PRODUCT MONOGRAPH

Pr**DURATOCIN®**

(Carbetocin Injection)

1mL ampoule – 100 mcg/mL Injection

For Intravenous Use Only

Uterotonic Agent

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DURATOCIN
(Carbetocin Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	100 mcg/mL	Glacial acetic acid, sodium chloride, water for injection.

INDICATIONS AND CLINICAL USE [5,6,10,11,22,25]

DURATOCIN (carbetocin injection) is indicated for the prevention of uterine atony and postpartum hemorrhage following cesarean section under epidural or spinal anaesthesia.

DURATOCIN has not been studied in cases involving patients with a history of hypertension, known coagulopathy or evidence of liver, renal or endocrine disease. Appropriate studies have not been undertaken and doses have not been established in women following labour or vaginal delivery.

Geriatrics (> 65 years of age):
Not recommended for use.

Pediatrics (< 18 years of age):
Not recommended for use.

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 over dosage, 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.
- In patients with serious cardiovascular disorders.
- Carbetocin is not intended for use in children.

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 (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.

Carbetocin has antidiuretic effects. The risk of water intoxication cannot be excluded.

Patients with eclampsia and pre-eclampsia should be monitored for changes in blood pressure. The safety of carbetocin in these patients has not been evaluated in formal clinical trials.

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.

Special Populations

Pregnant Women: DURATOCIN (carbetocin injection) use during pregnancy, prior to the delivery of the infant, is contraindicated (see CONTRAINDICATIONS).

Nursing Women: 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.

Pediatrics (< *18 years of age*): Not recommended for use.

Geriatrics (> *65 years of age*): Not recommended for use.

ADVERSE REACTIONS [5,6,10,11,22,25]

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The more commonly observed adverse reactions in the clinical trials of patients undergoing elective cesarean section are summarized by frequency in Table 1 (Boucher, M. 1998[11], Dansereau, J. 1999[22], Barton, Scott R. et al, 1993[6])

Table 1: Very Common (≥10%) and Common (≥1% and <10%) Adverse Drug Reactions for Carbetocin in clinical trials of Elective Cesarean 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	
Musculosceletal 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 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 2 (ref. Attilakos et al. 2010[5], Borruto et al. 2009[10] and El Behery et al. 2015[25])

Table 2: Adverse Drug Reactions for Carbetocin (≥1%) in clinical trials of Cesarean Section

	Attilakos et al, 2010*		Borruto et al, 2009**		El Behery et al, 2015***	
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, lightheadedness, 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 Pain			40.3	38.4		
Metallic Taste	1.1	0.5	5.7	-		
Skin and subcutaneous tissue disorders						
Pruitis Skin rashes			9.6	 19.2		
Musculoskeletal and connective tissue disorders						
Back Pain			3.8	-		
General disorders and administration site conditions						
Heat Sensation			19.2	-		
Chills						

	Attilakos et al, 2010*		Borruto et al, 2009**		El Behery et al, 2015***	
System Organ Class (MedDRA)	**Carbetocin N=188 (%)**	**Oxytocin N=189 (%)**	**Carbetocin N=52 (%)**	**Oxytocin N=52 (%)**	**Carbetocin N=90 (%)**	**Oxytocin N=90 (%)**
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, 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.

DRUG INTERACTIONS

During clinical trials, carbetocin has been administered in association with a number of analgesics, 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.

Severe hypertension has been reported when oxytocin was given 3-4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anaesthesia.

Some inhalation-anaesthetics, such as cyclopropane may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia

with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anaesthesia.

DOSAGE AND ADMINISTRATION

A single intravenous dose of 100 mcg (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 cesarean section under epidural or spinal anesthesia. DURATOCIN can be administered either before or after delivery of the placenta.

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. Symptoms of uterine hyperactivity include; uterine hypertonus, abdominal pain, discomfort associated with too frequent or too strong uterine contractions.

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.

ACTION AND CLINICAL PHARMACOLOGY

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

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

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 cesarean section under epidural anesthesia (CLN 6.3.5). 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.[12]

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 3: 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	
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 $\pm$ 0.5 minutes. Total duration of a single injection of intravenous carbetocin on uterine activity is about one hour.

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 Cmax and AUC0-4 show proportional changes with increasing dose.

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

injected dose excreted unchanged by the kidney, indicating that carbetocin, like oxytocin, is eliminated mainly by non-renal routes.

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

Table 4: Summary of Pharmacokinetic Parameters

		Intravenous Injection	
Parameter		**400 mcg IV**	**800 mcg IV**
AUC (0 to ∞) (mcg/min/L)	Mean Range	749.2±131.0 539.5-916.9	1,370.4±214.9 1,148-1,733
Clt (L/min)	Mean Range	0.549±0.105 0.436-0.741	0.595±0.089 0.462-0.696
Clr (L/min)	Mean Range	0.004±0.002 0.002-0.007	0.004±0.002 0.002-0.007
Clnr (L/min)	Mean Range	0.545±0.103 0.433-0.735	0.591±0.089 0.458-0.692
Vc (L)	Mean Range	9.27±2.98 5.2-13.6	8.38±1.78 6.4-11.3
Alpha HL (min)	Mean Range	5.54±1.6 3.3-7.8	6.05±1.15 5.1-8.2
Beta HL (min)	Mean Range	41.0±11.9 28.7-59.2	42.7±10.6 39.3-49.4
Cmax (mcg/L)	Mean Range	-	-
Tmax (min)	Mean Range	-	-
F (%)	Mean Range	-	-
Ae (%)	Mean Range	0.70±0.30 0.36-1.13	0.68±0.30 0.42-1.20

AUC = area under the curve; Clt = total body clearance; Clr = renal clearance; Clnr = nonrenal clearance; Vc = volume of the central compartment; alpha-HL = distribution half-life; beta-HL = elimination half-life; Cmax = peak concentration; Tmax = time to peak concentration; F= percent bioavailability of intramuscular carbetocin; Ae =percent carbetocin.

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.

STORAGE AND STABILITY

DURATOCIN (carbetocin injection) must be stored at refrigerator temperature (2-8°C). DURATOCIN should not be frozen. Once the ampoule has been opened, the product should be used immediately.

SPECIAL HANDLING INSTRUCTIONS

Instructions for Opening Ampoules

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

DURATOCIN (carbetocin injection) is available in 1 mL ampoules. Each ampoule contains 100 mcg carbetocin. Boxes contain 5 ampoules each.

Each ampoule contains 100 mcg (0.1 mg) of carbetocin, 9 mg sodium chloride, glacial acetic acid (6-14 mcg) and water for injection q.s. to 1 mL. Ampoules are clear glass with a white identification ring and a blue dot indicating the cut area.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

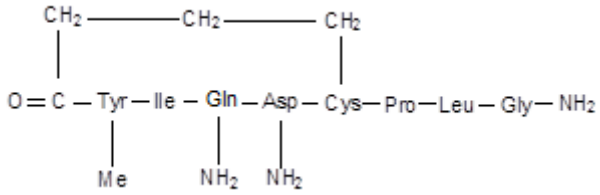
Drug Substance

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

CLINICAL TRIALS [5,6,10,11,22,25]

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

Elective Cesarean Section:

Table 5- Summary of Clinical Trials in Patients Undergoing Elective Cesarean 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 [11]	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 cesarean section under epidural anaesthesia	Intraoperative blood loss
Dansereau et al, (1999) CLN 6.3.9 Efficacy Safety [22]	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 cesarean section under epidural anaesthesia	Incidence of need for additional oxytocin intervention
Barton et al (1993) CLN 6.3.10 Efficacy Safety [6]	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 cesarean section under epidural anaesthesia	Incidence of need for additional oxytocin intervention

Study Results:

CLN 6.3.6 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.[11]

A second double-blind trial, CLN 6.3.9, compared a single intravenous dose of 100 mcg carbetocin to an 8-hour oxytocin infusion 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 5% of patients receiving carbetocin compared to 10% of patients administered 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).[22]

CLN 6.3.10 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).[6]

Emergency and Elective Cesarean Section:

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

Table 6a - Summary of Clinical Trials including Patients Undergoing Emergency and Elective Cesarean Section

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Population	Primary endpoint
Attilakos et al. (2010)* Efficacy Safety [5]	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 cesarean section under regional anaesthesia	Incidence of need for additional oxytocin intervention
Borruto et al.(2009)** Efficacy Safety [10]	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 cesarean section under peridural anaesthesia	Patients requiring additional oxytocic intervention for uterine atony
El Behery et al.(2015)*** Efficacy Safety [26]	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 cesarean section	Major primary postpartum haemorrhage defined as blood loss ≥ 1000 mL within 24 h of delivery

*60% elective and 40% emergency cesarean section patient population
**Mixed planned and emergency cesarean patient population
***All emergency cesarean sections

Study Results:

Attilakos et al, 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.[5]

The trial published by Borruto et al. 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 ($p=0.5$).[10]

The results of the El Behery study in women with an increased risk of postpartum hemorrhage are summarized in Table 6b. Carbetocin was 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 from the carbetocin group versus 71.11% in oxytocin group needed additional uterotonics ($p=0.002$). The uterine contractility was better in the carbetocin group at 2-h and 12-h postpartum ($p<0.05$). [25]

Table 6b – Summary of Results from Clinical Trials in Emergency and Elective Cesarean 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
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

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.

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PART III: CONSUMER INFORMATION

PrDURATOCIN®
carbetocin injection

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

ABOUT THIS MEDICATION

What the medication is used for:
DURATOCIN is used to prevent loss of muscle tone in the uterus (womb) and heavy bleeding in women who have delivered a baby by caesarean section.

What it does:
In some women, after a caesarean, the womb doesn't contract (shrink) quickly enough. This makes it more likely that they'll bleed more than normal. DURATOCIN makes the womb contract and so reduces the risk of bleeding.

When it should not be used:
DURATOCIN must not be given until after the baby has been delivered.

Before giving you DURATOCIN, your doctor needs to know about any medical conditions you may have. You should also tell your doctor about any new symptoms that develop while you are being treated with DURATOCIN.

DURATOCIN must not be used:
- If you are pregnant.
- If you are allergic to carbetocin or any of the ingredients of DURATOCIN.
- If you have any serious heart problems.
- If you ever have had an allergic reaction to oxytocin (sometimes given as a drip or injection during or after labour).
- In children younger than 18 years of age.
- In elderly patients over 65 years of age.

What the medicinal ingredient is:
Carbetocin

What the nonmedicinal ingredients are:
Glacial acetic acid, sodium chloride, water for injection

What dosage forms it comes in:
Solution for injection, 100 mcg/mL

WARNINGS AND PRECAUTIONS

BEFORE you use DURATOCIN talk to your doctor or pharmacist if you have/are:
- Liver or kidney problems
- Pre-eclampsia (high blood pressure in pregnancy) or eclampsia (toxaemia of pregnancy).
- If you have problems with your heart or your circulation (such as high blood pressure).
- Epilepsy.
- If you get migraines.
- If you have asthma.
- If you are breastfeeding. DURATOCIN may pass into your breast milk.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about your other medication, including the ones that you bought without prescription and natural health products.

The following may interact with DURATOCIN:
- Heart medication.
- Medications that cause you to retain water and decrease salt levels.

PROPER USE OF THIS MEDICATION

Usual adult dose:
DURATOCIN is given as an intravenous injection immediately after your baby has been delivered by caesarean section under an epidural or spinal anaesthetic.

Overdose:
If you are accidentally given too much DURATOCIN, your womb may contract strongly and you could experience abdominal pain. You may also suffer drowsiness, listlessness and headache, caused by water building up in your body.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DURATOCIN can have side effects, but not everybody gets them. If you experience any other side effects not listed in this leaflet talk to your doctor.

Side effects may include:
- Nausea, vomiting.
- Stomach pain.
- Itching, flushing.
- Feeling of warmth.
- Headache.
- Shakiness.
- Dizziness.

- Metallic taste in the mouth.
- Sweating, chills.
- Back pain.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek 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:** fatigue, loss of energy, weakness.		√	
	Chest pain		√	
	Rapid heart beat		√	
	Breathlessness; trouble breathing	√		
	Anxiety	√		

This is not a complete list of side effects. For any unexpected effects while taking DURATOCIN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at refrigerated temperature 2 – 8°C. Do not freeze. Once ampoule has been opened, product must be used immediately.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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

MORE INFORMATION

If you want more information about 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 (www.healthcanada.gc.ca); or by calling Ferring Pharmaceuticals at 1-866-384-1314.

This leaflet was prepared by Ferring Pharmaceuticals

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