Section 4.8 - Undesirable effects

Fetal Adverse Events

Pregnancy, puerperium and perinatal conditions: **foetal death*, stillbirths*, neonatal death***

***Foetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture (see sections 4.2, 4.3 and 4.4).**

The PIL will be updated with the changes reported above, accordingly.

PROPESS (Ferring S.p.A.) 10 mg vaginal device is indicated for the induction of the maturation process of the cervix uteri in full-term pregnant patients (from 37th week of completed gestation).

The SmPC and PL will be updated with safety recommendations as reported below:

SmPC

Section 4.2 - Posology and method of administration

"PROPESS should only be administered by qualified healthcare personnel in hospitals and clinics with specialised obstetric units with facilities for continuous foetal and uterine monitoring"

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

"**Only one administration of PROPESS is recommended".**

Section 4.3 - Contraindications

"PROPESS should not be used or left in place under the following circumstances:
3. When strong prolonged uterine contractions would be inappropriate such as in patients:

a) who have had previous major uterine surgery, e.g. caesarean section, myomectomy etc (see sections 4.4 and 4.8)
b) 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 foetal malpresentation
e) with suspicion or evidence of foetal distress.

Section 4.4 - Special warnings and precautions for use

"The condition of the cervix should be assessed carefully before PROPESS is used. After insertion, **uterine activity and foetal condition must be monitored carefully and regularly by qualified**

healthcare personnel. PROPESS must **only** be used **in hospitals and clinics with specialised obstetric units with facilities** for continuous foetal and uterine monitoring If there is any suggestion of maternal or foetal complications or if adverse effects occur, the vaginal delivery system should be removed from the vagina."

"Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contraindicated conditions (see section 4.3). Therefore, PROPESS 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.
If uterine contractions are prolonged or excessive, there is possibility of uterine hypertonus or rupture and the vaginal delivery system should be removed immediately."
"A second dose of PROPESS is not recommended, as the effects of a second dose have not been studied."

"PROPESS should be used with caution in patients with a previous history of uterine hypertonus, glaucoma or asthma."

"Women aged 35 and over, women with complications during pregnancy, such as gestational diabetes, arterial hypertension and hypothyroidism, and women at gestational age above 40 weeks have a higher post-partum risk for developing disseminated intravascular coagulation (DIC). These factors may additionally enhance the risk of in women with pharmacologically induced labour (see section 4.8). Therefore, **uterotonic drugs, such as** dinoprostone should be used with caution in these women.

In the immediate post-partum phase the physician should look out carefully for early signs of a developing DIC (e.g fibrinolysis)."

"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)."

"PROPESS should be used with caution when there is a multiple pregnancy as no studies in multiple pregnancy have been performed."

"PROPESS 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 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

Section 4.8 - Undesirable effects

Foetal adverse events

Pregnancy, puerperium and perinatal conditions - **Foetal death*,stillbirth*, neonatal death *** were added with a frequency not known together with common one.

*** Foetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture (see sections 4.2, 4.3 and 4.4).).**

The PIL will be updated with the changes reported above, accordingly

Call for reporting of adverse reactions

Healthcare professionals are reminded to continue to report the suspected adverse reactions, associated with the use of PREPIDIL and PROPESS, according to the national reporting system for spontaneous reporting, via the Italian Medicines Agency website: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

AIFA takes the opportunity to remind all Healthcare Professionals of the importance of reporting suspected adverse drugs reactions, as an indispensable tool for confirming a favorable benefit/risk ratio in real conditions of use.
Reporting of Suspected Adverse Reaction should be sent to the Head of Pharmacovigilance of the Facility the Healthcare Professional belongs to.
This Direct Healthcare Professional Communication is also published on AIFA website (http://www.agenziafarmaco.gov.it) and it's consultation is recommended for the best professional information and citizen service.