

AUSTRALIAN PI – DURATOCIN (CARBETOCIN) INJECTION

1 NAME OF THE MEDICINE

Carbetocin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DURATOCIN contains carbetocin 100 micrograms/mL.

Carbetocin is a white, fluffy lyophilized powder, soluble in water, ethanol, methanol and acetic acid. Carbetocin is insoluble in ether and petroleum ether.

For the full list of excipients, see [Section 6.1 List of Excipients](#)

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DURATOCIN is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarean section or vaginal delivery.

DURATOCIN must be administered after delivery of the infant.

4.2 DOSE AND METHOD OF ADMINISTRATION

DURATOCIN should be administered as a single dose only, when delivery of the infant has been completed. There are no efficacy or safety data on repeat doses of DURATOCIN following delivery of the infant. The use of carbetocin should occur in the context of other measures to prevent PPH and associated morbidity, including uterine massage, detection and correction of coagulopathies (refer to local clinical guidelines). Other uterotonic agents should be administered if additional treatment is required to reduce excessive postpartum bleeding and increase uterine tone.

Caesarean Section: A single dose of 100 micrograms (1 mL) of DURATOCIN (carbetocin injection) should be administered intravenously as a bolus injection, slowly over 1 minute after delivery of the infant. DURATOCIN can be administered either before or after delivery of the placenta.

Vaginal Delivery: A single dose of 100 micrograms (1 mL) of DURATOCIN (carbetocin injection) should be administered after delivery of the infant for the active management of the third stage of labour as an intramuscular injection or intravenously as a bolus injection slowly over 1 minute.

4.3 CONTRAINDICATIONS

Because of its long duration of action relative to oxytocin, uterine contractions produced by carbetocin cannot be stopped by simply discontinuing the medication. Therefore, carbetocin should not be administered prior to delivery of the infant for any reason, including elective or medical induction of labour. Inappropriate use of carbetocin during pregnancy could

theoretically mimic the symptoms of oxytocin overdose, including hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions, tumultuous labour, uterine rupture, cervical and vaginal lacerations, postpartum haemorrhage, utero-placental hypoperfusion and variable deceleration of foetal heart, foetal hypoxia, hypercapnia, or death.

Carbetocin should not be used in patients with a history of hypersensitivity to oxytocin or carbetocin.

Carbetocin should not be used in patients with cardiovascular disease, especially coronary artery disease, valvular heart disease, cardiomyopathy and heart failure.

Carbetocin is not intended for use in children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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.

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

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

There is limited data on the use of carbetocin under general anaesthesia, in women with a history of coagulopathy, placental abnormalities, and in women at high risk of postpartum haemorrhage, for example with parity greater than 4, with hypertension, following labour especially prolonged labour, or with general anaesthesia.

Carbetocin should be used cautiously in any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system.

Endocrine and Metabolism

There is limited data on the use of carbetocin in women with endocrine disorders (other than gestational diabetes).

Antidiuretic Effect

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

Neurologic

Carbetocin should be used cautiously in the presence of epilepsy and migraine.

Respiratory

Carbetocin should be used cautiously in the presence of asthma.

Use in hepatic impairment

There is limited data on the use of carbetocin in women with a history of liver disease.

Use in renal impairment

There is limited data on the use of carbetocin in women with a history of renal disease.

Use in the elderly

DURATOCIN is not recommended for use in elderly patients.

Paediatric use

Carbetocin is not intended for use in children (see [Section 4.3 Contraindications](#)).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific drug interactions have been reported with carbetocin. However, since carbetocin is closely related in structure to oxytocin, it is possible that some of the same drug interactions could occur. Severe hypertension has been reported when oxytocin was given 3-4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anaesthesia.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category C

Carbetocin induces uterine contraction and may cause premature or hypertonic labour. Therefore, DURATOCIN (carbetocin injection) use during pregnancy is contraindicated ([see Section 4.3 Contraindications](#)).

Use in lactation

Small amounts of carbetocin have been shown to cross over from plasma into the breast milk of nursing women who were given a 70 micrograms 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 not 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 micrograms carbetocin dose by the intramuscular route.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

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

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

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

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

Table.1

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

NS = Not Significant, * $p \leq 0.05$

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

Published Data

Caesarean section

The adverse event profile for patients receiving IV carbetocin was similar for patients undergoing either elective or emergency caesarean sections.

The adverse events experienced by women given carbetocin in comparison to oxytocin are similar, and include nausea, vomiting, flushing, headache, feeling of warmth, tremors, abdominal/back pain, metallic taste, sweating, and shortness of breath, tachycardia, hypotension, pruritus, chills and blurred vision.

Vaginal Delivery

The adverse event profile of carbetocin observed in trials with vaginal delivery is similar to that established in the clinical trials and during post-marketing elective caesarean section and is shown to be comparable to oxytocin infusion.

Carbetocin was also associated with a significantly improved tolerability profile in comparison to Syntometrine, with reduced incidence in gastrointestinal and cardiovascular adverse effects being reported.

Post marketing adverse effects

No new signals or potential safety concerns have been seen in the post-market reporting.

There have been reports of hypersensitivity, including anaphylactic reactions and shock, cardiac arrhythmias, and cardiac arrest associated with the use of carbetocin IV in patients undergoing caesarean section.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage of carbetocin can be expected to produce enhanced pharmacological effects. Therefore, when carbetocin is administered postpartum, overdosage may be associated with uterine hyperactivity and pain. Treatment consists of symptomatic and supportive management.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

DURATOCIN (carbetocin injection) is a long-acting synthetic octapeptide 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 anaesthesia, to prevent uterine atony and postpartum haemorrhage.

The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin, another posterior pituitary hormone. In in vitro studies, carbetocin was shown to bind to the oxytocin receptor with similar affinity as the natural peptide. Carbetocin elicited similar uteronic and galactogogic effects to oxytocin in animals and in vitro. Carbetocin was less potent than oxytocin, but its action was more prolonged. 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 in around 90% of patients. The total duration of action of a single intravenous injection of carbetocin on uterine activity is about one hour, and approximately 2 hours when given as an intramuscular injection suggesting that carbetocin may act long enough to prevent postpartum haemorrhage in the immediate postpartum period. The time course for the onset and duration of action of carbetocin reflects its pharmacokinetic profile. In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions. The prolonged effect can in part be attributed to the longer half-life of carbetocin.

Carbetocin, when administered immediately postpartum as a single intravenous bolus injection of 100 micrograms to women delivered by caesarean section under epidural or spinal anaesthesia, was found to be significantly more effective than placebo or oxytocin, as evidenced by the need for additional oxytocin therapy in the operating room.

Carbetocin administration also appears to enhance uterine involution in the early postpartum period, as evidenced by the repeated measurement of the uterine fundus.

Clinical trials

Elective Caesarean

Two large double-blind trials were conducted using carbetocin.

A randomised parallel group, double-blind, placebo-controlled multicentre clinical trial to evaluate the safety and efficacy of a single dose of carbetocin to control uterine bleeding after elective caesarean section.			
Inclusion Criteria:			
Women undergoing elective caesarean section under epidural anaesthesia, without a history of heart disease, hypertension, cardiac arrhythmia or evidence of liver, renal or endocrine disease, who gave informed consent.			
Primary Efficacy variable:			
The incidence of further oxytocic therapy following test drug administration.			
Treatment Group	No. Patients Randomised (Evaluable)	Efficacy Results	Safety Results
		Patients requiring further oxytocic therapy	Serious Adverse Events
Carbetocin 100 micrograms (single IV injection)	64 (62)	8	0

Placebo (IV injection)	58 (57)	41	0
Summary:			
<p>When given as a single bolus intravenous dose of 100 micrograms after delivery of the infant by elective caesarean section under epidural, carbetocin was found to be significantly more effective than placebo in preventing the clinician assessed need for additional oxytocin therapy with only 13% of patients requiring intervention with further oxytocic therapy compared to 72% of patients in the placebo group ($p = 0.001$). There were no serious or unexpected adverse events and no patient dropped out of the study due to safety concerns. There was an increased incidence of the following adverse events in the carbetocin group vs the placebo group; Flushing (34% vs 10%, $p = 0.002$), abdominal pain (27% vs 10%, $p = 0.02$), pruritus (48% vs 31%, $p = 0.05$). The overall incidence of nausea during the study was not significantly different between the groups but was higher in the carbetocin group whilst the patient was in the operating room (36% vs 17%, $p < 0.05$). There was no significant difference between the groups for other adverse events reported.</p>			

A randomised parallel group, double-blind, double-dummy, multicentre clinical trial to evaluate the safety and efficacy of a single dose of carbetocin vs 8 hours oxytocin infusion after caesarean section in maintaining adequate uterine contraction after caesarean section.			
Inclusion Criteria:			
Healthy women undergoing elective caesarean section under epidural anaesthesia, who gave written informed consent.			
Primary Efficacy variable:			
The incidence of further oxytocic therapy following test drug administration.			
Treatment Group	No. Patients Randomised (Evaluable)	Efficacy Results	Safety Results
		Patients requiring further oxytocic therapy	Serious Adverse Events
Carbetocin 100 micrograms (single IV injection)	348 (317)	15	4
Oxytocin: 5IU bolus + 8 hours 20IU IV infusion	346 (318)	32	4
Summary:			
<p>When given as a single intravenous dose of 100 micrograms, carbetocin was associated with lower incidence of "need for additional oxytocic intervention" when compared to an 8 hour oxytocin infusion: such intervention occurred in 15 (5%) of patients receiving carbetocin compared to 32 (10%) of patients administered oxytocin. Odds of intervention were 2.0 times lower for carbetocin vs oxytocin ($p = 0.031$).</p> <p>There were no significant differences in the frequency of adverse events between treatment groups. Four serious or unexpected adverse events occurred in each group.</p>			

The dose-response relationship of carbetocin and uterine contraction was evaluated in a clinical trial involving 18 patients. Here the intravenous dose of carbetocin required to produce sustained tetanic contraction after caesarean section was determined. Although 11 of 12 women responded with adequate uterine contraction to total doses of 30-90 micrograms carbetocin, none was considered to have adequate response to a starting dose less than 60 micrograms. All 6 women given 100 micrograms had an adequate uterine contraction although one did not satisfy the response criteria of the study. A single 100 micrograms intravenous injection was therefore selected for clinical use.

In a trial in 57 women undergoing elective caesarean section under epidural anaesthesia, carbetocin was compared to oxytocin for its ability to reduce intraoperative blood loss. A single 100 micrograms injection of carbetocin was compared to oxytocin (total dose 32.5IU).

It was found 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 micrograms intravenous 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.

Emergency Caesarean

Three randomised, double blind clinical studies identified in the literature (Whigham et al 2016, El Behery et al 2016, Razali et al 2016) investigated the safety and efficacy of carbetocin compared to oxytocin in the prevention of postpartum haemorrhage in patients undergoing emergency caesarean delivery. A total of 849 patients were enrolled, with 425 receiving 100 micrograms of carbetocin by slow bolus intravenous injection, and 424 receiving between 5 and 20 IU of oxytocin via intravenous infusion. In these studies, administration of carbetocin was associated with comparable blood loss and incidence of postpartum haemorrhage and in two of these studies a statistically significant reduction in the need for additional uterotonics compared to patients receiving oxytocin. No significant differences in tolerability between the treatment groups were observed. These results are broadly consistent with the clinical trial data obtained in patients receiving carbetocin following delivery by elective caesarean section.

Vaginal Delivery

Seven randomised, double blind, placebo or active controlled studies were identified in the literature that investigated the safety and efficacy of carbetocin in woman delivering vaginally. Two studies (Maged et al 2016, Boucher et al 2004) containing a total of 360 patients, compared the performance of a carbetocin 100 microgram intramuscular injection to that of oxytocin 5 IU delivered either intramuscularly or 10 IU via intravenous infusion in the prevention of postpartum haemorrhage. Similar to the data reported following delivery via caesarean section, carbetocin was associated with a comparable incidence of postpartum haemorrhage and a reduced need for uterine massage and additional uterotonic treatment, versus oxytocin, with one study additionally reporting a reduction in blood loss. No differences in tolerability were reported. Five clinical studies (Samimi et al 2013, Askar et al 2011, Su et al 2009, Nirmala et al 2009, Leung et al 2006) in 1230 patients, compared the safety and efficacy of 100 micrograms intramuscular carbetocin (615 patients) with intramuscular administration of Syntometrine® (oxytocin 5IU+ 0.5¹ mg ergometrine, 615 patients). In these studies, the efficacy of carbetocin was reported to be at least as good as the combination of oxytocin and ergometrine, with the majority of studies also recording a statistically significant reduction in blood loss and fall in haemoglobin.

Meta-analyses of Published Studies

The performance of carbetocin in the prevention of postpartum haemorrhage following caesarean and vaginal delivery was further assessed in two independent meta analyses (Su et al 2012, Jin et al

¹ One study utilised a dose of 0.2 mg ergometrine

2015). These meta-analyses concluded that carbetocin was associated with a statistically significant benefit over oxytocin following caesarean delivery (mixed elective and emergency population). There was a 32% reduction in the need for additional uterotonic agents in the carbetocin group relative to the oxytocin group (RR= 0.68; [95% CI: 0.55, 0.84])² and a 46% reduction in the need for uterine massage (RR= 0.54; [95% CI: 0.31, 0.96])². Following vaginal delivery, carbetocin was associated with a statistically significant reduction in the need for uterine massage versus oxytocin (RR= 0.70; [95% CI 0.51, 0.94])³. When carbetocin was compared to Syntometrine[®], there was a statistically significant reduction in blood loss (Δ = -48.84 mL; [95% CI: -94.82, -2.85]) and fall in haemoglobin (mean difference -0.10; [95% CI -0.17, -0.03]) as well as a significant reduction in gastrointestinal (e.g. nausea (RR = 0.24; [95% CI 0.15, 0.40]) and vomiting (RR = 0.21; [95% CI 0.11, 0.39]) and cardiovascular (e.g. hypertension (RR = 0.07; [95% CI 0.01, 0.49]) side effects³.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of carbetocin were evaluated in 25 non-pregnant healthy women after administration of 400 microgram and 800 microgram IV or IM (Study CLN 6.3.1). Clearance and the volume of distribution do not appear to be dose dependent, whereas C_{max} and $AUC_{0-\infty}$ show dose proportionality indicating linear pharmacokinetics.

Absorption

Following intramuscular administration of carbetocin, the peak concentration of carbetocin was achieved within 20-30 minutes and bioavailability was approximately 80%.

Distribution

The IV pharmacokinetics follows a 2 compartment model with a distribution half-life of 5.5 ± 1.6 minutes after a 400 micrograms intravenous dose. Similar values were obtained after administration of the 800 micrograms dose.

Metabolism

Approximately 0.7% of the carbetocin dose is eliminated in the unchanged form by the kidney, indicating that carbetocin, like oxytocin, is eliminated primarily by non-renal routes.

Excretion

The clearance of carbetocin was 0.55-0.60 L/min and the terminal elimination half-life of carbetocin was 41 ± 11.9 minutes after a 400 micrograms intravenous dose. Similar values were obtained after administration of the 800 micrograms dose..

² Jin *et al*, 2016. Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. *The Journal of Maternal-Fetal & Neonatal Medicine*, 29(3), pp.400-407.

³ Su *et al*, 2012. Carbetocin for preventing postpartum haemorrhage. *Cochrane Database Syst Rev*, 4.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Methionine 1mg, succinic acid 1.19 mg, mannitol 47.0 mg, sodium hydroxide 2 M to pH 5.5 and water for injections to 1 mL.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Once the vial has been opened, the product should be used immediately.

6.5 NATURE AND CONTENTS OF CONTAINER

DURATOCIN is a ready-for-use solution containing 100 micrograms carbetocin in a 1 mL clear glass vial with a bromobutyl rubber stopper and an aluminium crimp cap with a tear-off over cap. Each pack contains 5 vials.

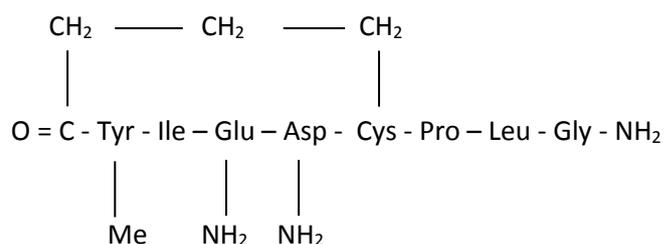
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Only particle free, clear solutions should be used.

Any unused product, or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular Formula: C₄₅H₆₉N₁₁O₁₂S **Molecular Weight:** 988.1

CAS number: 37025-55-1

Synonyms:

2,1-Desamino-4, 1-desthio-O4, 2-Methyl 1 [1-homocysteine] oxytocin 1-desamino-1-monocarba-2-(0-methyl)-tyrosine-oxytocin(2-0-methyltyrosine)-1-deaminocarba-1-oxytocin(6,1-β deaminocystathionine, 2-0-methyl-tyrosine)-oxytocin [Tyr(Me)²]-desamino-1-carba-oxytocin

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

9 DATE OF FIRST APPROVAL

17 April 2015

10 DATE OF REVISION

16 March 2018

For the most current approved PI, please refer to <https://www.ebs.tga.gov.au/> or <http://www.ferring.com.au/>

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Extension of indications to include use following emergency caesarean section and vaginal delivery.
4.2	Dosing information added for IM administration following vaginal delivery.
4.3	Contraindication relating to cardiovascular disease has been clarified.
4.4	Precautions updated in line with new indications.
4.8	Addition of sub-sections on caesarean section, vaginal delivery and post-marketing adverse effects.
5.1	Addition of clinical trials section for emergency caesarean and vaginal delivery.
5.2	Addition of pharmacokinetics following IM administration.
6.3	Shelf life extended to 3 years