

PRODUCT INFORMATION

disease (excluding gestational diabetes). Appropriate studies have not been undertaken and doses established in women following labour or vaginal delivery.

INDICATIONS

DURATOCIN is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by elective caesarean section under epidural or spinal anaesthesia. DURATOCIN is an oxytocic that reduces the need for additional oxytocics.

Duratocin has not been studied in women at high risk of postpartum haemorrhage, for example with parity greater than 4, with hypertension, following labour especially prolonged labour, or with general anaesthesia.

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 overdose, including hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions, tumultuous labour, uterine rupture, cervical and vaginal lacerations, postpartum haemorrhage, utero-placental hypoperfusion and variable deceleration of foetal heart, foetal 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 is not intended for use in children.

PRECAUTIONS

Some patients may not have an adequate uterine contraction after a single injection of DURATOCIN (carbetocin injection). In these patients, administration of 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 bleeding, the presence of retained placental fragments, coagulopathy, or trauma to the genital tract should be ruled out.

DURATOCIN is currently not indicated in emergency caesarean section or after vaginal delivery.

DURATOCIN is not recommended for use in elderly patients.

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.

Significant antidiuretic effect is not anticipated and has not been demonstrated at the recommended dose but, as carbetocin is closely related in structure to oxytocin, hyponatraemia and water intoxication should be considered in relevant clinical situations.

Carbetocin 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.

Patients with eclampsia and pre-eclampsia should be monitored for changes in blood pressure.

Carcinogenicity/Mutagenicity:

No long term studies in animals have been performed to evaluate the carcinogenic potential of carbetocin.

Carbetocin was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo)

Use in Pregnancy:

Category C. Carbetocin induces uterine contraction and may cause premature or hypertonic labour. Therefore, DURATOCIN (carbetocin injection) use during pregnancy is contraindicated (see CONTRAINDICATIONS).

Use in Lactation:

Small amounts of carbetocin have been shown to cross over from plasma into the breast milk of nursing women who were given a 70µg 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 70µg carbetocin dose by the intramuscular route.

In a pilot postnatal development study, administration of IV doses \geq 0.01 mg/kg/day (similar to the clinical dose based on body surface area) to lactating rats was associated with impaired pup growth. A no-effect-dose was not determined.

Interactions with other drugs:

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 anaesthesia.

Effects on Ability to Drive and Use Machines: Not applicable.

ADVERSE REACTIONS

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 caesarean section under epidural or spinal anaesthesia.

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

As most of these reactions also occurred in patients treated with placebo, it is likely that many were associated with caesarean section, spinal or epidural anaesthesia or drugs used during the procedure.

In a 122 patient placebo controlled study, the adverse events occurring in >5% of women are presented in Table 1, below.

Table 1

Adverse Event	Carbetocin (n=64)	Placebo (n=58)	Statistical Significance
	%	%	
Nausea	61	57	NS
Pruritus	48	31	*
Hypotension	45	38	NS
Vomiting	41	36	NS
Flushing	34	10	*
Abdominal pain	27	10	*
Feeling of warmth	19	10	NS
Anaemia	17	21	NS
Tremors	16	17	NS
Back Pain	13	7	NS
Dizziness	13	7	NS
Incisional abnormality	11	12	NS
Headache	9	16	NS
Sweating	8	0	NS
Fever	6	5	NS
Tachycardia	5	5	NS
Insomnia	3	7	NS
Chills	3	5	NS
Metallic Taste	2	5	NS
Paraesthesia	0	5	NS

NS = Not Significant, * p \leq 0.05

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

DOSAGE AND ADMINISTRATION

A single intravenous dose of 100µg (1 mL) of DURATOCIN (carbetocin injection) is administered by bolus injection, slowly over 1 minute, only when delivery of the infant has been completed by caesarean section under epidural or spinal anaesthesia. DURATOCIN can be administered either before or after delivery of the placenta. DURATOCIN is to be used as a single dose only.

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.

PRESENTATION

DURATOCIN is a ready - for - use solution containing 100µg carbetocin in a 1 mL clear glass ampoule with a white identification ring and a blue dot indicating the cut area. Each pack contains 5 ampoules.

Storage: DURATOCIN is stable for 2 years from date of manufacture when stored at 2-8°C (Refrigerate. Do not freeze) and protected from light. Once the ampoule has been opened, the product should be used immediately.

NAME AND ADDRESS OF THE SPONSOR

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