SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PROSTIN® E_2 0,5 mg (Tablets)

COMPOSITION

Each tablet contains 0,5 mg dinoprostone.

PHARMACOLOGICAL CLASSIFICATION

A 19 Oxytocics

PHARMACOLOGICAL ACTION

The exact mode of action of the prostaglandins is not yet completely understood. Dinoprostone PGE_2 has been shown to have a local action on isolated uterine musculature and clinically its main action is oxytocic. However, unlike other oxytocics, dinoprostone exhibits the capacity of the prostaglandins to influence uterine activity at any stage of gestation. Dinoprostone does not exhibit an antidiuretic effect.

INDICATIONS

PROSTIN E_2 0,5 mg tablets are indicated for the induction of labour when there are no foetal or maternal contra-indications.

CONTRAINDICATIONS

There are no absolute contraindications to the use of PROSTIN E_2 0,5 mg tablets. However, its use is not recommended in the following circumstances:

1. Where the patient is sensitive to prostaglandin.
2. For patients in whom oxytocic drugs are generally contraindicated, or where prolonged contractions of the uterus are considered inappropriate, such as:
    - Cases with a history of caesarean section or major uterine surgery.
    - Cases in which major degrees of cephalopelvic disproportion may be present.
    - Cases in which there is clinical suspicion or definite evidence of pre-existing foetal distress.
    - Cases in which there is a history of difficult labour and/or traumatic delivery.
    - Grand multiparae with six or more previous pregnancies.
    - Engagement of the head has not taken place.
    - Non-reassuring foetal heart rate pattern.
    - Obstetric conditions where either maternal or foetal benefit/risk ratio favours surgical intervention.

- Unexplained vaginal discharge and/or unexplained uterine bleeding during current pregnancy.
- Nonvertex presentation.

3. Cases with a recent history of pelvic inflammatory disease.

WARNINGS and SPECIAL PRECAUTIONS

Caution should be exercised in the administration of PROSTIN E_2 0,5 mg tablets for the induction of labour in patients with:

1. Glaucoma or raised intraocular pressure.
2. Asthma or a history of asthma.
3. Ruptured chorioamniotic membranes.
4. Impaired cardiovascular, hepatic or renal function.

Caution should also be exercised in the administration of oxytocic agents, including Prostin E_2 0,5 mg, for the induction of labour in patients with Multiple Gestation.

In addition, in labour induction cephalopelvic relationship should be carefully evaluated before use of PROSTIN E_2 0,5 mg tablets. During use, uterine activity, foetal status, and the progression of cervical dilation should be carefully monitored to detect possible evidence of unphysiological responses, e.g. hypertonus, sustained uterine contractions, or foetal distress. In cases where there is a known history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the foetus should be continuously monitored throughout labour. The possibility of uterine rupture should be borne in mind where high-tone myometrial contractions are sustained. Since it has been found that prostaglandins may potentiate the effect of oxytocin, it is recommended that these drugs not be used together, and if used in sequence, that the patient's uterine activity be carefully monitored.

Animal studies, lasting several weeks, at high doses have shown that prostaglandins of the E- and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who have received prostaglandin E_1 during prolonged treatment. There is no evidence that short-term administration of PROSTIN E_2 0,5 mg tablets can cause similar bone effects.

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. Therefore, in these women, use of PROSTIN E_2 Tablets should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

INTERACTIONS

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. Concurrent use with other oxytocic agents is not recommended. The sequential use of oxytocin

following administration of PROSTIN E_2 0,5 mg tablets is recommended, with a dosing interval of at least 6 hours.

PREGNANCY AND LACTATION

Pregnancy

Prostaglandin E_2 produced an increase in skeletal anomalies in rats and rabbits. Dinoprostone has been shown to be embryotoxic in rats and rabbits. Any dose that produces sustained increased uterine tone could put the embryo or foetus at risk.

Lactation

Prostaglandins are excreted in breast milk at very low concentrations.

DOSAGE AND DIRECTIONS FOR USE

PROSTIN E_2 0,5 mg tablets are not for vaginal use. Continuous administration of the drug for more than two days is not recommended. The dosage of PROSTIN E_2 0,5 mg tablets must be adapted to the patient's response and should always be maintained at the lowest level which will produce satisfactory uterine response. All doses should be taken with a small amount of water.
An initial dose of 0,5 mg (one tablet) should be given. Thereafter, doses should be given hourly. The usual dose will be 0,5 mg (one tablet), but if uterine activity is inadequate, 1 mg (2 tablets) may be given hourly until such time as adequate uterine activity is established. *It is recommended that a total SINGLE dose of 1,5 mg (three tablets) not be exceeded. Thereafter it may be possible to reduce the dosage to 0,5 mg (one tablet) hourly.*

SIDE EFFECTS

Clinical studies have not revealed any life-threatening adverse reactions. The incidence of side-effects is directly dose-related.

Very Common: ≥ 1/10 (≥ 10%)
Common: ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Very rare: < 1/10 000 (< 0,01%)

SYSTEM ORGAN CLASS	FREQUENCY	UNDESIRABLE EFFECTS
Immune system disorders	Very rare	Hypersensitivity reactions
Nervous system disorders	Very rare	Transient vasovagal symptoms (flushing, shivering, headache, dizziness)
Cardiac disorders	Very rare	Cardiac arrest
Vascular disorders	Very rare	Hypertension

Respiratory, thoracic and mediastinal disorders	Very rare	Asthma, bronchospasm
Gastrointestinal disorders	Very Common	Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Very rare	Rash
Musculoskeletal and connective tissue disorders	Very rare	Back pain
Pregnancy, puerperium and perinatal conditions	Common	Uterine contractile abnormalities (increase frequency, tone, or duration)
	Very rare	Abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation, uterine rupture, Neonatal death, still birth
General disorders and administration site conditions	Very rare	Fever
Investigations	Very Common	Foetal distress/altered foetal heart rate (FHR), Neonatal distress/low Apgar score

Post-marketing experience

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour was induced by pharmacological means, including PROSTIN E_2 Tablets. The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labours).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Uterine hypertonus of unduly severe uterine contractions have rarely been encountered, but might be anticipated to result from overdosage. In the rare instance where temporary discontinuation of therapy is not effective in reversing foetal distress or uterine hypertonus then prompt delivery is indicated.

Treatment of overdosage must be, at this time, symptomatic, since clinical studies with prostaglandin antagonists have not progressed to the point where recommendations may be made. It is currently believed that vomiting produced by overdosage may act as a self-limiting factor in protecting the patient.

IDENTIFICATION

PROSTIN E_2 0,5 mg tablets are presented as white, roughly rectangular tablets, embossed on one side to resemble the letter "U" with the number 76 on the reverse side.

PRESENTATION

PROSTIN E_2 0,5 mg tablets are available in glass bottles with 10 tablets.

STORAGE INSTRUCTIONS

PROSTIN E_2 0,5 mg tablets have a shelf-life of 2 years when stored at 2 - 8˚C, and three months after opening at 2 - 8 ˚C.

Store in refrigerator (2 - 8 ˚C).

Keep out of reach of children.

REGISTRATION NUMBER

J/19/8

NAME AND BUSINESS ADDRESS OFTHE HOLDER OF THE CERTIFICATE OF REGISTRATION

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