SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):
PROSTIN F2 ALPHA™ (Injection)

COMPOSITION:
Sterile aqueous solution dinoprost, 5 mg/ml (present as 6,71 mg/ml of dinoprost tromethamine salt) containing 0,9% m/v benzyl alcohol as preservative.

PHARMACOLOGICAL CLASSIFICATION:
A 19 Oxytocics

PHARMACOLOGICAL ACTION:
Although the exact mode of action in pregnancy termination in humans is not fully defined, when PROSTIN F2 ALPHA is administered by the intravenous route it initiates rhythmical uterine contractions which, if continued for a sufficient time, are capable of expelling the contents of the uterus.
Sensitivity of the pregnant uterus to prostaglandins is lower during early and mid-pregnancy than at term.
PROSTIN F2 ALPHA is also capable of inducing contractions of the smooth muscle of the intestinal tract. This action may be the cause of vomiting and diarrhoea which are associated with the use of PROSTIN F2 ALPHA but this is yet to be shown conclusively.

INDICATIONS:
PROSTIN F2 ALPHA has been found to be effective for the following purposes:
1. Induction of labour when there are no foetal or maternal contra-indications.
2. Induction of labour in cases of foetal death in utero.
3. When vaginal delivery is desired for the safety of the mother or child in conditions such as Rh incompatibility, maternal diabetes, maternal hypertension, pre-eclampsia, and premature rupture of the membranes.

CONTRA-INDICATIONS:
The use of PROSTIN F2 ALPHA is contra-indicated in:
1. Patients with a history of hypersensitivity to prostaglandins.
2. Cases with a history of severe pelvic inflammatory disease.
3. Patients with active cardiac, pulmonary, renal or hepatic disease.
4. Patients in whom prolonged contractions of the uterus are considered inappropriate, such as:
   a. Cases with a history of caesarean section or prior major uterine surgery.
   b. Cases in which major degrees of cephalopelvic disproportion may be present.
   c. Cases in which foetal malpresentation is present.
   d. Cases in which there is clinical suspicion or definite evidence of pre-existing foetal distress.
   e. Cases in which there is a history of difficult labour and/or traumatic delivery.
   f. In grand multiparae with six or more previous term pregnancies.
   g. Patients with unexplained vaginal bleeding during the second or third trimester of this pregnancy.

It has been found that prostaglandins might potentiate the effect of oxytocin, and it is therefore recommended that the use of these drugs, simultaneously or in sequence, be carefully monitored.

**WARNINGS:**
Post-partum intra-uterine injection of **PROSTIN F2 ALPHA** is not recommended as severe hypertension has occurred.

**DOSEAGE AND DIRECTIONS FOR USE:**
Continuous administration of the drug for more than two days is not recommended.
In all cases the dose should be adapted to the patient's response. For induction of labour by the intravenous route:
If an IV drip is to be employed, the following procedure should be observed:
   a. The number of drops per ml, delivered by the particular drip apparatus to be employed, should be determined BEFORE THE PGF2 ALPHA IS ADDED TO THE INFUSION BOTTLE.
   b. A screw-type clamp must be employed to control the drip adequately.
   c. Count the number of drops in the drip-chamber required to fill an accurately-calibrated container to the 5 ml mark (such as a calibrated centrifuge tube).
   d. Divide by 5 to calculate the number of drops in the drip-chamber per ml delivered.
e. Set the drip rate according to the dosage recommended below (e.g. if 24 drops make up one ml, to deliver 0.5 ml per minute set the drip rate at 12 drops per minute).

f. The drip rate must be monitored continuously by an attendant.

g. A solution containing 5 micrograms per ml should be employed (see directions for preparation).

The object of treatment is to induce and maintain labour to delivery using the smallest amount of drug possible. Accordingly, the initial rate of infusion should be 2.5 micrograms per minute, which should be maintained for at least the first 30 minutes. If a satisfactory uterine contractility response is produced, this rate should be maintained. If not, the rate should be increased to 5.0 micrograms per minute. In some circumstances after a fair trial (one or two hours), the rate may subsequently need to be increased to 10.0 micrograms per minute or, rarely, 20.0 micrograms per minute, depending on uterine response and freedom from side effects. If uterine hypertonus or foetal distress occur, the infusion should be stopped until the condition of the patient and the foetus return to normal. The infusion may then be restarted at 50% of the last dose level and subsequently increased with caution.

Cases of foetal death in utero may require higher doses than those given above. An initial rate of 5.0 mcg/minute may be used with stepwise increases, at intervals of not less than one hour, as described above. Side effects permitting, the final rate of infusion may be increased to 40 mcg/minute if uterine contractility response is inadequate at the lower dosage rates.

If a constant rate infusion pump is used, a more concentrated solution may be required, dependent on the type of pump, but the dosage rates (micrograms per minute) should remain as above.

**DIRECTIONS FOR USE OF THE AMPouLE:**

No ampoule file is needed to open the ampoule. The neck of the ampoule is prescored at the point of constriction. A coloured dot on the ampoule helps to orientate the ampoule. Take the ampoule and face the coloured dot. The ampoule opens easily by placing the thumb on the coloured dot and gently pressing downwards as shown.
Directions for the preparation of dilute solutions from the 5mg/ml sterile solution:

(5 mcg/ml solution)

For use by IV drip, withdraw 1,0 ml from the ampoule using an aseptic technique, and add to 1000 ml (or 0,5 ml to each 500 ml) of sterile normal saline or 5% dextrose in water. Shake to ensure uniformity. After dilution, attach the label provided. Use dilute solution within 24 hours of preparation. For use by constant rate infusion pump, see appropriate section under "Dosage".

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Nausea, vomiting, diarrhoea and local tissue reaction have been reported. Foetal distress, uterine hypertonus or tetanic contractions may result from overdosage, and are usually reversed by temporary discontinuation of therapy, in the rare instance where this is not effective, prompt delivery is indicated.

Clinical studies at dosages recommended herein have not revealed any life-threatening adverse reactions. When seen, adverse effects have generally been dose-dependent, transient and reversible on discontinuation of therapy.

Some transient symptoms have been reported, including:

- Blood loss, hypovolemic shock, bronchospasm, dyspnoea, coughing, pulmonary embolism, chest pain, hyperventilation, disseminated intravascular coagulation, hypertension, hypotension, tachycardia, bradycardia, congestive heart failure, second degree heart block, ventricular arrhythmia, hypocalcemia.
- Uterine infections, perforation of the cervix, uterine pain, perforated uterus-post instrumentation, pelvic thrombophlebitis.
- Urinary tract infections, urinary incontinence, dysuria, haematuria, urinary atony or hypertonicity.
- Excitement, drowsiness, weakness, malaise, syncope or dizziness.
- Fever, flushing, shivering, headache, unspecified pain, backache, unspecified muscle spasm, aggravation of diabetes, skin eruptions, pruritis, petechiae,
paralytic ileus, diplopia, pupil constriction, hiccough, polydipsia, burning sensation - eye, burning sensation - breast, paraesthesias, breast engorgement, sweating, nosebleed, dehydration, cyanosis and hypersensitivity.

Additional adverse reactions observed with PROSTIN F$_2$ ALPHA include: Uterine hypercontractility with foetal bradycardia, uterine hypercontractility without foetal bradycardia and low Apgar scores in the newborn.

Local tissue irritation and erythema have been observed at the infusion site when PROSTIN F$_2$ ALPHA was administered intravenously. There is, however, no evidence of true thrombophlebitis in the vein in which the infusion has been given. This irritation disappears usually within 2 to 5 hours after discontinuation of therapy or change in infusion site. A temporary pyrexia and elevation of the W.B.C. are not unusual. These appear late in the infusion and revert to normal soon after discontinuation of therapy. Caution should be exercised in the administration of PROSTIN F$_2$ ALPHA for induction of labour patients with asthma or a history of asthma, glaucoma, raised intra-ocular pressure, hypertension, cardiovascular disease or epilepsy.

In addition, cephalopelvic relationships should be carefully evaluated before use of PROSTIN F$_2$ ALPHA. During infusion, uterine activity, foetal status and the progression of the cervical dilation should be carefully monitored to detect possible evidence of unphysiological response eg. 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 fetus be monitored instrumentally throughout labour. The possibility of uterine rupture should be borne in mind where high tone myometrial contractions are sustained.

At the present time the product should only be used in hospitals or in locations with facilities for emergency obstetric and gynaecological care.

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 F$_2$ ALPHA can cause similar bone effects.

Large doses of PROSTIN F$_2$ ALPHA can bring about an increase in blood pressure, probably due to its effect on vascular smooth muscle. At the doses recommended for induction of labour, this effect has not been clinically significant.
Concomitant Medication:
Other drugs which have been employed during PROSTIN F₂ ALPHA administration for the symptomatic relief of side effects include:
   a. For suprapubic pain - Meperidine (pethidine).
   b. For nausea and vomiting - Prochlorperazine, metoclopramide.
   c. For diarrhoea - atropine, tincture opii, diphenoxylate.
These medications should be employed in their usual dosages.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT:
Treatment should be symptomatic and supportive.

IDENTIFICATION:
Colourless solution in 1ml ampoules

PRESENTATION:
PROSTIN F₂ ALPHA™ supplied as a 1ml ampoule.

STORAGE INSTRUCTIONS:
Store at room temperature (15 - 30 °C).
Keep out of reach of children.

REGISTRATION NUMBER:
G/19/39

NAME AND ADDRESS OF THE APPLICANT:
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