NAME OF THE MEDICINAL PRODUCT
GLANDIN-E2 3 mg Vaginal Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vaginal tablet contains Dinoprostone 3.000 mg

PHARMACEUTICAL FORM
Tablet for vaginal administration.
White coloured rectangular flat tablet, NQ engraved on one side and other side is plain.

CLINICAL PARTICULARS
Therapeutic indications
Oxytocic agent. Dinoprostone are indicated for the induction of labour, especially in patients with favourable induction features, when there are no foetal or maternal contraindications.

Posology and method of administration
The initial dose is 1 tablet (3 mg) of dinoprostone inserted high into the posterior fornix. A second tablet may be inserted after 6 – 8 hours if labor has not been established. The maximum or total dose in 24 hours is 6 mg.

Usage is restricted to qualified health care professionals and to hospitals and clinics with specialized 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.

Route of Administration
Vaginal

Contraindications
Hypersensitivity to the active substance(s) or to any of the excipients.

Dinoprostone should not be used where the patient is sensitive to prostaglandins or other constituents of the tablet.

Dinoprostone are not recommended in the following circumstances:

- 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 where there is cephalopelvic disproportion
- Cases in which foetal malpresentation is present
- Cases where 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
- Unexplained vaginal discharge and/or abnormal uterine bleeding during current pregnancy.
- In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.
- In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal bleeding during this pregnancy.
- Patients with active cardiac, pulmonary, renal or hepatic disease.

Special warnings and precautions for use

This product is only available to hospitals and clinics with specialized obstetric units and should only be used where 24-hour resident medical cover is provided.

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

As with any oxytocic agent, the risk of uterine rupture should be considered. Concomitant medication, maternal and foetal status should be taken into consideration in order to minimize 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.

Caution should be exercised in the administration of Glandin E2 Vaginal Tablets for the induction of labour in patients with:

- asthma or a history of asthma
- epilepsy or a history of epilepsy
- glaucoma or raised intra-ocular pressure
- compromised cardiovascular, hepatic, or renal function
- hypertension.
- ruptured chorioamniotic membranes

Continuous electronic monitoring of uterine activity and fetal heart rate should be conducted during use of dinoprostone. Patients who develop uterine hypertonus or hypercontractility, or in who unusual fetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the fetus and mother.

Dinoprostone should be used with caution in patients with multiple pregnancy.

In labour induction, cephalopelvic relationships should be carefully evaluated before use of Glandin E2 Vaginal Tablets. During use, uterine activity, foetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired 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 (where applicable) should be continuously monitored throughout labour. The possibility of uterine rupture should be borne in mind where high-tone uterine contractions are sustained.

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 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 may result in inadvertent distruption and subsequent embolization of antigenic tissue, causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

Interaction 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. The sequential use of oxytocin following administration of vaginal tablets is recommended, with a dosing interval of at least 6 hours.

Pregnancy and lactation
Pregnancy
Dinoprostone is for use in pregnant women at or near term.
Prostaglandin E2 produced an increase in skeletal anomalies in rats and rabbits. Dinoprostone has been shown to be embryotoxic in rats and rabbits, and any dose that produces sustained increased uterine tone could put the embryo or fetus at risk.

Lactation
Prostaglandins are excreted in breast milk at very low concentrations. No measurable differences were observed in the milk of mothers delivering prematurely and at term.

Effects on ability to drive and use machines
Not applicable

Undesirable effects
Maternal Adverse Events
The following maternal adverse events have been reported with use of vaginal tablets:
Immune system disorders: Hypersensitivity reactions (e.g., Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction)
Gastrointestinal disorders: Diarrhea, nausea, vomiting
Musculoskeletal and connective tissue disorders: Back pain
Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), uterine rupture, abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation
Reproductive system and breast disorders: Warm feeling in vagina
General disorders and administration site conditions: Fever
Vascular disorders: Hypertension
Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Fetal Adverse Events
The following fetal adverse events have been reported with use of vaginal tablets:
Pregnancy, puerperium and perinatal conditions: Foetal death, Still births, Neonatal death
Investigations: Fetal distress/altered fetal heart rate (FHR), neonatal distress/low Apgar score
Foetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture.

Overdose
Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE2-induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; i.e., maternal position change and administration of oxygen to the mother. B-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE2 for cervical ripening.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of Action/Effect

For uterine stimulation

Dinoprostone stimulates the myometrium of the gravid uterus to contract in a manner that is similar to the contractions seen in the term uterus during labor. Whether or not this action results from a direct effect of dinoprostone on the myometrium has not been determined. Nonetheless, the myometrial contractions induced by the vaginal administration of dinoprostone are sufficient to produce evacuation of the products of conception from the uterus in the majority of cases.

For cervical ripening

Dinoprostone has a local cervical effect in initiating softening, effacement, and dilation. These changes, referred to as cervical ripening, occur spontaneously as the normal pregnancy progresses toward term and allow evacuation of uterine contents by decreasing cervical resistance at the same time that myometrial activity increases.

Other actions

Dinoprostone is also capable of stimulating smooth muscle of the gastrointestinal tract in humans. This activity may be responsible for the vomiting and/or diarrhea that is occasionally seen when dinoprostone is used for preinduction cervical ripening.

In laboratory animals, and also in humans, large doses of dinoprostone can lower blood pressure, probably as a result of its effect on smooth muscle of the vascular system. Dinoprostone can also elevate body temperature; however, with the dose of dinoprostone used for cervical ripening, these effects have not been seen.

Pharmacokinetic properties

General characteristics of active substances

Absorption

When administered vaginally, dinoprostone is rapidly absorbed. Dinoprostone is 73% bound to human plasma albumin.

Following insertion of the vaginal tablet, PGE2 absorption (as measured by the presence of PGE2 metabolites) increases to reach a peak at about 40 minutes.

Distribution and Metabolism

Dinoprostone is widely distributed in the mother.

PGE2 is rapidly metabolized to 13, 14-dihydro-15-keto PGE2, which is converted to 13, 14- dihydro, 15-keto PGA2. Dinoprostone is completely metabolized in humans. It is extensively metabolized in the lungs, and the resulting metabolites are further metabolized in the liver and kidney.

Elimination

The drug and its metabolites are excreted primarily by the kidneys, with a small amount excreted in the feces.

PHARMACEUTICAL PARTICULARS

List of excipients

Aerosil # 200
Starch Maize
Avicel PH 112
Lactose Anhydrous
Magnesium Stearate

Incompatibilities

Not applicable.

Shelf life

2 years.

Special precautions for storage

Store in refrigerator (between 2-8˚C). After opening, store in refrigerator (2-8˚C) and use within 1 month.

Pack Size

3mg vaginal tablet is available in pack of 4 Vaginal Tablets.

Special precautions for disposal and other handling

- Not to be taken orally. For vaginal use only.
- The initial dose is 1 tablet (3 mg) of dinoprostone inserted high into the posterior fornix. A second tablet may be inserted after 6 to 8 hours if labor has not been established. The maximum or total dose in 24 hours is 6 mg.
- Usage is restricted to qualified health care professionals and to hospitals and clinics with specialized 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.
- Wash hands thoroughly with soap and water after administration.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufacturer

Nabiqasim Industries (Pvt.) Ltd.
17/24, Korangi Industrial Area, Karachi-Pakistan.

Product Registration Holder

Eucogen Sdn. Bhd.
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