Carbetocin

Duratocin® 100 mcg/mL

Solution for I.V. Injection

Oxytocic

FORMULATION:

Each ampoule contains: Carbetocin ……100 mcg
Sodium chloride …….. 9 mg
Glacial acetic acid …….. q.s.
Water for injection to …….. 1 mL

ACTION AND CLINICAL PHARMACOLOGY

Carbetocin (Duratocin®) is a long-acting synthetic nonapeptide analogue of oxytocin with agonist properties. It can be administered intravenously as a single dose immediately following delivery by cesarean section under epidural or spinal anesthesia, to prevent uterine atony and postpartum hemorrhage.

The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin, another posterior pituitary hormone. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions, and increased uterine tone. The oxytocin receptor content of the uterus is very low in the non-pregnant state, and increases during pregnancy, reaching a peak at the time of delivery. Therefore carbetocin has no effect on the non-pregnant uterus, and has a potent uterotonic effect on the pregnant and immediate postpartum uterus.

The onset of uterine contraction following carbetocin administration by either the intravenous or intramuscular route is rapid, with a firm contraction being obtained within 2 minutes. The total duration of action of a single intravenous injection of carbetocin on uterine activity is about one hour suggesting that carbetocin may act long enough to prevent postpartum hemorrhage in the immediate postpartum period. In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions.

Carbetocin, when administered immediately postpartum as a single intravenous bolus injection of 100 µg to women delivered by cesarean section under epidural or spinal anesthesia, was found to be significantly more effective than placebo in preventing uterine atony and minimizing uterine bleeding.

Carbetocin administration also appears to enhance uterine involution in the early postpartum period.

PHARMACOKINETICS

Carbetocin shows a biphasic elimination after intravenous administration with linear pharmacokinetics in the dose range of 400 to 800 micrograms. The terminal elimination half-life is approximately 40 minutes. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney.

In 5 healthy nursing mothers, plasma carbetocin concentrations were detectable by 15 min and peaked at a maximum of 1035 ± 218 pg/mL within 60 min. Peak concentrations in milk were approximately 56 times lower than in plasma at 120 min.

INDICATION

Carbetocin (Duratocin®) is indicated for the prevention of uterine atony and postpartum hemorrhage following elective cesarean section under epidural or spinal anesthesia.

Carbetocin (Duratocin®) has not been studied in cases involving emergency cesarean section, classical cesarean section, anesthesia other than epidural or spinal, or in patients presenting significant heart disease, history of hypertension, known coagulopathy or evidence of liver, renal or endocrine disease (excluding gestational diabetes). Appropriate studies have not been undertaken and doses have not been established in women following labour or vaginal delivery.

CONTRAINDICATIONS

Because of its long duration of action relative to oxytocin, uterine contractions produced by carbetocin cannot be stopped by simply discontinuing the medication. Therefore carbetocin should not be administered prior to delivery of the infant for any reason, including elective or medical induction of labour. Inappropriate use of carbetocin during pregnancy could theoretically mimic the symptoms of oxytocin overdosage, including hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions, tumultuous labour, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, utero-placental hypoperfusion and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, or death.

Carbetocin should not be used in patients with a history of hypersensitivity to oxytocin or carbetocin. Carbetocin should not be used in patients with vascular disease, especially coronary artery disease, except with extreme caution.

Carbetocin should not be used in patients with hepatic or renal disease.

Carbetocin is not intended for use in children.

WARNINGS

Some patients may not have an adequate uterine contraction after a single injection of Carbetocin (Duratocin®). In these patients, administration of Carbetocin (Duratocin®) should not be repeated and more aggressive treatment with additional doses of other available uterotonic drugs like oxytocin or ergometrine is warranted. In cases of persistent uterine bleeding, the presence of retained placental fragments, inadequate emptying or repair of the uterus, coagulopathy, or trauma to the genital tract should be considered.

Although no cases of partial retention or trapping of the placenta have been reported, this remains a theoretical possibility if the drug is administered before delivery of the placenta.

PRECAUTIONS

In general, Carbetocin (Duratocin®) should be used cautiously in the presence of epilepsy, migraine, asthma or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. The decision of administering Carbetocin (Duratocin®) can be made by the physician after carefully weighing the potential benefit Carbetocin (Duratocin®) may provide in these particular cases.

Patients with eclampsia and pre-eclampsia should be monitored for changes in blood pressure for up to 8 hours.

Carbetocin (Duratocin®) use during pregnancy, prior to the delivery of the infant, is contraindicated (see CONTRAINDICATIONS).

See WARNINGS section regarding potential requirement for further oxytocin therapy.

Carbetocin (Duratocin®) is not recommended for use in elderly patients.

Nursing Mothers

Small amounts of carbetocin have been shown to cross over from plasma in to the breast milk of nursing women who were given a 70 µg dose intramuscularly, between 7 and 14 weeks postpartum. The mean peak concentration in breast milk was approximately 50 times lower than in plasma, and the ratio of the milk to plasma area under the concentration versus time curves (M/P AUC) was only 2-3%. The small amount of carbetocin transferred into breast milk or colostrum after a single injection, and subsequently ingested by a breast feeding infant, would not be expected to present a significant safety concern. This is due to the fact that carbetocin would be rapidly degraded by peptidases in the infant gastrointestinal tract.

Oxytocin is known to cause contraction of the myoepithelial cells surrounding the mammary alveoli, thereby stimulating milk let-down. There is no sufficient evidence to determine whether carbetocin can also stimulate milk let-down. However, milk let-down was found to occur normally in 5 nursing women after receiving a 70 µg carbetocin dose by the intramuscular route.

DRUG INTERACTIONS

No specific drug interactions have been reported with carbetocin. However, since carbetocin is closely related in structure to oxytocin, it is possible that some of the same drug interactions could occur.

Severe hypertension has been reported when oxytocin was given 3-4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

ADVERSE EFFECTS

The adverse events observed with carbetocin during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin when administered after cesarean section under epidural or spinal anesthesia.

Intravenous carbetocin was frequently (10-40% of patients) associated with nausea, abdominal pain, pruritis, flushing, vomiting, feeling of warmth, hypotension, headache and tremor.

Infrequent adverse events (1-5% of patients) included back pain, dizziness, metallic taste, anaemia, sweating, chest pain, dyspnea, chills, tachycardia and anxiety.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of carbetocin can be expected to produce enhanced pharmacological effects.

Therefore, when carbetocin is administered postpartum, overdosage may be associated with uterine hyperactivity and pain. Treatment consists of symptomatic and supportive management. When signs or symptoms of overdosage occur oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur.

DOSAGE AND ADMINISTRATION

A single intravenous dose of 100 µg (1 mL) of Carbetocin (Duratocin®) is administered by bolus injection, slowly over 1 minute, only when

delivery of the infant has been completed by cesarean section under epidural or spinal anesthesia. Carbetocin (Duratocin®) can be administered either before or after delivery of the placenta.

STORAGE CONDITIONS
Carbetocin (Duratocin®) must be stored between 2°C - 8°C (under refrigeration). Carbetocin (Duratocin®) should not be frozen. Once the ampoule has been opened, the product should be used immediately.

AVAILABILITY
USP Type I clear glass ampoule in 1 mL, box of 5 ampoules.

INSTRUCTIONS FOR OPENING AMPOULES
1. Hold ampoule with blue dot pointing upwards. Shake or tap ampoule to empty the tip.
2. With blue dot pointing upwards, snap off the tip by forcing it downwards.

Manufactured by:
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Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.