

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrCARBETOCIN INJECTION

1 mL solution in pre-filled syringes – 100 mcg / mL

For Intravenous (IV) Use Only

Uterotonic Agent

Juno Pharmaceuticals Corp.
402-2233 Argentia Road
Mississauga, ON
L5N 2X7

Date of Initial Authorization:
June 7, 2019

Date of Revision:
September 18, 2023

Submission Control No: 274705

RECENT MAJOR LABEL CHANGES

4	DOSAGE AND ADMINISTRATION	SEPT 2023
1	INDICATIONS	NOV 2022
2	CONTRAINDICATIONS	NOV 2022
4	DOSAGE AND ADMINISTRATION	NOV 2022
7	WARNINGS AND PRECAUTIONS	NOV 2022

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION	4
1. INDICATIONS	4
1.1 PEDIATRICS	4
1.2 GERIATRICS	4
2. CONTRAINDICATIONS	4
4. DOSAGE AND ADMINISTRATION	4
4.4 ADMINISTRATION	5
5. OVERDOSAGE	5
6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	5
7. WARNINGS AND PRECAUTIONS	6
7.1 SPECIAL POPULATIONS	7
7.1.1 PREGNANT WOMEN:	7
7.1.2 BREAST-FEEDING	7
7.1.3 PEDIATRICS	7
7.1.4 GERIATRICS	7
8 ADVERSE REACTIONS	7
8.2 CLINICAL TRIAL ADVERSE REACTIONS	7
8.5 POST-MARKET ADVERSE REACTIONS	10
9. DRUG INTERACTIONS	10
9.2 DRUG INTERACTIONS OVERVIEW	10
9.3 DRUG-BEHAVIOURAL INTERACTIONS	11
9.4 DRUG-DRUG INTERACTIONS	11
9.5 DRUG-FOOD INTERACTIONS	11
9.6 DRUG-HERB INTERACTIONS	11
9.7 DRUG-LABORATORY TEST INTERACTIONS	11

10.	CLINICAL PHARMACOLOGY	11
10.1	MECHANISM OF ACTION	11
10.2	PHARMACODYNAMICS	12
10.3	PHARMACOKINETICS	13
11	STORAGE, STABILITY AND DISPOSAL	14
12	SPECIAL HANDLING INSTRUCTIONS	14
PART II: SCIENTIFIC INFORMATION		15
13	PHARMACEUTICAL INFORMATION	15
14	CLINICAL TRIALS	16
14.1	TRIAL DESIGN AND STUDY DEMOGRAPHICS	16
14.2	STUDY RESULTS.....	17
15	MICROBIOLOGY	19
16	NON-CLINICAL TOXICOLOGY	19
17	SUPPORTING PRODUCT MONOGRAPHS	20
PATIENT MEDICATION INFORMATION		21

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

Carbetocin Injection is indicated for:

- the prevention of uterine atony and postpartum hemorrhage following cesarean section under epidural or spinal anaesthesia.

Carbetocin Injection is not authorized for use in women following labour or vaginal delivery.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of carbetocin have not been established in the pediatric population. Accordingly, Carbetocin Injection is not recommended for use in this patient group.

1.2 Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2. CONTRAINDICATIONS

Because of its long duration of action relative to oxytocin, uterine contractions produced by Carbetocin Injection cannot be stopped by simply discontinuing the medication. Therefore, Carbetocin Injection should **not** be administered:

- Prior to delivery of the infant for any reason, including elective or medical induction of labour. Inappropriate use of Carbetocin Injection 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.
- In patients with a history of hypersensitivity to oxytocin or Carbetocin Injection.
- In patients with serious cardiovascular disorders.
- Carbetocin Injection is not recommended for use in children.

4. DOSAGE AND ADMINISTRATION

4.4 Administration

Caesarean section – Intravenous injection

A single intravenous dose of 100 mcg (1 mL) of Carbetocin Injection 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 Injection can be administered either before or after delivery of the placenta.

Administer carbetocin directly into a peripheral vein using a needle or pin-less IV tubing. A needle is not provided with the Carbetocin injection prefilled syringe. Should you require the use of a needle to inject Carbetocin Injection directly into a vein, the adaptable luer lock tip can accommodate a 20 - 25 gauge needle.

No further doses of Carbetocin Injection should be administered.

5. OVERDOSAGE

Overdosage of Carbetocin Injection can be expected to produce enhanced pharmacological effects. Therefore, when Carbetocin Injection is administered postpartum, overdosage may be associated with uterine hyperactivity and pain. Symptoms of uterine hyperactivity include: uterine hypertonus, abdominal pain, discomfort associated with too frequent or too strong uterine contractions. At single doses up to 800 mcg, tachycardia was observed.

Overdosage of oxytocin may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake. Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain
2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures

As carbetocin is an analogue of oxytocin, the possibility of a similar event cannot be excluded.

Treatment consists of symptomatic and supportive management.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution / 100 mcg / mL	Glacial acetic acid, sodium chloride, water for injection.

Carbetocin Injection is available in 1 mL pre-filled syringe. Each pre-filled syringe contains 100 mcg carbetocin. Boxes contain 5 pre-filled syringes each. The pre-filled syringes are clear and colourless glass.

The tip cap and stopper are not made with natural rubber latex.

7. WARNINGS AND PRECAUTIONS

General

Carbetocin Injection should only be used at well-equipped specialist obstetrics units.

Some patients may not have an adequate uterine contraction after a single injection of Carbetocin Injection. In these patients, administration of Carbetocin Injection should not be repeated and more aggressive treatment with additional doses of other available uterotonic drugs is warranted.

In cases of persistent uterine bleeding after administration of Carbetocin Injection, the presence of retained placental fragments, coagulopathy, or trauma to the genital tract should be ruled out.

Carbetocin Injection is intended for single administration intravenous (IV) Only.

Significant antidiuretic effect is not anticipated and has not been demonstrated at the recommended dose. However, since carbetocin is related in structure to oxytocin, which has been shown to have an intrinsic antidiuretic effect, the risk of water intoxication cannot be excluded.

Patients with eclampsia and pre-eclampsia should be carefully monitored for all signs and symptoms.

The safety of carbetocin in these patients has not been evaluated in formal clinical trials.

Carbetocin has not been studied in cases involving patients with known coagulopathy or evidence of liver, renal or endocrine disease.

Cardiovascular

Should be used with extreme caution in patients with cardiovascular disease, especially coronary artery disease.

Endocrine and Metabolism

Specific studies have not been undertaken in gestational diabetes mellitus.

Neurologic

Should be used cautiously in the presence of migraine and epilepsy.

Respiratory

Should be used cautiously in the presence of asthma.

7.1 Special Populations

7.1.1 Pregnant Women:

Carbetocin Injection use during pregnancy, prior to the delivery of the infant, is contraindicated ([see CONTRAINDICATIONS](#)).

7.1.2 Breast-feeding

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

7.1.3 Pediatrics (< 18 years of age):

Not recommended for use.

7.1.4 Geriatrics (> 65 years of age):

Not recommended for use.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Caesarean Section The more commonly observed adverse reactions in the clinical trials of patients undergoing elective cesarean section are summarized by frequency in Table 2 (Boucher 1998¹, Dansereau 1999², Barton 1993³)

Table 2: Very Common (≥10%) and Common (≥1% and <10%) Adverse Drug Reactions for Carbetocin in Clinical Trials of Elective Caesarean Section

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10
Blood and lymphatic system disorders		Anaemia
Nervous system disorders	Headache, tremor	Dizziness, anxiety
Vascular disorders	Hypotension, flushing	Tachycardia
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea
Gastrointestinal disorders	Nausea, abdominal pain, vomiting	Metallic taste
Skin and subcutaneous tissue disorders	Pruritus	
Musculoskeletal and connective tissue		Back pain
General disorders and administration site conditions	Feeling of warmth	Chills, pain, sweating

The adverse drug reactions observed with carbetocin during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin and placebo when administered after cesarean section under epidural or spinal anesthesia. The more commonly observed adverse reactions in the clinical trials of patients undergoing cesarean section are summarized by frequency in Table 3

Table 3: Adverse Drug Reactions for Carbetocin (≥1%) in Clinical Trials of Cesarean Section

System Organ Class (MedDRA)	Attilakos et al, 2010 ^{4*}		Borruto et al, 2009 ^{5**}		El Behery et al, 2015 ^{6***}	
	Carbetocin N=188 (%)	Oxytocin N=189 (%)	Carbetocin N=52 (%)	Oxytocin N=52 (%)	Carbetocin N=90 (%)	Oxytocin N=90 (%)
Blood and lymphatic system disorders						
Anaemia			23	-		
Cardiac disorders						
Tachycardia	1.1	-				

¹ Boucher M. Effectiveness of carbetocin and oxytocin on interoperative blood loss and uterine tone in patients undergoing caesarean section, 1998. CLN 6.3.6.

² Dansereau J, et al. Double-blind comparison of carbetocin vs oxytocin in preventing uterine atony post caesarean section. Int. J. Gyn. Obs. 1999; 46 (suppl.2):77. CLN 6.3.9.

³ Barton SR, et al. A randomized, parallel group, double-blind, placebo-controlled multicenter clinical trial, to evaluate the safety and efficacy of a single dose of carbetocin to control uterine bleeding after elective caesarean section. Study period: Feb 1992 to Jul 1993. CLN 6.3.10.

⁴ Attilakos G, Psaroudakis D, Ash J, et al. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG. 2010; 117:929–936.

⁵ Borruto F, Treisser A, Comparetto C. Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical trial. Arch Gynecol Obstet. 2009; 280:707–712.

⁶ El Behery, M. et al. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency caesarean delivery. J Matern Fetal Neonatal Med. 2016; 29(8):1257-60.

	Attilakos et al, 2010 ^{4*}		Borruto et al, 2009 ^{5**}		El Behery et al, 2015 ^{6***}	
System Organ Class (MedDRA)	Carbetocin N=188 (%)	Oxytocin N=189 (%)	Carbetocin N=52 (%)	Oxytocin N=52 (%)	Carbetocin N=90 (%)	Oxytocin N=90 (%)
Arrhythmia			-	28.8		
Nervous system disorders						
Headache			13.4	28.8	25.6	33.3
Tremor	1.1	2.1	11.5	-		
Dizziness	1.1	1.6	3.8	-		
Vascular disorders						
Hypotension	2.1	1.1	21.1			
Fall in blood pressure (causing dizziness, lightheadedness, feeling faint)				23		
Flushing	2.2	1.6	25	-		
Respiratory, thoracic and mediastinal disorders						
Chest Pain			3.8	-		
Dyspnoea	1.1		9.6			
Shortness of breath Difficulty in breathing		1.6		7.6		
Gastrointestinal disorders						
Nausea	5.3	4.2	26.9	38.4	3.3	25.6
Vomiting	2.7	4.2	7.6	-		
Abdominal Pain			40.3	38.4		
Metallic Taste	1.1	0.5	5.7	-		
Skin and subcutaneous tissue disorders						
Pruritus			9.6			
Skin rashes				19.2		
Musculoskeletal and connective tissue disorders						
Back Pain			3.8	-		
General disorders and administration site conditions						
Heat Sensation			19.2	-		
Chills						
Pain			3.8	-		
Sweating					1.1	30
Fever					8.9	-
Loss of appetite			-	9.6		

* 60% elective and 40% emergency cesarean section patient population

** Mixed planned and emergency cesarean patient population
*** All emergency cesarean sections

The nature and frequency of the adverse drug reactions experienced by study participants receiving intravenous carbetocin were similar for patients undergoing either elective or emergency cesarean sections. Intravenous carbetocin was very commonly associated with anaemia, nausea, abdominal pain, pruritus, flushing, vomiting, feeling of warmth, hypotension, headache and tremor. Commonly associated adverse events included back pain, dizziness, metallic taste, sweating, chest pain, dyspnoea, chills, tachycardia and anxiety.

8.5 Post-Market Adverse Reactions

Cardiac disorders: bradycardia*, myocardial ischemia*, QT prolongation*

*Reported with oxytocin (carbetocin is an analogue of oxytocin)

9. DRUG INTERACTIONS

9.2 Drug Interactions Overview

During clinical trials, carbetocin has been administered in association with a number of analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anaesthesia, and no drug interactions have been identified. However, dedicated interaction studies have not been undertaken.

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 known to be associated with oxytocin cannot be excluded with carbetocin.

- Oxytocin may potentiate the blood pressure enhancing effect of vasoconstriction agents. Severe hypertension has been reported when oxytocin was given 3 to 4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anaesthesia.
- Some inhalation-anaesthetics, such as halothane and cyclopropane, may have a hypotensive effect and weaken the effect of oxytocin on the uterus. Arrhythmias have been reported for oxytocin during concomitant use.
- Prostaglandins have been found to potentiate the effect of oxytocin. Therefore, prostaglandins and oxytocin are not recommended to be used together. If they are concomitantly administered, the patient should be carefully monitored.
- Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for Torsades de Pointes such as drugs which prolong the QT interval or in patients with history of long QT syndrome.

9.3 Drug-Behavioural Interactions

There have been no reports of abuse or dependence with Carbetocin.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Carbetocin Injection 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 selectively 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.

A single 100 mcg dose of carbetocin administered IV immediately after the delivery of the infant is comparable to oxytocin in preventing uterine atony and minimizing uterine bleeding.

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

10.2 Pharmacodynamics

In vivo studies in rats demonstrated that carbetocin has an uterotonic effect comparable to oxytocin. The maximum intensity is lower but the duration is longer.

The dose-response relationship of carbetocin and uterine contraction was evaluated in an open-label clinical trial involving 18 healthy pregnant women undergoing elective cesarean section under epidural anesthesia (Boucher, 1990^{6,7}). Here the intravenous dose of carbetocin required to produce sustained tetanic contraction after cesarean section was determined. "Minimally effectiveness dose" was determined, and was defined as the dose that produces adequate uterine contraction in 100% of patients. A single 100 mcg intravenous injection was capable of maintaining contraction after cesarean section.

An exploratory study in women after normal vaginal delivery was undertaken to determine the intravenous dose of carbetocin required to produce a sustained contraction of the postpartum uterus. Seventeen (17) women received a single intravenous dose of 8-100 mcg carbetocin on day 1 to 2 postpartum. In total, 14 women achieved tetanic uterine contraction while no response was observed in 3 women after 10, 12 and 40 mcg carbetocin, respectively. Dose levels of 50 mcg and 100 mcg carbetocin produced a tetanic uterine contraction. Results of the above trial are seen in the following table.

Table 4: Breakdown of Patients by Number of Doses Required to Produce Tetany

Increment size (mcg)	Case No.	No. of increments administered	Total dose (mcg)	Tetantic dose (mcg)	Efficacy of a single dose
100	5	1	100	100	1/1 (100%)
50	1	1	50	50	1/1 (100%)
10	2	2	20	20	6/10 (60%)
	3	4	40	No tetany ^a	
	4	4	40	30	
	6	2	20	10	
	7	3	30	10	
	8	1	10	No tetany ^b	
	9	1	10	10	
	10	1	10	10	
	14	1	10	10	
	15	1	10	10	

⁷ Boucher M. Dose-ranging study of effectiveness of carbetocin in producing uterine contraction following delivery of the infant at caesarean section. Study period May 1990 to Nov 1990. CLN 6.3.5

Increment size (mcg)	Case No.	No. of increments administered	Total dose (mcg)	Tetanic dose (mcg)	Efficacy of a single dose
2	11	5	10	10	0/5 (0%)
	12	5	10	8	
	13	4	8	8	
	16	6	12	No tetany ^c	
	17	5	10	No tetany ^d	

- a Record not analyzable. Patient reported cramping starting 2 minutes after first injection which continued for about 5 minutes after injection of last dose.
- b Record not analyzable. Patient reported cramping starting 2 minutes after first injection. c Record not analyzable. Patient reported no cramping.
- d Record not analyzable. Patient reported definite contractions starting at 1 min. 40 sec., and lasting for 60 min. after injection.

The onset of uterine activity after intravenous carbetocin is rapid, occurring within 1.2 ± 0.5 minutes. Total duration of a single injection of intravenous carbetocin on uterine activity is about one hour.

10.3 Pharmacokinetics

The clearance of carbetocin from the body (both total and renal), the volume of distribution, and the distribution and elimination half-life do not appear to be dose dependent, whereas C_{max} and AUC_{0-4} show proportional changes with increasing dose.

The pharmacokinetics of carbetocin have been investigated in healthy female subjects. Carbetocin shows a biphasic elimination after intravenous administration with linear pharmacokinetics in the dose range of 400 to 800 micrograms. The geometric mean terminal half-life is 33 minutes after intravenous administration. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney, indicating that carbetocin, like oxytocin, is eliminated mainly by non-renal routes.

The pharmacokinetic parameters of intravenous carbetocin are seen in the following Table 5.

Table 5 Summary Statistics of Key Carbetocin Pharmacokinetic Parameters following Intravenous (IV) Administration

Parameter	Geometric Mean (Geometric %CV)
	Carbetocin 100 mcg IV (N = 19)
$AUC_{0-\infty}$ (ng*h/mL)	2.762 (21.6%)
AUC_t (ng*h/mL)	2.697 (21.8%)
C_{max} (ng/mL)	7.232 (17.4%) ^a
t_{max} (h) ^b	NA
$t_{1/2}$ (h)	0.5480 (25.8%)

$AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_t = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = observed maximum concentration; %CV = coefficient of variation (percent);

IV = intravenous; NA = not applicable; t_{max} = time of observed maximum concentration, $t_{1/2}$ = terminal half-life.

^a Measured concentration at 5 minutes postdose

After IV administration, less than 1% of the carbetocin dose is excreted unchanged in urine.

Small amounts of carbetocin are transferred into human breast milk. In 5 healthy nursing mothers, plasma carbetocin concentrations peaked at 1035 ± 218 pg/ml between 15 and 30 min of administering the drug. Peak concentrations in milk at 120 min were approximately 56 times lower than peak concentrations in plasma.

11 STORAGE, STABILITY AND DISPOSAL

Carbetocin Injection must be stored at refrigerator temperature (2°C - 8°C). Protect from light. Single dose pre-filled syringe. Use only if the syringe contents are clear and colourless. Once the pre-filled syringe has been opened, the product should be used immediately. Discard the unused portion.

12 SPECIAL HANDLING INSTRUCTIONS

None. Carbetocin Injection does not require special handling.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

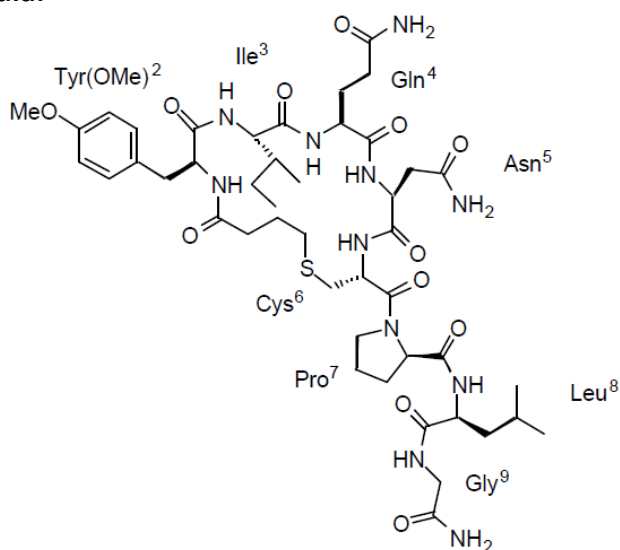
Drug Substance

Proper name: Carbetocin (INN)

Chemical name: 1-desamino-1-monocarba-2-(0-methyl)-tyrosine oxytocin

Molecular formula and molecular mass: $C_{45}H_{69}N_{11}O_{12}S$
988.17 g/mol

Structural formula:



Physicochemical properties: Carbetocin is a white, fluffy lyophilized powder, soluble in water, ethanol, methanol and acetic acid. Carbetocin is insoluble in ether and petroleum ether. The pH of carbetocin is 3.9.

Other Names:

[2-0-methyltyrosine]-1-deaminocarba-1-oxytocin

[6,1,B-deaminocystathionine,2-0-methyl-tyrosine-oxytocin]

[tyr(me)²]-deamino-1-carba-oxytocin

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Caesarean Section Program

Study Design – Elective Caesarean Section

Three pivotal randomised controlled clinical trials were conducted in support of the use of carbetocin in healthy pregnant women undergoing elective caesarean section.

Table 6: Summary of Clinical Trials in Patients Undergoing Elective Caesarean Section

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Population	Primary endpoint
Boucher et al, 1998 CLN 6.3.6 Efficacy Safety	Randomised, active- controlled, double- blind, double- dummy, parallel- group trial	Carbetocin: 100 mcg IV bolus Oxytocin: 32.5 IU, 16 h IV infusion	Carbetocin: n = 29 Oxytocin: n = 28	Healthy pregnant women undergoing elective caesarean section under epidural anaesthesia	Intra- operative blood loss
Dansereau et al, 1999 CLN 6.3.9 Efficacy Safety	Randomised, active- controlled, double- blind, double dummy, parallel- group trial	Carbetocin: 100 mcg IV bolus Oxytocin: 25 IU, 8 h IV infusion	Carbetocin: n = 329 Oxytocin: n = 330	Healthy pregnant women undergoing elective caesarean section under epidural anaesthesia	Incidence of need for additional oxytocin intervention
Barton et al, 1993 CLN 6.3.10 Efficacy Safety	Randomised placebo- controlled, double- blind, parallel- group trial	Carbetocin: 100 mcg IV bolus Placebo: 0.9% sodium chloride IV	Carbetocin: n = 64 Placebo: n = 58	Healthy pregnant women undergoing elective caesarean section under epidural anaesthesia	Incidence of need for additional oxytocin intervention

Study Design – Emergency and Elective Caesarean Section

Three randomised controlled trials were conducted including pregnant subjects undergoing emergency and elective Caesarean section.

Table 7: Summary of Clinical Trials including Patients Undergoing Emergency and Elective Caesarean Section

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Population	Primary endpoint
Attilakos et al, 2010* Efficacy Safety	Randomised, active- controlled, double- blind, parallel- group trial	Carbetocin: 100 mcg IV Oxytocin: 5 IU IV	Carbetocin: n = 188 Oxytocin n = 189	Healthy pregnant women undergoing elective or emergency caesarean section under regional anaesthesia	Incidence of need for additional oxytocin intervention

Borruto et al, 2009** Efficacy Safety	Randomised, active- controlled, single- blinded, parallel- group trial	Carbetocin: 100 mcg IV Oxytocin: 10 IU, 2 h IV infusion	Carbetocin: n = 52 Oxytocin n = 52	Pregnant women with at least one risk factor for PPH undergoing elective or emergency caesarean section under peridural anaesthesia	Patients requiring additional oxytocic intervention for uterine atony
El Behery et al, 2015*** Efficacy Safety	Randomised, active- controlled, double-blind, double dummy, parallel- group trial	Carbetocin: 100 mcg IV Oxytocin: 20 IU, 8 h IV infusion	Carbetocin: n = 90 Oxytocin n = 90	Obese (BMI>30), nulliparous, pregnant women undergoing emergency caesarean section	Major primary postpartum haemorrhage defined as blood loss ≥ 1000 mL within 24 h of delivery

*60% elective and 40% emergency caesarean section patient population

**Mixed planned and emergency caesarean patient population

***All emergency caesarean sections

14.2 Study Results

Caesarean Section

Elective Caesarean Section

Boucher (1998) showed no significant difference between carbetocin 100 mcg IV and oxytocin 32.5 IU, 16 h IV infusion in terms of preventing excessive intraoperative blood loss. The mean blood loss in the carbetocin group was 159 ± 92 mL vs. 188 ± 115 mL in the oxytocin group ($p=0.30$). However, the percentage of subjects with blood loss ≤ 200 mL in the carbetocin group was significantly higher than in the oxytocin group (79% vs. 53%; $p<0.05$). No subjects in the carbetocin group required additional oxytocic therapy for uterine atony or excessive bleeding whereas additional oxytocic intervention was required in 3 subjects in the oxytocin group (11%).

This study demonstrated that a single intravenous bolus injection of carbetocin was at least as effective as 16 hours of continuous oxytocin infusion, in terms of efficacy in maintaining uterine contraction after cesarean section, and in preventing excessive intraoperative blood loss following cesarean delivery. This study confirmed the ability of a 100 mcg intravenous dose of carbetocin to maintain adequate uterine tone after cesarean section. Carbetocin also appeared to accelerate the initial stages of uterine involution, associated with the return of the uterus to the non-pregnant size and position.

A second double-blind trial, (Dansereau, 1999), compared a single intravenous dose of 100 mcg carbetocin to an 8-hour oxytocin infusion in 659 healthy pregnant women after elective cesarean section done under epidural or spinal anesthesia. The primary objective was to compare the safety and efficacy of the two treatments in maintaining adequate uterine contraction after cesarean section. The primary efficacy variable was the incidence rate of the need for further oxytocic therapy for 48 hours after delivery. Carbetocin was associated with lower incidence of "need for additional oxytocic intervention" when compared to oxytocin: such intervention occurred in 15 (5%) of the patients receiving Carbetocin 100 mcg IV compared to 32 (10%) of the patients

administered oxytocin ($p=0.031$). Carbetocin was associated with a significantly longer time to intervention when compared to 25 IU oxytocin: 2.03 versus 0.18 hours respectively (medians)

Barton (1993) evaluated the safety and efficacy of carbetocin versus placebo for control of bleeding after cesarean section. This multicentre trial included 122 patients. Efficacy was determined as the requirement for intervention with additional oxytocic therapy following test drug administration. When given as a single bolus intravenous dose of 100 mcg after delivery of the infant at elective cesarean section done under epidural, carbetocin was found to be significantly more effective than placebo in preventing uterine atony and excessive bleeding with only 13% of patients requiring intervention with further oxytocic therapy compared to 72% of patients in the placebo group ($p=0.001$).

Emergency and Elective Cesarean Section

Attilakos (2010) demonstrated that carbetocin 100 mcg IV was significantly better than oxytocin 5 IU IV in reducing the need for additional oxytocic intervention. Additional oxytocic intervention was required in 33.5% of the subjects receiving carbetocin compared to 45.5% of the subjects receiving oxytocin (relative risk 0.74, 95% CI: 0.57-0.95; $p=0.023$). There were no significant differences between the treatment groups with respect to number of subjects experiencing postpartum haemorrhage with blood loss >1000 mL, estimated intraoperative blood loss, difference in haemoglobin, uterine tone, and incidence of blood transfusions.

The trial by Borruto (2009) showed that additional oxytocic intervention was required in significantly fewer subjects in the carbetocin group compared to the oxytocin group (3.8% vs. 9.6%; $p<0.01$). Also, significantly fewer subjects in the carbetocin group compared to the oxytocin group required uterine massage (38.4% vs. 57.7%, $p<0.01$). The mean time to intervention (oxytocin infusion as well as uterine massage) was comparable between the two treatment groups. The position of the fundus was below the umbilicus in a greater number of subjects in the carbetocin group (indicating enhanced uterine involution) at all times points after transfer to the ward reaching statistical significance after 24 h ($p<0.05$). The percentage of subjects with blood loss ≤ 500 mL was higher in the carbetocin 100 mcg IV group than in the oxytocin 10 IU, 2 h IV infusion group (81% vs. 55%; $p=0.05$). There was no significant difference in mean blood loss between the two treatment groups although it was 30 mL less in the carbetocin group ($p=0.5$).

The results of the El Behery (2015) study in women with an increased risk of postpartum hemorrhage are summarized in Table 8. The carbetocin group had statistically significantly lower incidence of postpartum hemorrhage ($p=0.03$), estimated blood loss ($p=0.002$) and need for transfusion ($p=0.04$) when compared to the oxytocin group. Haemoglobin levels before and 24-h postpartum were similar. 2.22% of patients in the carbetocin group versus 71.11% of patients in the oxytocin group needed additional uterotonics ($p=0.002$). The uterine contractility was better in the carbetocin group at 2-h and 12-h postpartum ($p<0.05$).

Table 8 – Summary of Results from Clinical Trials in Emergency and Elective Cesarean Section

Study	Carbetocin 100 mcg IV	Oxytocin****	p value
<i>Need for Additional Oxytocic n/N (%)</i>			

Attilakos et al. ^{*1}	63/188 (33.5)	86/189 (45.5)	RR 0.74 (95% CI: 0.57-0.95) 0.023
Borruto et al. ²	2/52 (3.8)	5/52 (9.6)	RR 1.83 (95% CI: 0.9-2.6) <0.01
El Behery et al. ³	2/90 (2.2)	64/90 (71.1)	0.0002
Incidence of PPH n/N (%)			
Attilakos et al. ¹	9/186 (4.8)	9/189 (4.8)	ns
Borruto et al. ²	-	-	-
El Behery et al. ^{*3}	2/90 (2.2)	12/90 (13.33)	0.03
Blood Loss (mLs)			
Attilakos et al. ^{***1}	500 (400-700)	500 (400-600)	
Borruto et al. (IOP) ^{**2}	370.1	400.5	0.5
El Behery et al. ^{**3}	689 ± 580	1027 ± 659	0.002
Mean Hemoglobin Decrease dl			
Attilakos et al. ^{**1}	1.6 (95% CI 1.5-1.8)	1.6 (95% CI 1.5-1.8)	
Borruto et al. ²	-	-	-
El Behery et al. ^{**3}	1.74 (0.87)	0.94 (0.64)	0.03
Need for Transfusion			
Attilakos et al. ¹	4/188 (2.1)	5/189 (2.6)	<0.99
Borruto et al. ²	-	-	-
El Behery et al. ³	0/90 (0)	14/90 (15.6)	0.04
El Behery et al. ³	0/90 (0)	14/90 (15.6)	0.04

* Primary Outcome Measure, ** Mean ± SD, *** Median (IQR), ns – non-significant, IOP – intraoperative

**** Attilakos et al. = 5 IU, Borruto et al. = 10 IU, El Behery et al. = 20 IU

¹ 60% elective and 40% emergency cesarean section patient population

² Mixed planned and emergency cesarean patient population

³ All emergency cesarean sections

15 MICROBIOLOGY

No microbial information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

In acute toxicology studies, the LD₅₀ was estimated at 10 mg/kg in an intravenous rat study. Marked clinical signs (lethargy, hunched posture, piloerection, rapid breathing and uncoordinated movement) were noted for all animals. Using this LD₅₀, the corresponding dose for a 100 g rat would be 1,000 mcg, which is ten times the dose used in humans.

Four groups of 20 rats were given carbetocin intravenous at doses of up to 1.0 mg/kg/day for 28 days. There were no deaths or clinical signs attributable to treatment.

Sixteen female beagles were given carbetocin by intravenous injection daily for 28 days at doses of up to 1.0 mg/kg/day. There were no deaths or clinical signs attributable to treatment. No treatment related changes in hematology, clinical chemistry or urinalysis occurred. Carbetocin was found to be devoid of mutagenic activity in a battery of mutagenicity tests. Carcinogenicity studies have not been performed.

Reproduction and teratology studies have not been performed since the drug is intended for a single administration immediately after delivery.

17 SUPPORTING PRODUCT MONOGRAPHS

1. DURATOCIN® (carbetocin injection; 100 mcg / vial), Submission Control No.: 236432, Product Monograph, Ferring Inc., April 28, 2020.
2. DURATOCIN® (carbetocin injection; 100 mcg / vial), Submission Control No.: 257210, Product Monograph, Ferring Inc: March 22, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr**CARBETOCIN INJECTION**

Read this carefully for information on **Carbetocin Injection**. This leaflet is a summary and will not tell you everything about Carbetocin Injection. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Carbetocin Injection**.

What is Carbetocin Injection used for?

Carbetocin Injection makes the uterus (womb) shrink. This will help prevent heavy bleeding in women who have delivered a baby by caesarean section.

How does Carbetocin Injection work?

Carbetocin is the active ingredient in Carbetocin Injection. It locks onto special parts of the muscle cells of the uterus. This causes the uterus to contract.

What are the ingredients in Carbetocin Injection?

Medicinal ingredient: Carbetocin

Non-medicinal ingredients: Glacial acetic acid, sodium chloride and water for injection.

Carbetocin Injection comes in the following dosage form:

Solution, 100 mcg / mL.

You must not be given Carbetocin Injection if you:

- are pregnant. Carbetocin Injection must only be given after your baby has been delivered.
- are allergic to carbetocin or any of the ingredients of Carbetocin Injection.
- have any serious heart problems.
- ever have had an allergic reaction to oxytocin. This is a medicine that is sometimes given during or after labour.
- are younger than 18 years of age or older than 65 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given Carbetocin Injection. BEFORE you receive Carbetocin Injection, talk about any conditions or problems you may have, or have had, including:

- liver or kidney problems;
- pre-eclampsia (high blood pressure in pregnancy) or eclampsia (seizures if pre-eclampsia worsens);
- problems with your heart or your circulation (such as high blood pressure);
- epilepsy;
- migraines;
- asthma; or
- if you are breastfeeding. A small amount of Carbetocin Injection will pass into your breast milk.

However, you do not need to stop breastfeeding your baby because of this.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Carbetocin Injection:

- Medicines that cause blood vessels to narrow.
- Medicines you breathe to put you to sleep for surgery, like halothane and cyclopropane.
- Prostaglandins, which are medicines used to induce labour.

How Carbetocin Injection is given:

Carbetocin Injection will be given to you right after your baby has been delivered.

Carbetocin Injection will be given by intravenous injection immediately after your baby has been delivered by cesarean section under an epidural or spinal anaesthetic.

Usual dose:

100 mcg given as a single injection of 1 mL of Carbetocin Injection.

Overdose:

If you are accidentally given too much Carbetocin Injection, your womb may contract strongly. This can cause you to experience abdominal pain. You may also feel drowsy, a loss of energy and get a headache. This is caused by water building in your body.

If you think you, or a person you are caring for, have received too much Carbetocin Injection, tell your healthcare professional or contact your hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using Carbetocin Injection?

These are not all the possible side effects you may feel when given Carbetocin Injection. If you experience any side effects not listed here, talk to your healthcare professional.

- Nausea, vomiting.
- Stomach pain.
- Itching, flushing.
- Feeling of warmth.
- Fever
- Headache.
- Shakiness.
- Dizziness.
- Metallic taste in the mouth.
- Sweating, chills.
- Back pain.
- Fast heartbeat.

Side effects seen with similar products that might be expected with Carbetocin include:

- Slow heartbeat.
- Irregular heartbeat.
- Chest pain.
- Fainting.
- Palpitations (may feel like your heart is racing, pounding, fluttering or skipping beats), which may mean the heart is not beating properly

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if Severe	In all cases	
VERY COMMON			
Low blood pressure: dizziness, fainting, light-headedness may occur when you go from lying or sitting to standing up.		✓	
COMMON			
Anemia: (decreased number of red blood cells): Fatigue, loss of energy, weakness.		✓	
Chest pain		✓	
Rapid heart beat		✓	
Breathlessness; trouble breathing	✓		
Anxiety	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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) (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.

Storage:

- Store at: 2°C - 8°C. Protect from light. Single dose pre-filled syringe. Use only if the syringe contents are clear and colourless. Once the pre-filled syringe has been opened, the product should be used immediately. Discard the unused portion.
- The tip cap and stopper are not made with natural rubber latex

Keep out of reach and sight of children.

If you want more information about Carbetocin Injection:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication 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, Juno Pharmaceuticals Corp.: 1-855-819-0505.

This leaflet was prepared by:
Juno Pharmaceuticals Corp.
402-2233 Argentia Road
Mississauga, ON, L5N 2X7

Last Revised: September 18, 2023