

PRODUCT MONOGRAPH

HEMABATE* STERILE SOLUTION

(carboprost tromethamine injection USP)

250 µg/mL

Prostaglandin

Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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ACTION AND CLINICAL PHARMACOLOGY

Carboprost tromethamine given intramuscularly during the immediate postpartum period stimulates myometrial contractions. The result of postpartum contractions provides effective hemostasis at the site of placentation. The mechanism of action of these contractions has not been determined.

Uterine atony is the leading cause of postpartum hemorrhage. Extensive clinical experience with prostaglandins in term labour induction trials and pregnancy termination has established them as effective uterotonic agents. Prostaglandins appear to be involved in postpartum hemostatic mechanisms by virtue of their pharmacodynamic properties relative to myometrial stimulation, vasoactive effects and platelet function. Carboprost tromethamine, a methylated analogue of PGF_{2α}, has been shown to be a more potent uterotonic agent with longer duration of action than the parent compound.

Carboprost tromethamine also stimulates the smooth muscle of the human gastrointestinal tract. This activity may produce the vomiting and/or diarrhea that is common when carboprost tromethamine is used. In laboratory animals and humans, carboprost tromethamine can elevate body temperature. With the clinical doses of carboprost tromethamine, some patients do experience transient temperature increases.

In laboratory animals, and in humans, large doses of carboprost tromethamine can raise blood pressure, probably by contracting the vascular smooth muscle. With the doses of carboprost tromethamine used for terminating pregnancy, this effect has not been clinically significant. In some patients, carboprost tromethamine may cause transient bronchoconstriction.

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

INDICATIONS AND CLINICAL USE

HEMABATE (carboprost tromethamine) is indicated for the treatment of postpartum hemorrhage due to uterine atony which has not responded to conventional methods of management. Prior treatment should include the use of intravenously administered oxytocin, manipulative techniques such as uterine massage and, unless contraindicated, intramuscular ergot preparations. Studies have shown that in such cases, the use of HEMABATE has resulted in satisfactory control of hemorrhage, although it is unclear whether or not ongoing or delayed effects of previously administered uterine agents have contributed to the outcome. In a high proportion of cases, HEMABATE used in this manner has resulted in the cessation of life threatening bleeding and the avoidance of emergency surgical intervention.

CONTRAINDICATIONS

1. Hypersensitivity to any of the components of the preparation (carboprost, tromethamine, sodium chloride, benzyl alcohol).
2. Patients with known active cardiac, pulmonary, renal, or hepatic disease.
3. Acute pelvic inflammatory disease.

WARNINGS

HEMABATE (carboprost tromethamine), like other potent oxytocic agents, should be used with strict adherence to recommended dosages, by medically trained personnel in hospital surroundings with appropriate intensive care and acute surgical facilities.

Use of HEMABATE is associated with transient pyrexia that may be due to hypothalamic thermoregulation. Fever was reported by 8 of 115 (7%) patients treated in an open-label clinical trial of patients with postpartum hemorrhage due to uterine atony who had not responded to conventional non-surgical treatment of fundal massage, intravenous oxytocin and/or intramuscular methylergonovine.

On rare occasions, cardiovascular collapse has been reported with some of the prostaglandins, so this should always be considered when using HEMABATE.

Bronchoconstriction has been reported after exposure to HEMABATE, but it is rarely clinically important except in asthmatic patients.

PRECAUTIONS

General

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 (carboprost tromethamine) can cause similar bone effects.

Prostaglandins in general affect platelet aggregation by inhibiting it. Clinical experience on the effect of HEMABATE on human coagulation factors is limited. Due to this lack of information, it is advised that coagulation parameters be measured.

HEMABATE should be used cautiously in patients with a history of asthma, hypo- or hypertension, cardiovascular, renal, or hepatic disease, anemia, jaundice, diabetes, or epilepsy; or patients with previously compromised (scarred) uteri.

Nine of 248 patients (4%) treated for postpartum hemorrhage had an increase of blood pressure reported as a side effect. The degree of hypertension was moderate and it is not certain as to whether this was in fact due to a direct effect of HEMABATE or a return to a status of pregnancy-associated hypertension manifest by the correction of hypovolemic shock. In any event, the cases reported did not require specific therapy for the elevated blood pressure.

In a post-marketing trial of 333 cases of postpartum hemorrhage, investigator's considered 17 cases (5%) of increased blood pressure to be drug related.

Chorioamnionitis was identified as a complication contributing to postpartum uterine atony and hemorrhage in eight of 115 patients, 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.

Nursing Mothers

Human pharmacokinetics studies were not conducted on the excretion of HEMABATE in breast milk. However based on plasma clearance rates it is recommended that breast feeding not occur for at least 6 hours after administration.

Drug Interactions

Concomitant use with other oxytocic agents is not recommended. However, 578 (92%) out of 628 patients who received HEMABATE had prior treatment with conventional oxytocics such as oxytocin and ergometrine (ergonovine) maleate. It must be considered that HEMABATE may augment the activity of these oxytocic agents.

ADVERSE REACTIONS

The adverse effects of HEMABATE (carboprost tromethamine) are generally transient and reversible when therapy ends. The most frequent adverse reactions are related to its contractile effect on smooth muscle. The following table lists the medical events of 248 patients who received HEMABATE.

MEDICAL EVENTS			
N = 248 patients (all routes)*			
BODY SYSTEM	EVENT	N	%
GASTROINTESTINAL	Nausea	25	10.1
	Diarrhea	21	8.5
	Vomiting	19	7.7
	Abdominal Pain/Cramp	1	0.4
CARDIOVASCULAR	Increased Blood Pressure	9	3.6
	Flushing	5	2.0
	Tachycardia	2	0.8
ALLERGIC	Fever	16	6.4
	Chills	1	0.4
CENTRAL NERVOUS SYSTEM	Headache	4	1.6
OTHER	Dyspnea	1	0.4
	Erythema at Injection Site	1	0.4
	Sweating	1	0.4

*Most patients received HEMABATE intramuscularly. There were some patients who received HEMABATE intramyometrially (IMM) or intravenously (IV). The safety of the IMM and IV route has not been fully established at this time.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with HEMABATE (carboprost tromethamine) should result in the accentuation of expected side effects such as nausea, vomiting and diarrhea. Elevated blood pressure and body temperature may occur. Supportive therapy, particularly fluid replacement, should be given if serious vomiting and diarrhea occur.

Although prostaglandin antagonists are known to exist, no experience has been obtained at the present time with their usage in overdosage. Therefore, no specific therapy for overdosage is available.

DOSAGE AND ADMINISTRATION

HEMABATE (carboprost tromethamine) is administered by deep intramuscular injection. Initially a 250 µg (1 mL, the entire contents of the ampoule) dose of HEMABATE is given. In clinical trials, 80% of successful cases responded to ≤ 250 µg and 95% of successful cases responded to ≤ 500 µg. In some cases, multiple dosing of 250 µg at intervals of 15 to 90 minutes was carried out with successful outcome. The need for additional injections and the interval at which these should be given can be determined only by the attending physician as dictated by the course of clinical events. The total dose of HEMABATE (carboprost tromethamine) should not exceed 2 mg (8 doses).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: carboprost tromethamine injection

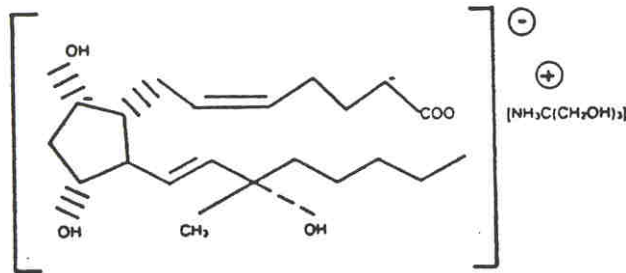
Chemical name:

- a) (15S)-15-methyl prostaglandin F_{2α} tromethamine salt
- b) 7-[3α,5α-dihydroxy-2β-[(3S)-3-hydroxy-3-methyl-*trans*-1-octenyl]-1α-cyclopentyl]-*cis*-5-heptenoic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol
- c) (5Z,9α,11α,13E,15S)-9,11,15-trihydroxy-15-methylprosta-5,13-dienoic acid tromethamine salt
- d) (15S)-15-methyl PGF_{2α}-THAM

Molecular formula: C₂₅H₄₇O₈N

Molecular weight: 489.64

Structural Formula:



Description: Carboprost tromethamine is a white to slightly off-white crystalline powder. It generally melts between 95° to 105°C, depending on the rate of heating. It dissolves readily in water at room temperature at concentrations greater than 75 mg/mL.

Composition

Carboprost tromethamine 332 µg (equivalent to 250 µg carboprost), tromethamine 83 µg, sodium chloride 9 mg, benzyl alcohol 9.45 mg per mL. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

Stability and storage recommendations

HEMABATE (carboprost tromethamine) must be refrigerated at 2° to 8°C.

AVAILABILITY OF DOSAGE FORMS

HEMABATE (carboprost tromethamine) is available in 1 mL ampoules (250 µg/mL) in cartons of 10.

PHARMACOLOGY

Carboprost is a synthetic compound with a structural modification that has been shown to block the initial step in metabolic degradation, and has altered its biological activity accordingly. This compound interrupted pregnancy in the hamster and the monkey, accelerated the transport of ova through the fallopian tubes in rabbits, and increased the tone of longitudinal muscle of the human oviduct *in vitro*. Carboprost was about 10 times as potent a uterine stimulant as prostaglandin F_{2α} when administered intravenously or intramuscularly and it is also active on vaginal application. In general, carboprost's minimal effective dose was lower and its effect lasted longer than prostaglandin F_{2α}. The binding affinity of carboprost to a human myometrial *in vitro* preparation or to a bovine luteal particulate fraction was lower than prostaglandin F_{2α}.

In the anaesthetized dog, intramuscular or intravenous carboprost produced a greater and more sustained rise in pulmonary artery pressure than prostaglandin F_{2α} and intramuscular carboprost also elicited a more prolonged increase in pulmonary vascular resistance, caused a greater initial fall in systemic arterial oxygen tension and cardiac output and a greater increase in systemic resistance. Carboprost was also shown to be more potent than prostaglandin F_{2α} in altering the relative blood pressure of the anaesthetized, pentolinium treated rat.

Carboprost, in doses of 30 or 60 µg, lowered the body temperature of the Rhesus monkey by 0.5 or 1.5°C respectively for 4 to 5 hours.

Carboprost stimulated platelet aggregation *in vitro*, inhibited gastric secretions in dogs and had no analgesic activity in rats as measured by the hotplate method.

Animal Drug Kinetics

Following single intravenous administration of 200 µg of carboprost to two Rhesus monkeys, the initial disappearance half-life of carboprost from plasma was approximately one minute as compared with 20 to 30 seconds for prostaglandin F_{2α}. After three minutes, however, the rate of disappearance from plasma slowed markedly so that significant plasma levels of 16 to 19 ng/mL were still present 30 minutes after dosing. By contrast, prostaglandin F_{2α} plasma levels return to baseline values five minutes after dosing. Intravenous infusion of carboprost at the rate of 1 µg per minute for 30 minutes elevated the plasma level to 4.2 ng/mL. Detectable levels (2 ng/mL) were still present 90 minutes after discontinuing the infusion whereas, prostaglandin F_{2α} concentrations returned to baseline levels within five minutes after discontinuation. In the Rhesus monkey, a single intramuscular injection of 20 to 130 µg of carboprost gave peak plasma levels of drug of 0.4 to 5 ng/mL at 30 to 60 minutes which then declined to baseline levels 6 to 8 hours after injection. These plasma concentrations were comparable to those resulting from the continuous infusion of carboprost for 30 minutes at the rate of 1 µg per minute and indicated rapid uptake from the site of injection as well as rapid distribution. Monkeys were injected during both the follicular and luteal phase of the menstrual cycle, but no significant differences in plasma levels of carboprost were observed. Co-injection of epinephrine did not affect the rate of absorption from the injection site.

In the Rhesus monkey, absorption of carboprost from the vagina was slower than that of prostaglandin F_{2α}. Maximum blood levels were only 0.016% of the dose and after 22.5 hours only 12% of the dose was excreted in the urine.

Urinary excretion represents the major route of elimination of carboprost in monkeys. Urinary excretion of metabolites is rapid and nearly complete 24 hours after subcutaneous or intramuscular administration in Cynomolgus monkeys, with the majority of the dose being excreted within the first 5 to 10 hours.

Following the intramuscular administration of ^3H -carboprost in rats, 64% of the dose was excreted in the urine, mostly in the first 24 hour period after dosing. Less than 0.2% remained in the body 72 hours after dosing and a similar excretion and residue pattern was observed after intravenous dosing.

Human Drug Kinetics

Blood samples collected during the 0 to 5 and 5 to 15 minute intervals following intravenous administration of radiolabelled carboprost to a normal female were analyzed for intact drug. Of the total radioactivity extracted from the earlier sample, 80% was still carboprost. In the 5 to 15 minute sample, 30% was still intact drug and it was evident that carboprost remains in the peripheral circulation much longer than does prostaglandin $\text{F}_{2\alpha}$.

When pregnant women (second trimester) were administered carboprost by continuous intravenous infusion for six hours at the rate of 2.5 $\mu\text{g}/\text{minute}$, the plasma level of intact drug increased from 1.1 to 1.3 ng/mL after 1 to 2 hours and then remained essentially constant for the balance of the infusion period. When the infusion rate was increased to 5 $\mu\text{g}/\text{minute}$, the plasma level rose continuously until the infusion was stopped. Following cessation of the infusion, plasma levels decreased, with a half-life of approximately 30 to 45 minutes.

Peak plasma levels of 1 to 1.6 ng/mL were obtained 20 to 30 minutes after a single intramuscular injection of 100 to 400 μg of carboprost to pregnant women. Levels gradually declined to 0.2 to 0.4 ng/mL three hours after drug administration. When carboprost (250 μg) was given intramuscularly every two hours to pregnant women, pre-injection plasma levels of carboprost stabilized after four injections at 1.2 ng/mL , approximately the same as that during the intravenous infusion of 2.5 $\mu\text{g}/\text{minute}$ (300 μg every two hours). The data indicate that the intramuscular route, at comparable total dosages, resulted in minimum plasma drug levels similar to those obtained by continuous intravenous infusion.

Limited drug distribution data from other routes of administration of carboprost have also been obtained. Tritium labelled carboprost (2.5 mg), administered intra-amniotically to mid-trimester

abortion patients, disappeared from the amniotic fluid with a half-life of 27 to 31 hours, about twice that of prostaglandin $F_{2\alpha}$. The disappearance rate of total radio-activity from the fluid was similar for carboprost and prostaglandin $F_{2\alpha}$, indicating less rapid metabolism of the synthetic analogue. Urinary excretion accounted for 6 to 30% of the dose.

Significant amounts of free drug and lesser amounts of metabolites (total of 0.4 to 2.9 $\mu\text{g/gm}$ of tissue) were found in fetal lung, liver and kidney.

Urinary excretion represents the major route of elimination of carboprost in man. Urinary excretion of metabolites is rapid and nearly complete 24 hours after intravenous or subcutaneous administration in women. About 80% of the dose is excreted within the first 5 to 10 hours and an additional 5% of the dose is excreted in the next 20 hours. After subcutaneous administration in women, the extent and rate of urinary excretion of the metabolic products of carboprost and prostaglandin $F_{2\alpha}$ are very similar.

Three metabolites of carboprost have been characterized from human (and monkey) urine. These account for approximately 75% of the urinary metabolites. About 1% of the dose is excreted as intact drug. The remaining uncharacterized metabolites C of which there are several, all in small amounts C are both more and less polar than the parent compound. The major metabolite found in plasma or amniotic fluid is the dinor metabolite.

TOXICOLOGY

Acute Toxicity

Species	Route	LD_{50}
Mouse	intravenous	131.6 mg/kg
Rat	intravenous	25.1 mg/kg

Depression, defecation, emaciation and severe dehydration were the signs of toxicity in the above studies. For reference, the recommended clinical dose of 250 µg with a 2 mg maximum represents at least a thousand-fold margin of safety.

In another study, carboprost was not well tolerated by rats receiving a single dose in excess of 3.2 mg/kg. Rapid weight loss, diarrhea and depression were the signs of intolerance.

Myometrial Irritation Study - Monkey

The uteri of Rhesus monkeys showed focal coagulation necrosis and sero-hemorrhagic endometritis when examined 3 and 7 days following intramyometrial injection of 0.125 mg or 1.25 mg carboprost. Necrosis extending through much of the myometrial wall was found in two of four monkeys injected with 1.25 mg and one of four injected with 0.125 mg. No uterine contractions were noted.

Myometrial Irritation Study - Monkey

Hypertonic saline (20%) and 5 mg PGF_{2α} were injected intramyometrially into various sites of pregnant monkey uterus. Saline caused myometrial necrosis, hemorrhage and thrombosis. There was no histologic change caused by PGF_{2α}, although uterine contractions were achieved. The authors concluded that myometrial necrosis was unlikely to occur after intramyometrial injection of PGF_{2α}.

Irritation Study - Rabbit

Rabbits administered intramuscular injections of 0.014 mg/kg carboprost showed no evidence of local tissue irritation 4, 7 and 14 days following injection.

Three Day Study - Monkey

In a 3 day acute tolerance study, one monkey was given carboprost intramuscularly at dosage levels of 0.5, 1.6 and 3.2 mg/kg on successive days and another monkey received successive daily doses of 0.32, 1.0 and 10 mg/kg. Emesis, diarrhea and weight loss were found in the male monkey receiving the first regimen and the female monkey experienced diarrhea, emesis,

abdominal cramps and depression following daily administration of 1.0 mg/kg. The female monkey showed weight loss at the end of the treatment period.

Long-Term Toxicity

Eight Day Study - Monkey

No evidence of toxicological response was seen in female monkeys receiving intravaginal injections of carboprost at a dosage level of 0.08 mg/kg/day over 8 days.

One Month Study - Monkey

Four groups of monkeys, consisting of 2 male and 2 female animals each, received daily intramuscular injections at dosage levels of 0, 0.008, 0.025 and 0.08 mg/kg/day of carboprost respectively over a one-month time span. No evidence of drug-related toxicity was found.

One Month Study - Rat

Four groups of rats consisting of 5 male and 5 female animals each, received daily subcutaneous injections amounting to 0, 0.5, 1.0 and 2.0 mg/kg/day of carboprost respectively over a one-month period. Evidence of adverse response to drug administration was minimal. Depression was the most consistent clinical response.

Reproduction and Teratology

Segment I Study - Rat

In one study, male rats were injected subcutaneously with 0.25, 0.5, or 1.0 mg/kg for 3 or 6 days before breeding and in a second study, female rats were treated with the same carboprost dosage schedule. In both studies, diarrhea and weight loss were seen but the drug did not interfere with breeding or conception. Dams given 1.0 mg/kg delivered fewer fetuses per litter, but the average fetal body weights were comparable to the control weights.

Segment II Study - Rabbit

Carboprost was given to bred rabbits by subcutaneous injection at doses ranging between 0.0025 and 0.5 mg/kg body weight on 3 consecutive days during the period of active organogenesis. At doses larger than 0.025 mg/kg, carboprost interfered with implantation, was embryolethal or induced abortion, depending on when it was administered. Dams carried fetuses to term only when given the smaller doses of 0.0025 or 0.005 mg/kg. These low doses were not teratogenic and did not interfere with reproduction.

Segment III Study - Rat

Carboprost was given daily by subcutaneous injection to bred rats at doses ranging from 0.001 to 1.0 mg/kg beginning on the 15th day of gestation. Dams given doses larger than 0.025 mg/kg aborted between day 15 to 20 of gestation. Other dams, given doses as small as 0.003 mg/kg, aborted or delivered litters one or two days before full term. Most of their pups died shortly after birth and those that survived for several hours postpartum either died before weaning or weighed less than control pups because lactation was impaired.

Only the 0.001 mg/kg dose of carboprost did not induce labour prematurely. Dams given that dose carried normal litters to term, had normal deliveries and raised their offspring until weaning at 21 days postpartum.

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