PRODUCT INFORMATION

HEMABATE® Injection 250 μg/mL

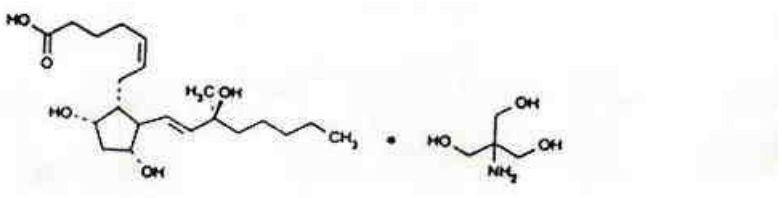
NAME OF DRUG

Carboprost trometamol

DESCRIPTION

HEMABATE Injection is a colourless, sterile aqueous solution for intramuscular administration. It contains carboprost trometamol equivalent to 250 μg carboprost in 1mL ampoules.

Carboprost trometamol is the trometamol salt of the (15S)-15 methyl analogue of naturally occurring prostaglandin F2α (CAS 58551-69-2). The chemical name is (15S)-9α, 11α, 15-trihydroxy-15-methyl-prosta-cis-5, trans-13-dienoic acid trometamol salt. The structural formula is presented below:



The molecular formula is C_{25} H_{47} N O_8 and the molecular weight of carboprost trometamol is 489.65.

Excipients included in the formulation are trometamol, sodium chloride and benzyl alcohol (as preservative). When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

PHARMACOLOGY

Carboprost is a synthetic 15-methyl analogue of dinoprost (prostaglandin F2α). It is a uterine stimulant with a more prolonged action than dinoprost. When used in postpartum haemorrhage, it stimulates the uterus to contract in a manner similar to that normally observed in the uterus following delivery. The resulting myometrial contractions provide haemostasis at the site of placentation and hence prevent further blood loss. Whether or not this action results from a direct effect on the myometrium has not been determined with certainty at this time. The fundamental actions of prostaglandins include inhibition or stimulation of smooth muscle contraction and inhibition of the release of

noradrenaline or modulation of its effects at neuroeffector sites. In addition to effects on the uterus, carboprost stimulates the smooth muscle of the gastrointestinal tract, which commonly results in vomiting or diarrhoea or both when used at recommended doses. It may cause a transient elevation of body temperature and transient bronchoconstriction.

At higher doses in both animals and humans, carboprost can increase blood pressure, possibly through the contraction of vascular smooth muscle.

PHARMACOKINETICS

Five women who had spontaneous vaginal deliveries (at term) were treated immediately post partum with a single intramuscular injection of 250 μg carboprost. Peripheral blood samples were collected at several times during the four hours following treatment. The highest concentration was observed at 15 minutes in two patients (3009 and 2916 picogram/mL), at 30 minutes in two patients (3097 and 2792 picogram/mL) and at 60 minutes in one patient (2718 picogram/mL).

CLINICAL TRIALS

Two open label clinical trials have been conducted to support the efficacy and safety of HEMABATE in the treatment of postpartum haemorrhage due to uterine atony and refractory to conventional therapeutic measures. The first was an uncontrolled, multicentre study in 115 patients with refractory postpartum haemorrhage conducted in the USA by Pharmacia & Upjohn (Study # 7055). HEMABATE was reported to achieve haemostasis, thus avoiding further intervention, such as surgery, in 87.8% of patients, with the majority of patients (73.3%) requiring only a single dose. Adverse events reported were dose related and not serious.

The second report relates to a post-marketing study conducted over 12 months at 14 centres in the USA as a condition of FDA approval for HEMABATE. In this uncontrolled epidemiological study, a total of 333 patients were evaluated and HEMABATE was found to control the postpartum haemorrhage, thus avoiding surgical intervention in 83.8% of cases. 81.4% of patients required only a single dose of HEMABATE. Adverse events did not appear to be dose-related.

INDICATION

HEMABATE is indicated for the treatment of postpartum haemorrhage due to uterine atony which has not responded to conventional methods of management.

CONTRAINDICATIONS

1. Hypersensitivity to carboprost trometamol or any of the excipients of HEMABATE.
2. Acute pelvic inflammatory disease.
3. Patients with active cardiac, pulmonary, renal or hepatic disease.

WARNINGS

HEMABATE should be used by appropriately trained personnel in hospitals and clinics with specialised obstetric units.

This preparation should not be used for the induction of labour.

HEMABATE, as with other potent oxytocic agents, should be used only with strict adherence to recommended dosages.

HEMABATE must not be given intravenously. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Very rare cases of cardiovascular collapse have been reported following the use of prostaglandins. This should always be considered when using HEMABATE.

HEMABATE contains benzyl alcohol which has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS

HEMABATE should be used with caution in patients with a history of glaucoma or raised intra-ocular pressure, asthma, hypotension or hypertension, cardiovascular, renal or hepatic disease, anaemia, jaundice, diabetes or epilepsy.

During the clinical trials with HEMABATE, 5/115 (4%) patients had an increase in blood pressure reported as a side effect. The degree of hypertension was moderate. The cases reported did not require specific therapy for the elevated blood pressure.

Since prostaglandins may potentiate the effect of oxytocin, it is recommended that the use of these drugs simultaneously or in sequence should 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 E1 during prolonged treatment. There is no evidence that short term administration of HEMABATE can cause similar bone effects.

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

Use in patients with chorioamnionitis

During the clinical trials with HEMABATE, chorioamnionitis was identified as a complication contributing to postpartum uterine atony and haemorrhage in 8/115 (7%) of cases, 3 of which failed to respond to HEMABATE. This complication during labour

may have an inhibitory effect on the uterine response to HEMABATE similar to what has been reported for other oxytocic agents.

Use in patients with pre-existing cardio-pulmonary problems

Decreases in maternal arterial oxygen content have been observed in patients treated with carboprost trometamol. A causal relationship to carboprost trometamol has not been established, however, it is recommended that patients with pre-existing cardio-pulmonary problems receiving HEMABATE are monitored during treatment and given additional oxygen if necessary.

Impaired Liver Function

HEMABATE should be used with caution in patients with a history of impaired liver function and is contra-indicated in patients with active liver disease.

Impaired Renal Function

HEMABATE should be used with caution in patients with a history of impaired renal function and is contra-indicated in patients with active renal disease.

Use in pregnancy: Category D

Administration of prostaglandins such as carboprost during pregnancy stimulates the uterus and may cause inability to sustain pregnancy and irreversible fetal damage or death. HEMABATE is indicated in the postpartum period. It is not indicated for use during pregnancy.

Carboprost has been found to cross the placenta and distribute to the fetus in pregnant women. Any dose of carboprost that produces increased uterine tone could put the fetus at risk.

In animal studies, administration of carboprost for 3 or more days during gestation caused a high incidence of resorptions in rats and rabbits and embryotoxic effects in rats. The lowest dose of carboprost which caused these effects was approximately 6 and 36 times lower, in rats and rabbits respectively, than the recommended maximum dose in humans (based on surface area comparisons).

Administration of carboprost to rats for 7-8 days prior to delivery was associated with shortened gestation length, dystocia, increased incidence of still births and decreased offspring body weight. The lowest dose of carboprost which caused these effects was approximately 100 times lower than the recommended maximum dose in humans (based on surface area comparisons).

Use in Lactation

It is not known if carboprost is secreted into breast milk, however, this possibility cannot be ruled out.

Administration of carboprost to rats during the pre- and post-natal period resulted in failure of dams to lactate. The lowest dose of carboprost which caused these effects was approximately 100 times lower than the recommended maximum dose in humans (based on surface area comparisons).The effect was reversible.

The relevance of these findings to lactation in humans treated with carboprost is unclear. However, based on plasma clearance rates it is recommended that breast feeding does not occur for at least 6 hours after administration.

Carcinogenicity, Mutagenicity, Impairment of fertility

Long term studies have not been conducted to evaluate the carcinogenic potential of carboprost, nor has comprehensive battery of genotoxicity assays.

Carboprost showed no evidence for mutagenic activity in the AMES test or for clastogenic activity in a rat micronucleus test. However, the genotoxic potential of the human metabolites of carboprost was not assessed in these studies.

Administration of carboprost at doses up to 3 times the expected maximum human dose (based on surface area) for 3 or 6 days prior to mating had no effect on male or female fertility in rats, although other carboprost-like drugs are known to disrupt fertility.

ADVERSE REACTIONS

The adverse effects of HEMABATE are generally transient and reversible on cessation of therapy.

Clinical Trials

The most frequent adverse effects observed with the use of HEMABATE in clinical trials (n = 448 patients) are related to its contractile effect on smooth muscle. In Study # 7055 (n = 115 patients) events occurring at an incidence >1% were vomiting, diarrhoea and/or nausea (19%), temperature elevation (7%) and increased blood pressure (4%). In the post-marketing study (n = 333 patients) adverse events did not appear to be dose related and included diarrhoea (8.1%), vomiting (4.8%) and increased blood pressure (5.1%).

Other adverse effects reported rarely in clinical use include pulmonary oedema, diaphoresis, dizziness, asthma & wheezing.

Adverse effects are listed below by body system:

Body system	Adverse effect	Frequency
Local effects	Injection site erythema, pain	Uncommon
Gastrointestinal	Diarrhoea	Very common
	Nausea, vomiting	Common
	Abdominal cramp, pain	Uncommon
Cardiovascular	Elevated blood pressure	Common
	Tachycardia	Uncommon
Respiratory	Dyspnoea	Uncommon
CNS	Headache, dizziness	Uncommon
Body as a whole	Fever	Common
	Chills, flushing, sweating	Uncommon

Very common >10%; Common 1% to <10%: uncommon 0.1% to 1%; rare <0.01%

Hyperthermia and flushing have been observed after intramuscular HEMABATE but, if not complicated by endometritis, temperature will usually return to normal within several hours of the last injection.

DOSAGE AND ADMINISTRATION

An initial dose of 250 μg (1.0 mL) of HEMABATE should be administered by deep intramuscular injection. If necessary, further doses of 250 μg may be administered at intervals of approximately 1.5 hours. In severe cases the interval between doses may be reduced at the discretion of the attending physician, but it should not be less than 15 minutes. The total dose of HEMABATE should not exceed 2mg (8 doses).

Vials are for single use only and any residue should be discarded.

Paediatrics

Safety & efficacy in paediatrics patients have not been established.

OVERDOSAGE

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. If evidence of adverse effects appears, the frequency of administration of HEMABATE should be decreased or administration discontinued.

PRESENTATION

HEMABATE Injection is available as 250 μg/1mL ampoules, packaged in cartons of 1* or 10 ampoules.

*Pack sizes currently marketed.

STORAGE

Store at 2 to 8°C (Refrigerate. Do not freeze)

SPONSOR

Pharmacia Australia Limited
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RYDALMERE NSW 2116

For medical inquiries call 1300 362 486

Date of TGA Approval: 7 June 2001