PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**DURATOCIN®**

Carbetocin Injection

1 mL vial, 100 mcg / mL, Intravenous and intramuscular use

Uterotonic Agent

Ferring Inc.
200 Yorkland Blvd., Suite 500
North York, Ontario
M2J 5C1

Date of Initial Approval:
JUN 20, 1997

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MAR 22, 2022

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	MAR 2022
4 DOSAGE AND ADMINISTRATION	MAR 2022
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DURATOCIN (carbetocin injection) is indicated for:

- the prevention of postpartum haemorrhage by controlling uterine atony.

1.1 Pediatrics

Pediatrics (< 18 years of age):

The safety and efficacy of carbetocin have not been established in the pediatric population. Accordingly, DURATOCIN 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 DURATOCIN cannot be stopped by simply discontinuing the medication. Therefore, DURATOCIN should **not** be administered:

- Prior to delivery of the infant for any reason, including elective or medical induction of labour. Inappropriate use of DURATOCIN 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 DURATOCIN.

- In patients with serious cardiovascular disorders.

- DURATOCIN is not recommended for use in children.

4 DOSAGE AND ADMINISTRATION

4.4 Administration

Vaginal delivery – Intramuscular or Intravenous injection

Withdraw 1 mL solution containing 100 mcg of DURATOCIN and administer by intramuscular injection or slowly over 1 minute by intravenous bolus injection, under adequate medical supervision. DURATOCIN must be administered as soon as possible after delivery of the infant, preferably before the delivery of the placenta.

No further doses of DURATOCIN should be administered.

Caesarean section – Intravenous injection

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

No further doses of DURATOCIN should be administered.

5 OVERDOSAGE

Overdosage of DURATOCIN can be expected to produce enhanced pharmacological effects. Therefore, when DURATOCIN 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	1 mL vial / 100 mcg carbetocin	mannitol, L-methionine, sodium hydroxide for pH adjustment, succinic acid, and water for injection q.s. to 1 mL
Intramuscular		

DURATOCIN is available in 1 mL vials as a sterile solution. Each vial contains 100 mcg carbetocin. Boxes contain 5 vials each.

Vials are colourless glass vial with bromobutyl rubber stoppers and aluminium crimp cap.

7 WARNINGS AND PRECAUTIONS

General

DURATOCIN should only be used at well-equipped specialist obstetrics units.
Some patients may not have an adequate uterine contraction after a single injection of DURATOCIN. In these patients, administration of DURATOCIN 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 DURATOCIN, the presence of retained placental fragments, coagulopathy, or trauma to the genital tract should be ruled out.

DURATOCIN is intended for single administration only, intramuscular (IM) or intravenous (IV).

Significant antidiuretic effect is not anticipated and has not been demonstrated at the recommended dose. However, since DURATOCIN 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 DURATOCIN in these patients has not been evaluated in formal clinical trials.

DURATOCIN 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

DURATOCIN use during pregnancy, prior to the delivery of the infant, is contraindicated (see 2 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 DURATOCIN 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.

The adverse events observed with DURATOCIN (IV or IM) during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin.

Vaginal Delivery

In a large, randomized, active controlled, double-blind clinical trial (Study A65870; see 14 CLINICAL TRIALS), 14,754 subjects received carbetocin (IM) and 14,743 subjects received oxytocin (IM). Carbetocin and oxytocin have a similar safety profile in the prevention of PPH following vaginal delivery (see Table 2).

Table 2 Summary of Treatment-Emergent Adverse Events (TEAEs) in Study A65870

	CARBETOCIN N=14,754		OXYTOCIN N=14,743		Total N=29,497	
	n	%	n	%	n	%
Participants with at least one TEAE	595	4.03	578	3.92	1173	3.98

Most frequent TEAEs for Carbetocin (≥0.2% and <1%) in Study A65870

Blood and lymphatic system disorders – Anemia
Gastrointestinal disorders – Abdominal pain, vomiting
General disorders and administration site conditions – Pyrexia
Injury, poisoning and procedural complications – Post-procedural swelling
Pregnancy, puerperium and perinatal conditions – Postpartum haemorrhage

The overall safety profile of carbetocin (IM) in women who delivered vaginally is consistent with the established safety profile reported for carbetocin (IV) in the prevention of uterine atony following delivery by Caesarean section. No new risks associated with IM administration of carbetocin were seen in the study.

Caesarean Section

The more commonly observed adverse reactions in the clinical trials of patients undergoing

elective caesarean section are summarized by frequency in Table 3 (Boucher 1998[1]; Dansereau 1999[2]; Barton 1993[3]).

Table 3 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 disorders		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 caesarean section under epidural or spinal anesthesia. The more commonly observed adverse reactions in the clinical trials of patients undergoing caesarean section are summarized by frequency in Table 4.

[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.

Table 4 Adverse Drug Reactions for Carbetocin (≥1%) in clinical trials of Caesarean Section

	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 (%)**
Blood and lymphatic system disorders						
Anaemia			23	-		
Cardiac disorders						
Tachycardia	1.1	-				
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 Fall in blood pressure (causing dizziness, light headedness, feeling faint)	2.1	1.1	21.1	23		
Flushing	2.2	1.6	25	-		
Respiratory, thoracic and mediastinal disorders						
Chest Pain			3.8	-		
Dyspnoea Shortness of breath Difficulty in breathing	1.1	1.6	9.6	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			40.3	38.4		

[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 (%)**
Pain						
Metallic Taste	1.1	0.5	5.7	-		
Skin and subcutaneous tissue disorders						
Pruitis			9.6	19.2		
Skin rashes						
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 caesarean section patient population

** Mixed planned and emergency caesarean patient population

*** All emergency caesarean 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 caesarean sections. Intravenous carbetocin was very commonly associated with anaemia, nausea, abdominal pain, pruritis, 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-anesthetics, 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

DURATOCIN (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 caesarean 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 or IM 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 a 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 caesarean section under epidural anesthesia (Boucher, 1990[7]). Here the intravenous dose of carbetocin

[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

required to produce sustained tetanic contraction after caesarean 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 caesarean 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 5 Breakdown of Patients by Number of Doses Required to Produce Tetany

Increment size (mcg)	Case No.	No. of increments administered	Total dose (mcg)	Tetanic 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	
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 mcg. The geometric mean terminal half-life is 33 minutes after intravenous administration and 55 minutes after intramuscular administration. After intramuscular administration, peak concentrations are reached after 30 minutes and the geometric mean bioavailability is 77%. The mean volume of distribution at pseudo-equilibrium (Vz) is 22 L. 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 Table 6.

Table 6 Summary Statistics of Key Carbetocin Pharmacokinetic Parameters following Intravenous (IV) and Intramuscular (IM) Administration of Heat-stable Carbetocin Formulation (Pharmacokinetic Analysis Set)

Parameter	Geometric Mean (Geometric %CV)	
	Carbetocin 100 mcg IV (N = 19)	Carbetocin 100 mcg IM (N = 20)
$AUC_{0-\infty}$ (ng*h/mL)	2.762 (21.6%)	2.147 (18.7%)
AUC_t (ng*h/mL)	2.697 (21.8%)	2.022 (20.3%)
C_{max} (ng/mL)	7.232 (17.4%)[a]	1.030 (30.4%)
t_{max} (h)[b]	NA	0.500 (0.250, 0.750)
$t_{1/2}$ (h)	0.5480 (25.8%)	0.9157 (28.4%)

AUC0-∞ = 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);
IM = intramuscular; 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.
[b] Results presented are median (minimum, maximum).
Source: Table 9-1 and Appendix A9.3.2.3.1, CTR 000146 [5.3.1.1]

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

Store at room temperature (15°C to 30°C).

Single use vial. Use only if the vial contents are clear and colourless. Once the vial has been opened, the product should be used immediately. Discard the unused portion.

12 SPECIAL HANDLING INSTRUCTIONS

None. DURATOCIN does not require special handling.

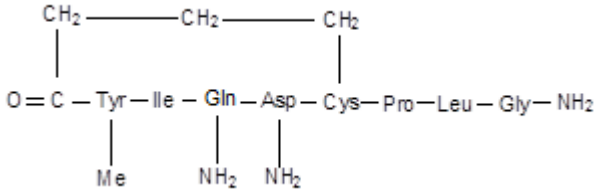
PART II: SCIENTIFIC INFORMATION

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: $C_{45}H_{69}N_{11}O_{12}S$
988.1

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

Vaginal Delivery Program
Overall, 14,791 subjects received carbetocin in the vaginal delivery clinical research program described below.

Study design
Two studies (

Table 7) comprise the clinical research program for carbetocin use in vaginal delivery. Study 000146 compared the pharmacokinetics of carbetocin in healthy non-pregnant women following intravenous and intramuscular routes of administration (see 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics). Pivotal study A65870 compared the use of IM carbetocin with IM oxytocin.

Table 7 Overview of Vaginal Delivery Clinical Research Program

Trial ID	Phase	Design	Treatments	Number of subjects	Population
000146 Bioavailability Pharmacokinetics	1	Randomised, open-label, 2-sequence, crossover	Carbetocin: 100 mcg IV slow injection and 100 mcg IM	Carbetocin: 20	Healthy non-pregnant women
A65870 Efficacy Safety	3	Randomised, active-controlled, double-blind, parallel-group	Carbetocin: 100 mcg IM Oxytocin: 10 IU IM	Carbetocin: 14,771 Oxytocin: 14,768	Healthy pregnant women undergoing vaginal delivery

IM = intramuscular; IU = international units; IV = intravenous; PPH = postpartum haemorrhage

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 8 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

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Population	Primary endpoint
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 9 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

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Population	Primary endpoint
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

Vaginal Delivery Program

Study A65870

The efficacy of carbetocin (IM) in the prevention of postpartum haemorrhage following vaginal delivery was established in one randomized, active controlled, double-blind trial. In total 29,645 subjects were randomised to receive a single intramuscular dose of either carbetocin (100 mcg) or oxytocin 10 IU. For the primary endpoint of blood loss of ≥500 mL or use of additional uterotonics, similar rates were obtained in both treatment groups (carbetocin: 2,135 subjects, 14.47%; oxytocin: 2,122 subjects, 14.38%; relative risk [RR] 1.01; 95% CL: 0.95 to 1.06). The upper limit of the 95% CI was lower than the non-inferiority margin of 1.16 preset for this endpoint, demonstrating that carbetocin was at least as effective as oxytocin with

regards to the primary endpoint. For the secondary endpoints there were no differences at the 5% level of significance between groups (Widmer, 2018[8]).

Paediatric population
The safety and efficacy of carbetocin have not been established in the pediatric population. However, the clinical research program of carbetocin for prevention of postpartum haemorrhage following vaginal delivery (A65870) included 151 women between 12 and 18 years of age who received carbetocin at the recommended dosage of 100 mcg.

Publications – Intravenous carbetocin after vaginal delivery
In a published randomized, controlled, triple-blinded study (Amornpetchakul, 2018[9]), intravenous carbetocin 100 mcg was more effective than intravenous oxytocin 5 IU for the prevention of atonic PPH among singleton pregnancies with at least one risk factor for PPH after vaginal delivery. The carbetocin group (n=174) had a lower incidence of atonic PPH (blood loss ≥ 500 ml) than the oxytocin group (n=176) [0% vs. 6.3%; nominal p-value < 0.01]. No significant differences regarding side effects were evident between the groups.

There are currently no adequate studies comparing the efficacy and safety of intravenous carbetocin 100 mcg to intravenous oxytocin 10 IU for the prevention of PPH following vaginal delivery.

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 caesarean section, and in preventing excessive intraoperative blood loss following caesarean delivery. This study confirmed the ability of a 100 mcg intravenous

[8] Widmer M, Piaggio G, Nguyen TMH, et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018 Aug 23; 379(8):743-752.

[9] Amornpetchakul, P., Lertbunnaphong, T., Boriboonhiransarn, D. et al. Intravenous carbetocin versus intravenous oxytocin for preventing atonic postpartum hemorrhage after normal vaginal delivery in high-risk singleton pregnancies: a triple-blind randomized controlled trial. Arch Gynecol Obstet. 2018; 298: 319.

dose of carbetocin to maintain adequate uterine tone after caesarean 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 caesarean 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 caesarean 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 25 IU oxytocin (p=0.031). Carbetocin was associated with a significantly longer time to intervention when compared to 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 caesarean 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 caesarean 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 Caesarean 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 10. The carbetocin group had statistically significantly lower in the 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 10 Summary of Results from Clinical Trials in Emergency and Elective Caesarean Section

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

Study	Carbetocin 100 mcg IV	Oxytocin****	p value
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 caesarean section patient population

[2] Mixed planned and emergency caesarean patient population

[3] All emergency caesarean sections

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

In acute toxicology studies, the LD_{50} 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 LD_{50}, 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

DURATOCIN

Carbetocin injection

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

What is DURATOCIN used for?
- DURATOCIN makes the uterus (womb) shrink. This will help to prevent heavy bleeding in women who have delivered a baby.

How does DURATOCIN work?
Carbetocin is the active ingredient in DURATOCIN. It locks onto special parts of the muscle cells of the uterus. This causes the uterus to contract.

What are the ingredients in DURATOCIN?
Medicinal ingredients: Carbetocin
Non-medicinal ingredients: mannitol, L-methionine, sodium hydroxide, succinic acid, water for injection.

DURATOCIN comes in the following dosage forms:
Solution, 100 mcg / mL

You must not be given DURATOCIN if you:
- are pregnant. DURATOCIN must only be given after your baby has been delivered.
- are allergic to carbetocin or any of the ingredients of DURATOCIN.
- 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 DURATOCIN. BEFORE you receive DURATOCIN, talk about any health 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 DURATOCIN 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 DURATOCIN:
- 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 DURATOCIN is given:
DURATOCIN will be given to you right after your baby has been delivered.
If you deliver your baby vaginally, DURATOCIN will be given either as:
- an injection in your vein. This is called an intravenous injection; or
- an injection into your muscle. This is called an intramuscular injection.

If you have your baby by Caesarean section (C-section), DURATOCIN will be given by intravenous injection.

Usual dose:
100 mcg given as a single injection of 1 mL of DURATOCIN.

Overdose:
If you are accidentally given too much DURATOCIN, 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 up in your body.

If you think you, or a person you are caring for, have received too much DURATOCIN, 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 DURATOCIN?
These are not all the possible side effects you may feel when given DURATOCIN. If you experience any side effects not listed here, tell 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 **Hypotension** (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.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: 15°C to 30°C. DURATOCIN should be used immediately after opening the vial.

Keep out of reach and sight of children.
If you want more information about DURATOCIN:

- 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; Ferring Inc.'s website www.ferring.ca, or by calling Ferring Inc. at 1-866-384-1314.

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