

**PRODUCT MONOGRAPH**

**PrCARBOPROST TROMETHAMINE INJECTION, USP**

(carboprost tromethamine)  
250 mcg / mL

For Intramuscular Use

**Prostaglandin**

**Manufactured by:**  
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**Imported and Distributed by:**  
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**Pr Carboprost Tromethamine Injection, USP**

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**PART I: HEALTH PROFESSIONAL INFORMATION****SUMMARY OF PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Nonmedicinal Ingredients</b>
Intramuscular injection	250 mcg / mL	Benzyl alcohol, sodium chloride, Sodium hydroxide and/or hydrochloric acid, tromethamine and water for injection.

**INDICATIONS AND CLINICAL USE**

Carboprost Tromethamine Injection, USP 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 carboprost tromethamine has resulted in satisfactory control of hemorrhage, although it is unclear whether or not ongoing or delayed effects of previously administered ecbolic agents have contributed to the outcome. In a high proportion of cases, carboprost tromethamine 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 AND PRECAUTIONS****General**

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.

Carboprost Tromethamine Injection, USP should not be used for induction of labour.

Carboprost Tromethamine Injection, USP must not be given intravenously.

Carboprost Tromethamine Injection, USP should not be used during pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Carboprost Tromethamine Injection, USP is not indicated in pediatric patients. This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

### **Cardiovascular**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of hypo- or hypertension, or cardiovascular disease.

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

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 carboprost tromethamine 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.

### **Endocrine and Metabolism**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of diabetes.

### **Hematologic**

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

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of anemia.

### **Hepatic/Biliary/Pancreatic**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of hepatic disease or jaundice.

### **Immune**

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 carboprost tromethamine. This complication during labour may have an inhibitory effect on the uterine response to carboprost tromethamine similar to what has been reported for other oxytocic agents.

### **Musculoskeletal**

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<sub>1</sub> during prolonged treatment. There is no evidence that short term administration of carboprost tromethamine can cause similar bone effects.

### **Neurologic**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of epilepsy.

### **Ophthalmologic**

Carboprost Tromethamine Injection, USP should be used with caution in patients with a history of glaucoma or raised intra-ocular pressure.

### **Renal**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of renal disease.

### **Respiratory**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with a history of asthma.

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

### **Sensitivity/Resistance**

Cases of hypersensitivity reactions including anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and angioedema have been reported in patients treated with carboprost tromethamine in the post-marketing experience (see ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

### **Sexual Function/Reproduction**

Carboprost Tromethamine Injection, USP should be used cautiously in patients with previously compromised (scarred) uteri.

### **Other**

Use of carboprost tromethamine 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.

## **Special Populations**

**Pregnant Women:** Animal studies have shown reproductive toxicity and any dose of carboprost that produces increased uterine tone could put the embryo or fetus at risk. Carboprost Tromethamine Injection, USP is indicated in the postpartum period. It is not indicated for use during pregnancy.

Carboprost Tromethamine Injection, USP contains benzyl alcohol which can cross the placenta.

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

**Pediatrics:** The safety and efficacy of carboprost tromethamine in the pediatric population have not been established. Carboprost Tromethamine Injection, USP is not indicated in pediatric patients.

Carboprost Tromethamine Injection, USP contains benzyl alcohol. Benzyl alcohol has been associated with serious adverse events, including fatal “gaspings syndrome” in pediatric patients. Manifestations of the disease included: metabolic acidosis, respiratory distress, gasping respirations, central-nervous system dysfunction, convulsions, intracranial hemorrhages, hypotonia, cardiovascular collapse and death.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The adverse effects of Carboprost Tromethamine Injection, USP (carboprost tromethamine) are generally transient and reversible when therapy ends. The most frequent adverse reactions are related to its contractile effect on smooth muscle.

In patients studied, approximately two-thirds (66%) experienced vomiting and diarrhoea, approximately one third (33%) had nausea, one eighth (12%) had a temperature increase greater than 1.1°C, and one-fourteenth (7%) experienced flushing.

Prior treatment with, or concomitant administration of anti-emetics and antidiarrhoeal drugs significantly reduces the very high incidence of the gastrointestinal side effects common to all prostaglandins. Their use should be considered an integral part of the management of patients.

### **Clinical Trial Adverse Drug Reactions**

The table below lists the adverse effects identified through clinical trials by System Organ Class (SOC) and frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

<b>System Organ Class</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt; 1/10)</b>	<b>Uncommon (≥ 1/1000 to &lt; 1/100)</b>	<b>Not known</b>
<b>Cardiac disorders</b>			Tachycardia	
<b>Ear and labyrinth disorders</b>			Tinnitus Vertigo	
<b>Eye disorders</b>			Eye pain Vision Blurred	
<b>Gastrointestinal disorders</b>	Diarrhoea <sup>†</sup> Vomiting <sup>†</sup> Nausea <sup>†</sup>		Haematemesis Epigastric pain Dry mouth	Gastralgia
<b>General disorders and administration site conditions</b>	Retrosternal discomfort	Chills, Shivering	Tightness in chest Injection site pain	
<b>Infections and Infestations</b>		Endometritis <sup>†</sup>	Septic shock Urinary tract infection	
<b>Investigations</b>	Body temperature increased			
<b>Musculoskeletal and connective tissue disorders</b>			Back pain Myalgia Torticollis	
<b>Nervous system disorders</b>		Headache <sup>†</sup>	Syncope vasovagal Pre-syncope Lethargy Dystonia Paraesthesia Dysgeusia Dizziness <sup>†</sup> Somnolence	
<b>Psychiatric disorders</b>			Sleep disorder	
<b>Reproductive system and breast disorders</b>		Retained placenta or membranes Uterine haemorrhage	Uterine rupture Perforation of uterus Pelvic pain <sup>†</sup> Breast tenderness	
<b>Respiratory, thoracic and mediastinal disorders</b>		Cough	Respiratory distress Hyperventilation <sup>†</sup> Dyspnoea Asthma Wheezing Hiccups	
<b>Skin and subcutaneous tissue disorders</b>			Diaphoresis Perspiration	
<b>Vascular disorders</b>		Flushing	Hypertension	

		Hot flush		
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† Events reported for both intramuscular and intra-amniotic routes of administration. All other events were reported only for the intramuscular route. The safety of the IMM and IV routes has not been fully established at this time.

### **Post-Market Adverse Drug Reactions**

The following adverse reactions have been identified during post-approval use of carboprost tromethamine:

**Infections and Infestations:** Upper respiratory tract infection.

**Immune System Disorders:** Hypersensitivity reactions (e.g., anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, angioedema) (see WARNINGS AND PRECAUTIONS).

**Endocrine disorders:** Thyrotoxic crisis.

**Psychiatric disorders:** Anxiety, nervousness.

**Nervous system disorders:** Syncope.

**Cardiac disorders:** Palpitations.

**Respiratory, thoracic and mediastinal disorders:** Throat tightness, choking sensation, epistaxis, dry throat, bronchospasm, pharyngeal oedema, pulmonary oedema.

**Gastrointestinal disorders:** Retching.

**Skin and subcutaneous tissue disorders:** Rash.

**Musculoskeletal and connective tissue disorders:** Leg cramps, blepharospasm.

**Reproductive system and breast disorders:** Uterine sacculation.

**General disorders and administration site conditions:** Chest pain, excessive thirst, asthenia.

### **DRUG INTERACTIONS**

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

### **Drug-Lifestyle Interactions**

No studies on the effects of carboprost tromethamine on the ability to drive and use machines have been performed.



## DOSAGE AND ADMINISTRATION

### **Dosing Considerations**

Carboprost Tromethamine Injection, USP must not be given intravenously.

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

### **Recommended Dose and Dosage Adjustment**

Carboprost Tromethamine Injection, USP (carboprost tromethamine) is administered by deep intramuscular injection. Initially a 250 mcg (1 mL, the entire contents of the vial or pre-filled syringe) dose of Carboprost Tromethamine Injection, USP is given.

In clinical trials, 80% of successful cases responded to  $\leq 250$  mcg and 95% of successful cases responded to  $\leq 500$  mcg. In some cases, multiple dosing of 250 mcg 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 Carboprost Tromethamine Injection, USP should not exceed 2 mg (8 doses).

## OVERDOSAGE

Overdosage with Carboprost Tromethamine Injection, USP (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.

For management of a suspected drug overdose, contact your regional poison control centre.
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## ACTION AND CLINICAL PHARMACOLOGY

### **Mechanism of Action**

Carboprost Tromethamine Injection, USP (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.

### **Pharmacodynamics**

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  $\text{PGF}_{2\alpha}$ , 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.

### **Pharmacokinetics**

Five women who had spontaneous vaginal deliveries (at term) were treated immediately postpartum with a single intramuscular injection of 250 mcg 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).

### **STORAGE AND STABILITY**

Carboprost Tromethamine Injection, USP (carboprost tromethamine) must be refrigerated at 2° to 8°C.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

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

Carboprost Tromethamine Injection, USP, 250 mcg/mL is available as 1 mL (nominal volume) in 2 mL clear glass vial with 13 mm Neck (type I Tubular), closed with a 13 mm grey Teflon coated chlorobutyl (4432/50) and sealed 13 mm Aluminum cap with a blue plastic flip-off cap in cartons of 10. The vial stopper is not made with natural rubber latex

Carboprost Tromethamine Injection, USP, 250 mcg/mL is also available as 1 mL Pre-filled Single-dose Syringes with luer lock.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: carboprost tromethamine injection USP

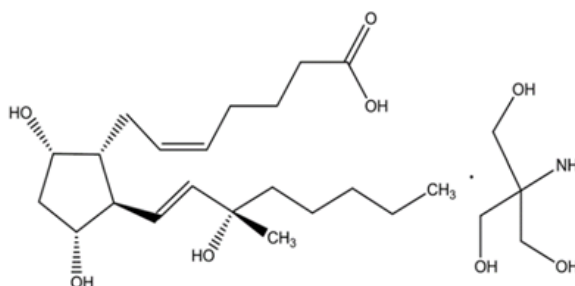
Chemical name:

- Prosta-5,13-dien-1-oic acid,9,11,15-trihydroxy-15-methyl-,(5Z,9 $\alpha$ ,11 $\alpha$ ,13E,15S)-,compound with 2-amino-2-(hydroxy- methyl)-1,3-propanediol(1:1)
- (Z)-7-[(1R, 2R,3R,5S)-3,5-Dihydroxy-2-[(E)-(3S)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl]-5-heptenoic acid compound with 2-amino-2 (hydroxymethyl)-1,3- propanediol (1:1).
- (15S)-15-methyl prostaglandin F<sub>2 $\alpha$</sub>  tromethamine

Molecular formula: C<sub>21</sub>H<sub>36</sub>O<sub>5</sub>.C<sub>4</sub>H<sub>11</sub>NO<sub>3</sub>

Molecular mass: 489.65 g / mol

Structural Formula:



Physicochemical properties: Carboprost tromethamine is a white to 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.

#### DETAILED 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<sub>2 $\alpha$</sub>  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<sub>2 $\alpha$</sub> . The binding affinity of carboprost to a human myometrial *in vitro* preparation or to a bovine luteal particulate fraction was lower than prostaglandin F<sub>2 $\alpha$</sub> .

In the anaesthetized dog, intramuscular or intravenous carboprost produced a greater and more sustained rise in pulmonary artery pressure than prostaglandin  $F_{2\alpha}$  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  $F_{2\alpha}$  in altering the relative blood pressure of the anaesthetized, pentolinium treated rat.

Carboprost, in doses of 30 or 60 mcg, 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 mcg 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  $F_{2\alpha}$ . 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  $F_{2\alpha}$  plasma levels return to baseline values five minutes after dosing. Intravenous infusion of carboprost at the rate of 1 mcg 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  $F_{2\alpha}$  concentrations returned to baseline levels within five minutes after discontinuation. In the Rhesus monkey, a single intramuscular injection of 20 to 130 mcg 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 mcg 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  $F_{2\alpha}$ . 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  $^3\text{H}$ -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  $F_{2\alpha}$ .

When pregnant women (second trimester) were administered carboprost by continuous intravenous infusion for six hours at the rate of 2.5 mcg/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 mcg/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 mcg of carboprost to pregnant women. Levels gradually declined to 0.2 to 0.4 ng/mL three hours after drug administration. When carboprost (250 mcg) 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 mcg/minute (300 mcg 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 mcg/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 <sub>50</sub>
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 mcg 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<sub>2α</sub> 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<sub>2α</sub> although uterine contractions were achieved. The authors concluded that myometrial necrosis was unlikely to occur after intramyometrial injection of PGF<sub>2α</sub>.

#### 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 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 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 and 2 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 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 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 embryo-lethal 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 mg/kg beginning on the 15<sup>th</sup> 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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## PART III: CONSUMER INFORMATION

### PrCARBOPROST TROMETHAMINE INJECTION, USP For Intramuscular Use

This leaflet is part III of a three-part "Product Monograph" published when Carboprost Tromethamine Injection, USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Carboprost Tromethamine Injection, USP. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

Carboprost Tromethamine Injection, USP is used to stop excessive bleeding in women who have just given birth, when bleeding is due to the uterus (womb) failing to return to its normal size, and who have not responded to conventional treatments.

##### What it does:

Carboprost Tromethamine Injection, USP belongs to a group of medicines called prostaglandins that acts to increase the contractions of the uterus (womb). This helps to control bleeding after delivery.

##### When it should not be used:

You should not be given Carboprost Tromethamine Injection, USP if you:

- are allergic to carboprost tromethamine or any of the other ingredients of Carboprost Tromethamine Injection, USP, in particular benzyl alcohol.
- have a heart, lung, kidney or liver disease.
- have an infection of your uterus, ovaries or fallopian tubes.

##### What the medicinal ingredient is:

Carboprost

##### What the nonmedicinal ingredients are:

Benzyl alcohol, sodium chloride, tromethamine, and water for injections. Small amounts of hydrochloric acid and sodium hydroxide (used to regulate the acidity or alkalinity of the solution) may also be present.

##### What dosage forms it comes in:

Carboprost Tromethamine Injection, USP is available as a sterile solution contained in a vial or pre-filled syringe. Each ml contains 250 micrograms of carboprost.

#### WARNINGS AND PRECAUTIONS

**Carboprost Tromethamine Injection, USP must be given only by a health care professional experienced in the use of the drug in hospitals or clinics with specialized units for pregnancy and childbirth.**

Carboprost Tromethamine Injection, USP may cause temporary high fever, and rarely, heart and blood circulation failure or airway constriction.

**BEFORE you are given Carboprost Tromethamine Injection, USP, talk to your doctor or pharmacist if you currently have, or have had in the past any of the following conditions:**

- lung disease, including asthma
- high or low blood pressure (including high blood pressure in pregnancy)
- heart disease or anaemia (low blood count)
- kidney or liver disease (including jaundice)
- glaucoma (raised pressure in your eyes)
- diabetes or epilepsy
- a caesarean section or any other operation on your womb

Carboprost Tromethamine Injection, USP is not indicated for use in children. Carboprost Tromethamine Injection, USP contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

##### Pregnancy

Carboprost Tromethamine Injection, USP will only be given shortly after you have delivered your baby and not while you are still pregnant as it could put the embryo or foetus at risk.

##### Breast-feeding

It is not known if carboprost tromethamine is excreted in human breast milk. However, breast-feeding is not recommended at least 6 hours after receiving the last dose of Carboprost Tromethamine Injection, USP.

##### Driving and using machines:

Do not drive, use any tools or operate machinery soon after receiving Carboprost Tromethamine Injection, USP as it may affect your ability to do so safely.

#### INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking, have recently taken or might take any other medicines, including any that you have bought without a prescription.

Tell your doctor if you are taking or have received oxytocin or ergometrine (ergonovine).

#### PROPER USE OF THIS MEDICATION

##### Usual dose:

Carboprost Tromethamine Injection, USP must be given to you as an injection deep into a muscle (intra-muscular). It must never be given by injection into a vein.

The first dose is usually 1 ml of solution (250 micrograms of carboprost). If needed the dose of 1 ml may be repeated between 15 to 90 minutes.

You should not be given more than 8 doses (8 x 250 micrograms of carboprost) altogether.

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<b>SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM</b>				
<b>Symptom / effect</b>		<b>Talk to your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
		<b>Only if severe</b>	<b>In all cases</b>	
Uncommon	Breathing difficulties, asthma, wheezing, hyperventilation		√	
	Septic shock		√	
	Uterine rupture, perforation of uterus		√	
	Vomiting of blood		√	
Unknown	Anaphylactic shock/reactions: swelling of the neck area, throat tightness, choking sensation or any difficulty with breathing, not present before using this medicine.		√	

*This is not a complete list of side effects. For any unexpected effects while taking Carboprost Tromethamine Injection, USP, contact your doctor or pharmacist.*

#### **HOW TO STORE IT**

Vials or pre-filled syringes must be stored in a refrigerator between 2 – 8°C. Your pharmacist will check the vials or pre-filled syringes are still clear and colourless before use.

**Keep out of reach and sight of children.**

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION****If you want more information about Carboprost Tromethamine Injection, USP:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); or by contacting the manufacturer Dr. Reddy's Laboratories Ltd., at 1-855-845-1739.

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