PHYSICIAN LEAFLET

PROSTIN® E2 STERILE SOLUTION 1 MG/ML
(dinoprostone)

For intravenous use only.

Presentation
This pack contains one ampoule containing 0.75 ml of a colourless, sterile solution of 1 mg/ml dinoprostone (prostaglandin E₂) in ethanol.

Uses
Oxytocic agent. Prostin E2 Sterile Solution 1 mg/ml is indicated for the induction of labour by the intravenous route.

Dosage and administration
Directions for the Preparation of a Dilute Solution: For use by IV. drip (a drip set delivering 60 drops per ml must be used) or constant rate infusion pump. Withdraw 0.75 ml from the ampoule using an aseptic technique and add to 500 ml sterile normal saline or 5% dextrose. Shake to ensure uniformity.

After dilution attach label provided. Use dilute solution within 24 hours of preparation and store in a refrigerator at 2-8°C.

The dose of Prostin E2 used, normally depends not only upon the indication, but also on patient response.

The following is a guide to dosage:

Dilute with normal saline or 5% dextrose as above to produce a 1.5 micrograms/ml solution. The 1.5 micrograms/ml solution is infused at 0.25 micrograms/minute for 30 minutes and then maintained or increased. Cases of fetal death in utero may require higher doses. An initial rate of 0.5 micrograms/minute may be used with stepwise increases, at intervals of not less than one hour.

The appearance of fetal distress or uterine hypertonus requires cessation of therapy until the state returns to normal. The situation should be re-assessed and, if necessary, the infusion can be recommenced but at lower dosage rates, 50% of the last dose level used.

If no response is seen within the first 12-24 hours of treatment, the medication should be discontinued.

Children and elderly patients: Not applicable.

Contra-indications, warnings etc.
Contra-indications: Prostin E2 Sterile Solution 1 mg/ml should not be used where the patient is sensitive to prostaglandins.

Prostin E2 Sterile Solution 1 mg/ml is not recommended in the following circumstances:

1. For patients in whom oxytocic drugs are generally contra-indicated 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 there is cephalopelvic disproportion;
   - Cases in which fetal malpresentation is present;
   - Cases in which there is clinical suspicion or definite evidence of pre-existing fetal distress;
   - Cases in which there is a history of difficult labour and/or traumatic delivery;
   - Grand multiparae with six or more previous term pregnancies.

2. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.

3. In patients where there is clinical suspicion or definite evidence of placenta praevia or with unexplained vaginal bleeding during this pregnancy.

4. Patients with active cardiac, pulmonary, renal or hepatic disease.

Interactions with other medicaments and other forms of interaction: Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

Effects on ability to drive and to use machines: Not applicable.

Other undesirable effects: The most commonly reported events are vomiting, nausea and diarrhoea. Certain rare events that should be especially noted are: hypersensitivity to the drug; uterine rupture; and cardiac arrest. Other adverse effects, reported in decreasing order of severity are:

- Pulmonary/amniotic fluid embolism;
- Abruptio placenta;
- Stillbirth, neonatal death;
- Uterine hypercontractility or hypertonus;
- Fetal distress;
- Hypertension - systemic (maternal);
- Bronchospasm/asthma;
- Nausea, vomiting, diarrhoea;
- Rapid cervical dilation;
- Fever;
- Backache;
- Rash.
In addition, other adverse reactions that have been seen with the use of prostaglandin E₂ for term labour induction have included: uterine hypercontractility with fetal bradycardia; uterine hypercontractility without fetal bradycardia; and low Apgar scores in the newborn.

Transient vasovagal symptoms, including flushing, shivering, headache and dizziness, have been recorded. Local tissue irritation and erythema have occurred on intravenous use of Prostin E₂ Sterile Solution.

No evidence of thrombophlebitis has been recorded and local tissue erythema at the infusion site has disappeared within two to five hours after infusion. A temporary pyrexia and elevated WBC are not unusual, but both have reverted after termination of infusion.

*Use in pregnancy and lactation:* Prostin E₂ Sterile Solution 1 mg/ml is only used during pregnancy, to induce labour.

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the product is used.

*Other special warnings and precautions:*

*Warnings:* This product is available only to hospitals and clinics with specialised 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.

It is advised that Prostin E₂ Sterile Solution should not be administered by the intramyometrial route, as there have been reports of a possible association between this route of administration and cardiac arrest in severely ill patients.

*Precautions:* Caution should be exercised in the administration of prostaglandins to patients with:

(i) asthma or a history of asthma;
(ii) epilepsy or a history of epilepsy;
(iii) glaucoma or raised intra-ocular pressure;
(iv) compromised cardiovascular, hepatic or renal function;
(v) hypertension.

As with any oxytocic agent, prostaglandins should be used with caution in patients with compromised (scarred) uteri.

In labour induction, cephalopelvic relationships should be carefully evaluated before use of prostaglandins. During use, uterine activity, fetal 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 fetal 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 fetus (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.
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 received prostaglandin E\textsubscript{1} during prolonged treatment. There is no evidence that short-term administration of prostaglandin E\textsubscript{2} can cause similar bone effects.

\textit{Overdosage (symptoms, emergency procedures, antidotes):} Uterine hypertonus or 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 fetal distress or uterine hypertonus, then prompt delivery is indicated. Treatment of overdosage must be symptomatic at this time, as clinical studies with prostaglandin antagonists have not progressed to the point where recommendations may be made.

\textit{Incompatibilities:} None known.

\textbf{Pharmaceutical precautions}
Prostin E\textsubscript{2} Sterile Solution 1 mg/ml has a shelf-life of 24 months when stored under refrigeration at 4\textdegree C. It should be diluted before use only with the diluents stated. Diluted solutions should be used within 24 hours and stored in a refrigerator at 2-8\textdegree C.

\textbf{Manufacturer}
The product is manufactured by Pfizer Manufacturing Belgium NV, Rijksweg 12, B-2870 Puurs, Belgium and distributed in the United Kingdom by Pharmacia Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

\textbf{Marketing Authorisation Holder}
Pharmacia Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

\textbf{Product licence number}
PL 0032/0020R

\textbf{Legal category}
POM

\textbf{Package quantities}
Pack containing 1 x 0.75 ml ampoule of Prostin E\textsubscript{2} Sterile Solution 1 mg/ml.

\textbf{Further information}
Oral Prostin E\textsubscript{2} Tablets, Prostin E\textsubscript{2} Vaginal Tablets and Prostin E\textsubscript{2} Vaginal Gel are also available for the induction of labour.

\textbf{Date of preparation or last review}
October 2007

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Perforation line
PROSTIN® E2 STERILE SOLUTION 1 MG/ML
(dinoprostone)

This leaflet gives you a summary of information about Prostin E2 Sterile Solution 1 mg/ml. Please read the leaflet carefully before or after you have been given Prostin E2 Sterile Solution 1 mg/ml. The leaflet cannot tell you everything about your medicine. If you have any questions or are not sure about anything ask your doctor or midwife. Keep this leaflet; you may want to read it again.

What is in Prostin E2 Sterile Solution?
Prostin E2 Sterile Solution contains 1 mg/ml of the active ingredient dinoprostone (prostaglandin E₂) dissolved in ethanol (alcohol) to make a clear, colourless solution.

Prostin E2 Sterile Solution 1 mg/ml is available in a pack that contains a small, closed, glass container (ampoule) containing 0.75 ml of Prostin E2 Sterile Solution 1 mg/ml.

Who makes Prostin E2 Sterile Solution 1 mg/ml?
Prostin E2 Sterile Solution 1 mg/ml is made by Pfizer Manufacturing Belgium NV, Rijksweg 12, B-2870 Puurs, Belgium. The company licensed to sell it in the United Kingdom is Pharmacia Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

How does Prostin E2 Sterile Solution 1 mg/ml work?
Prostin E2 is a prostaglandin. Prostaglandins produced naturally in the body are very important in spontaneous labour. Prostin E2 Sterile Solution 1 mg/ml is used to start off (induce) labour in normal pregnant women, particularly when the baby is healthy and ready to be born. This means that the medicine will help your uterus (womb) to start contracting and you will go into labour. Your uterus will start to contract in exactly the same way as if you had gone into labour without any help.

Is Prostin E2 Sterile Solution right for you?
Your doctor or midwife will ask you questions before giving you Prostin E2 Sterile Solution to make sure it is safe for you to be given it. If you do not understand any of the questions, ask your doctor or midwife to explain. Most women can be given Prostin E2 Sterile Solution. Some women may need extra checks during treatment and for some women a different treatment may be better. Your doctor may choose not to give you Prostin E2 Sterile Solution if he or she or your midwife thinks that to start off labour or speed it up would be unsuitable for you, for example if:

· you have had a Caesarean section or any other operation on your womb;
· you have been told that your baby is too big for your pelvis, is lying awkwardly or may be physically stressed;
- there has been, or there is, suspected fetal distress (your baby is short of oxygen);
- you had a difficult labour or traumatic delivery in a previous pregnancy;
- you have had six or more babies already;
- you had any abnormal contractions of your womb that were too strong or went on for too long during a previous labour;
- you have had an allergic reaction, such as a rash, swelling, wheezing or breathing problems after being given dinoprostone or any other prostaglandin, or any of the other ingredients in Prostin E2 Sterile Solution that may cause such reactions;
- you have an infection of your womb, ovaries or tubes (pelvic inflammatory disease) or have ever had these in the past;
- you have been told that you have, or might have, placenta praevia (where the placenta lies across the entrance to the womb, rather than being high up and out of the way during birth), which causes bleeding from the vagina during pregnancy and may require that your baby is delivered by Caesarean section;
- you have had vaginal bleeding or ‘spotting’ at any time during months four to nine (second and third trimester) of your pregnancy;
- you have any infection or irritation in your cervix (the neck of your womb) or in your vagina, for example you might notice an unusual discharge or an unpleasant smell;
- the baby is not lying with his or her head down;
- you have a current heart, lung, kidney or liver disease.

If you answer YES to any of the following questions or you are not sure, tell your doctor. Your doctor may want to monitor you more closely or he or she may decide that you are not suitable for treatment with Prostin E2 Sterile Solution.

- Do you have glaucoma (raised pressure in the eye)?
- Do you have asthma or have you ever suffered from asthma?
- Do you have epilepsy or have you ever had an epileptic fit?
- Have you had, or been told you had, abnormally strong contractions of your womb during a previous labour?
- Do you have kidney, liver or heart problems?
- Do you have scars on your womb from a previous operation?
· Have you had high blood pressure (hypertension) at any time, including during this or any previous pregnancy?

**Are you taking any other medicines?**
Tell your doctor if you are taking any medicines before you are given Prostin E2 Sterile Solution. This includes medicines that you buy yourself. Prostin E2 Sterile Solution may make you more sensitive to other medicines which strengthen contractions. If you need any of these other medicines, your doctor or midwife will watch over the contractions very carefully.

Your doctor may give you antibiotics before you start this prostaglandin treatment.

If you are given the drug oxytocin (another type of oxytocic drug) before or after you are given Prostin E2 Sterile Solution, Prostin E2 Sterile Solution may increase the effect of oxytocin, so the doctor will check the activity of your womb particularly carefully. Oxytocin should not be given at exactly the same time as Prostin E2 Sterile Solution.

**How will Prostin E2 Sterile Solution be given?**
Prostin E2 Sterile Solution can only be used in a hospital or a clinic with a specialised unit for pregnancy and childbirth (obstetric unit). Medical staff should be available at all times.

Before you are given Prostin E2 Sterile Solution you will be examined by your doctor or midwife. They need to know, for example, the position of your baby's head and how dilated (widened) your cervix (neck of the womb) is. They will also check your contractions (to make sure they are not too strong). They will also check your baby's heartbeat to make sure he or she does not get distressed.

Prostin E2 Sterile Solution 1 mg/ml is given by an intravenous drip, into a vein. It is always diluted before use with a saline (salt) or dextrose (sugar) solution. Your doctor or midwife will adjust the dose to suit you.

Prostin E2 Sterile Solution 1 mg/ml must be diluted ready for use only with the recommended solutions. Once diluted, it must be used within 24 hours.

The mixture is made up to contain 1.5 micrograms per ml of Prostin E2 Sterile Solution and the drip is set to deliver 0.25 micrograms per minute (a microgram is a millionth of a gram – a very small unit of measurement) for 30 minutes. This dose is then either kept the same or increased. (If the baby has died (a 'still birth'), a higher dose may be needed so the drip may be set to deliver 0.5 micrograms per minute and this may be adjusted hourly).

Your doctor or midwife will be keeping a very close eye on you during your treatment. They should be able to act quickly if you have side-effects. If your baby becomes distressed or the muscles of your womb become very tense (uterine hypertonus), or your contractions become very strong and painful your doctor or midwife will stop your treatment temporarily. When the muscles of your womb have relaxed and your baby is not distressed any more your doctor or midwife may start your treatment again with
half the last dose used. If your doctor or midwife stops your treatment temporarily and your condition does not return to normal then he or she may deliver your baby by Caesarean section.

If labour does not start within the first 12 to 24 hours of your being given prostaglandin E$_2$, your doctor or midwife will stop treatment.

**What if you are given too much Prostin E2 Sterile Solution?**
Tell your doctor or midwife if you think you have been given too much Prostin E2 Sterile Solution.

If you have been given too much you may feel frequent, strong (hypertonic) contractions of your womb or very severe contractions. Your doctor may stop your treatment and if your contractions do not return to normal then your doctor may deliver your baby by Caesarean section.

**Does Prostin E2 Sterile Solution have side-effects?**
Most women who are given this medicine find that it causes them no problems. Women sometimes suffer from sickness or diarrhoea during treatment. These have seldom been bad enough for the woman to stop the treatment.

If you have asthma, Prostin E2 Sterile Solution could cause you to have an asthmatic attack. **You must tell your doctor or midwife if you suffer from asthma or if you have difficulty breathing.**

Because Prostin E2 Sterile Solution makes the body start into labour in the same way as it would naturally, anything that can happen in a natural labour can also happen if you are being given Prostin E2 Sterile Solution. Talk to your midwife or doctor about this if you want to know more, as they will be able to give you the information that you need.

There may be a link between Prostin E2 Sterile Solution and cardiac arrest (stopping of the heart) in women who were already severely ill and who were given Prostin E2 Sterile Solution by injection into the muscle of the womb. This method of injection is not recommended.

Women having prostaglandin E$_2$, have reported the following:

- heart attack;
- sudden blocking of a blood vessel by either amniotic fluid or blood clots;
- detached placenta;
- stillbirth or neonatal death;
- abnormally strong, frequent or long contractions of the womb;
- itching and rash of the vaginal area;
- slowing or quickening of the baby's heart rate and distress in the baby;
- high blood pressure in the mother;
- breathlessness;
- feeling or being sick;
- diarrhoea;
- very quick opening of the cervix;
- running a temperature;
- backache;
- rash;
- baby born with an Apgar score lower than seven. (The Apgar score, which is measured on a scale of one to ten, is used to describe the baby's condition at birth. A low Apgar Score means that the baby's heart or lungs are not working properly).

These have also been reported by women who have not taken prostaglandins.

If you have very long and strong contractions, the wall of the uterus could tear. (This can happen in natural labour too.) This is one reason for close monitoring during treatment.

You might have reddening and irritation in the area around the needle for two to five hours after the needle has been removed.

Studies in animals given prostaglandins in high doses for several weeks have shown proliferation (thickening) of bone. There is no evidence that this occurs with short-term treatment.

If you are breast-feeding after having Prostin E2 Sterile Solution 1 mg/ml, small amounts of products formed from prostaglandins could pass into your baby through your breast milk. No studies have been done to find out if any of these products get into your breast milk and if they do, whether they will then pass into the baby's blood, but as your own body produces prostaglandins during childbirth, Prostin E2 Sterile Solution 1 mg/ml is not expected to cause any harm to your baby. If you are worried about the effects of Prostin E2 Sterile Solution when it is passed onto your baby through breast milk, talk to your doctor or midwife.

If you notice any of the above or any other unpleasant effects, in yourself or your baby tell your doctor or midwife.

**Looking after Prostin E2 Sterile Solution**
The hospital pharmacy will store this medicine in a fridge at 4°C and make sure that it is not used after the use-by date ‘EXP’ on the pack.

Prostin E2 Sterile Solution must be diluted ready for use only with the recommended diluents. Once diluted, it must be used within 24 hours.

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