Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Carbetocin

Proprietary Product Name: Duratocin

Sponsor: Ferring Pharmaceuticals Pty Ltd

First round report: 15 May 2017

Second round report: 23 October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words (Information redacted), where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi> .

Contents

List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
AUC	Area under the curve
BP	Blood pressure
bpm	Beats per minute
CER	Clinical evaluation report
CI	Confidence interval
CS	Caesarean section
FDA	Food and Drug Administration
h	Hour(s)
Hb	Haemoglobin
Hct	Haematocrit
IM	Intramuscular(ly)
ITT	Intent-to-Treat
LBS	Literature based submission
MHRA	Medicines and Health Care products Regulatory Agency
µg	Microgram(s)
mg	Milligram(s)
min	Minute(s)
PPF	Pre-submission planning form
PPH	Postpartum haemorrhage
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSUR	Periodic safety update report
RANZCOG	Royal Australian College of Obstetricians and Gynaecologists
RCOG	Royal College of Obstetricians and Gynaecologists

Abbreviation	Meaning
SAE	Serious adverse events
SD	Standard deviation
WHO	World Health Organisation

1. Submission details

1.1. Identifying information

Submission number	PM-2016-04273-1-5
Sponsor	Ferring Pharmaceuticals Pty Ltd
Trade name	Duratocin
Active substance	Carbetocin

1.2. Submission type

This is Category 1 (Type C) application to extend the indications of carbetocin.

1.3. Drug class and therapeutic indication

The approved indication is:

> *Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by elective Caesarean section under epidural or spinal anaesthesia. Duratocin is an oxytocic that reduces the need for additional oxytocics. Duratocin has not been studied in women at high risk of postpartum haemorrhage, for example with parity greater than 4, with hypertension, following labour especially prolonged labour, or with general anaesthesia.*

The proposed indication is:

> *Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery. Duratocin is an oxytocic that reduces the need for additional oxytocics.*

1.4. Dosage forms and strengths

The registered dosage strength of carbetocin is 100 µg/mL and the dosage form is an injection vial. No changes to the current dosage form or dosage strength are being proposed.

1.5. Dosage and administration

The approved carbetocin dosage:

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

The proposed carbetocin dosage is:

> *Caesarean: A single dose of 100 micrograms (1 mL) of Duratocin (carbetocin injection) should be administered intravenously as a bolus injection, slowly over 1 minute.*
>
> *Vaginal delivery: A single dose of 100 micrograms (1 mL) of Duratocin (carbetocin injection) should be administered as an intramuscular injection or intravenously as a bolus injection, slowly over 1 minute*.

Duratocin can be administered either before or after delivery of the placenta. Duratocin is to be used as a single dose only.

1.6. Proposed changes to the product documentation

The sponsor proposes amendments to the *Pharmacology*, *Clinical Trials, Indications*, *Precautions*, and *Dosage and Administration* sections of the Duratocin PI.

Comments: Recommendations and questions for the sponsor relating to the amended PI are provided later in this clinical evaluation report (CER).

2. Background

2.1. Information on the condition being treated

Postpartum haemorrhage (PPH) remains a major cause of both maternal mortality and morbidity within Australia and internationally. PPH occurs commonly, with an incidence in Australia estimated to be between 5% and 15% (RANZCOG; NSW Health Procedures ((PD2010_064))).

PPH has been traditionally defined as blood loss of 500 mL or more during or after childbirth, and severe PPH as blood loss of 1000 mL or more or any amount or blood loss that causes haemodynamic compromise. PPH has been further classified as primary, which occurs within the first 24 h of birth, and secondary, which occurs between 24 h and 6 weeks postpartum (RANZCOG; NSW Health Procedures ((PD2010_064)).)

While a large number of risk-factors for PPH have been identified most cases of PPH have no identifiable risk-factors (RANZCOG; NSW Health Procedures ((PD2010_064))). Caesarean section has a greater risk of significant blood loss compared to vaginal delivery. Risk-factors (broad categories) for PPH include abnormalities of uterine contraction (70%), genital tract trauma (20%), retained placental tissue (10%), and abnormalities of coagulation (1%) (NSW Health Procedures ((PD2010_064))).

2.2. Current treatment options

2.2.1. Guidelines

In the Clinical Overview, the sponsor refers to numerous international and national guidelines supporting the active management of the third stage of labour, which includes the use of uterotonic agents, to reduce the incidence of PPH following vaginal delivery. In addition, the sponsor notes that uterotonic agents are also recommended following CS to encourage uterine contraction.

The sponsor comments that the treatment approach to the prevention of PPH in Australia is generally aligned with international guidelines recommending the use of oxytocin following vaginal delivery and CS. The sponsor notes that in Australian states with specific guidelines relating to the prevention of PPH the standard approach is to administer oxytocin (5-10 IU) by IM, slow bolus IV injection, or by IV infusion. The sponsor comments that oxytocin is most commonly used by the IV route following CS, and that there has been a switch in the preferred administration method from bolus IV injection to IV infusion. The sponsor notes that Syntometrine (5 IU oxytocin/0.5 mg) is also recommended for the active management of the third stage of labour following vaginal delivery, but comments that in recognition of the issues associated with the use of this drug that international guidelines recommend the use of oxytocin alone during delivery by CS in preference to Syntometrine. The sponsor comments that

prostaglandins are also used in the prevention of PPH, but that treatment guidelines generally recommend the use of oxytocic agents over prostaglandins due to their better benefit-risk balance profile.

Comment: The sponsor's summary of the pharmacological management of the third stage of labour following vaginal delivery to prevent PPH and following CS to increase uterine tone is satisfactory. The following additional information has been prepared by the evaluator.

2.2.1.1. Australian guidelines

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guideline on the Management of Post Partum Haemorrhage (PPH) (C-Obs 43) recommends that '*prophylactic oxytocics should be used for the management of the third stage of labour, whether following vaginal or caesarean birth, as they reduce the risk of PPH by 50%'*. Oxytocin is the drug of first choice for the active management of the third stage of labour following vaginal delivery and for CS, with the TGA recommended doses being 5-10 IU IM or 5 IU IV by slow injection following vaginal delivery, and 5 IU by slow bolus IV injection or IV infusion for CS. Oxytocin is recommended as the drug of first choice following vaginal delivery and for CS at doses consistent with the TGA approved doses in Australian guidelines for the prevention of PPH, including the RANZCOG, NSW Department of Health, South Australian Department of Health, Queensland Department of Health and the Royal Women's Hospital, Melbourne, Victoria.[1] The main advantages of oxytocin over other uterotonic agents used for the active management of the third stage of labour are stated to be its rapid onset of action and lack of side effects such as elevated blood pressure and uterine tetanic contractions.

In Australia, Syntometrine (5 IU oxytocin/0.5 mg ergometrine maleate per 1 mL) administered by IM injection is also available for the active management of the third stage of labour following vaginal delivery. The TGA approved dose of Syntometrine for the active management of the third stage of labour is 1 mL IM following delivery of the anterior shoulder or immediately after delivery of the infant. In practice, Syntometrine is generally used as the second line agent after oxytocin for the prevention of PPH following vaginal delivery. However, it may be considered for women at higher risk of PPH following vaginal delivery, in the absence of hypertension (RHW (2012)). Syntometrine is reported to be associated with a small but statistically significant reduction in the risk of PPH compared to oxytocin where blood loss is less than 1000 mL (NSW Health Procedures (PD2010_064)). However, this advantage has to be weighed against the adverse effects of nausea, vomiting, abdominal pain, headache, dizziness, rash, hypertension, cardiac arrhythmias and chest pain associated with the use of Syntometrine.

The Queensland Maternity and Neonatal Clinical Guideline: PPH (2012) refers to carbetocin and states that '*high-level evidence indicates that prophylactic Carbetocin is no more effective then Oxytocin in preventing PPH greater than 500 mL or 1000 mL'*. However, the guideline recommends that in elective CS consideration could be given to substituting oxytocin infusion with carbetocin 100 µg IV in 1 mL, given slowly after the birth of the baby. In addition, the South Australian Maternal and Neonatal Community of Practice Clinical Guideline (SA (2016)) refers to carbetocin and notes that it is indicated to prevent uterine atony and PPH at elective CS. The RANZCOG guideline (C-Obs 43), NSW Health Procedures Document (PD2010-064), and RHW (2012) guideline do not refer to the use of carbetocin for the prevention of PPH.

2.2.1.2. Overseas guidelines

Relevant information from UK and Canadian guidelines are briefly summarised below, as both of these guidelines comment on the use of carbetocin. In addition, clinical practice in these two countries is comparable to clinical practice in Australia.

[1] RANZCOG; NSW Health Procedures (PD2010_064); Queensland (2012); RWH (2012); SA (2016)

The Royal College of Obstetricians and Gynaecologists (RCOG) guideline on the Prevention and Management of Postpartum Haemorrhage (Green-top Guideline No. 52), states that for women without risk factors for PPH delivering vaginally, oxytocin 5 IU or 10 IU is the agent of choice for prophylaxis in the third stage of labour. The guidelines also state that for women delivering by CS, oxytocin (5 IU by slow IV injection) should be used to encourage contraction of the uterus and to decrease blood loss. The guidelines indicate that Syntometrine may be used in the absence of hypertension (for instance, antenatal low haemoglobin) as it reduces the risk of minor PPH but increases vomiting. The guideline comments that misoprostol is not as effective as oxytocin but it may be used when the latter is not available, such as the home-birth setting. However, the NSW Health Procedure document (PD2010_064) states that misoprostol is not currently recommended for routine control or prevention of PPH.

The *RGOG Green-top Guideline No. 52 was dated May 2009*, with minor revisions November 2009 and April 2011. The guideline refers to carbetocin and notes that this '*longer-acting oxytocin derivative …. is licensed in the UK specifically for the indication of prevention of PPH in the context of caesarean delivery*'. The guideline states that randomised trials suggest that a single dose of carbetocin 100 µg is at least as effective as oxytocin by infusion (Boucher et al., 1999; Dansereau et al., 1999), but notes that '*there are no comparisons of carbetocin with the oxytocin regimen recommended in the (Green-top No.52) guideline*'. The guideline also comments that trials have compared carbetocin to Syntometrine (Leung et al., 2009) by IM injection and to oxytocin by IV infusion (Boucher et al., 2004) in the context of vaginal delivery and *'(a)gain, carbetocin appeared to be at least as effective as the more conventional regimen*'. Overall, the guideline concluded that carbetocin *'is not currently recommended for routine use because of the paucity of data and its high price'*.

The *Society of Obstetricians and Gynecologists of Canada (SOGC)* Clinical Practice Guidelines No. 235 of October 2009 relating to the prevention of PPH (Leduc et al., 2010) states that oxytocin (10 IU) administered IM after delivery of the anterior shoulder is the preferred medication and route for the prevention of PPH in low risk vaginal deliveries, with oxytocin 20 to 40 IU administered by infusion being recommended an acceptable alternative. The guidelines state that while oxytocin 5-10 IU given as an IV bolus can be used for the prevention of PPH after vaginal birth, it is '*not recommended at this time'* for elective CS. The guideline states that carbetocin 100 µg given as an IV bolus over 1 minute should be used instead of continuous oxytocin infusion in elective CS for the prevention of PPH and to decrease the need for therapeutic uterotonics. In addition, the guidelines recommend the use of carbetocin 100 µg IM for women with 1 risk-factor for PPH as it decreases the need for uterine massage to prevent PPH when compared to continuous infusion of oxytocin. The recommendations relating to the use of carbetocin probably reflects the fact that Canada was the first country in which the drug was approved (IBD 24 June 1997), which has resulted in greater clinical experience with the drug in that country than in other jurisdictions. The guideline states that ergonovine can be used for prevention of PPH but may be considered second choice to oxytocin owing to the greater risk of maternal adverse effects and the need for manual removal. The drug is also contraindicated in women with hypertension. The guideline does not refer to the use of Syntometrine for the prevention of PPH as the drug is not registered in Canada.

In a relatively recent review of international guidelines for the prevention and treatment of PPH it is stated that the use of carbetocin is only addressed by international guidelines from the UK (RCOG), Canadian (SCOG) and WHO (Bohlmann and Rath, 2014). With regard to carbetocin, the WHO (2012) guidelines state that oxytocin (IV or IM) is the recommended uterotonic drug for the prevention of PPH in CS, and remark that carbetocin is associated with reduction in the use of additional uterotonic agents but with no difference in the occurrence of major PPH. The WHO guidelines comment that the remark relating to carbetocin and CS 'is equally applicable to vaginal deliveries'. The WHO guidelines also remark that the use of carbetocin is more expensive than oxytocin.

The *Bohlmann and Rath (2014)* review notes that Syntometrine is currently approved for use in less than 10 countries, which include Australia, the UK and New Zealand.

2.3. Clinical rationale

The Clinical Overview stated that there is a '*medical need for a safe and effective prophylactic uterotonic agent (such as carbetocin) for reducing the risk of PPH in a broad postpartum population, one with a rapid onset and longer duration of action than oxytocin, without side-effects that are common to ergometrine products, that can be easily administered intravenously or intramuscularly as a single dose over a short duration. While carbetocin, a long-acting oxytocic (Duratocin) has been available in Australia since 2004, its use has been confined to IV administration following delivery by elective caesarean section. The expansion of the target population to include prevention of uterine atony and thereby PPH in patients following vaginal delivery and emergency caesarean section, would significantly improve the therapeutic options available to obstetricians, and would also improve patient comfort*'.

Comment: The sponsor's clinical rationale is acceptable.

2.4. Formulation

No change from the currently registered product.

2.5. Guidance

The sponsor states that a pre-submission was held with the TGA on 9 December 2015 to discuss submission of a literature based submission (LBS) to extend the indications of carbetocin.

2.6. Evaluator's commentary on the background information

The background information including the clinical rationale provided by the sponsor is satisfactory. However, it is noted that the approved use of carbetocin in overseas countries appears to be mainly limited to women undergoing elective CS under regional anaesthesia. Approval of the additional use of carbetocin in women following vaginal delivery, undergoing emergency CS, and undergoing CS under general anaesthesia appears to be limited to a few overseas countries. Of note, the use of carbetocin for the broad extensions of indication being sought by the sponsor for approval in Australia does not appear to be approved in overseas jurisdictions of particular interest to Australia (that is, EU, USA, Canada, Switzerland, New Zealand and Singapore). There was no information in the background information on whether the carbetocin formulation used in the submitted publications is the same as that currently registered in Australia. The sponsor is requested to comment on this matter (see Questions, Section 12 of this CER). The TGA has granted the sponsor a conditional waiver from the requirement to provide a RMP. However, for the reasons discussed later in this CER it is recommended that the sponsor provide an Australian specific RMP (Section 11.3 of this CER).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier provided a literature based submission to support the proposed extension of indications of carbetocin. The sponsor provided a detailed summary of the search strategy used

to identify the relevant studies. The search strategy was undertaken in consultation with the TGA. The search strategy is considered to be satisfactory.

3.1.1. Clinical data

- 13 publications supporting the extensions to the indication, including 7 relating to vaginal delivery, 3 related to emergency caesarean section, and 3 related to women at high risk of PPH.
- 2 published meta-analyses and systematic reviews relating to the use of carbetocin to prevent postpartum haemorrhage.
- 2 Periodic Safety Update Reports (PSURs) covering the periods 1 July 2015 to 30 June 2015 (13th PSUR) and 1 July 2015 to 30 June 2016 (14th PSUR).
- Tabular listing of the submitted studies.
- Literature references.

3.2. Paediatric data

The sponsor stated that carbetocin is not intended for use in patients under the age of 11 years on the grounds that the indications of the product are not relevant in this age group. The sponsor stated that although adolescents (12-17 years) may become pregnant and give birth there is insufficient safety-benefit information to support studies on carbetocin in this age group. The sponsor stated that it is not submitting data to the EU to support use in a paediatric population and that it does not have an agreed Paediatric Investigation Plan (PIP) in Europe. The sponsor stated that it is not submitting paediatric data to the USA FDA, does not hold waivers from the FDA relating to submission of such data, and has not received a request from the FDA to submit such data. It is noted that the product is not approved in the USA

Comment: The sponsor's rationale for not submitting paediatric data is acceptable.

3.3. Good clinical practice

The individual studies provided information on ethical clearance obtained for the study centres.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier is satisfactory. The content of the dossier appears to reflect that agreed to by the TGA and the sponsor for this literature based submission.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The dossier included no new PK studies. The Clinical Overview provided summary PK information supporting the proposed IM route of administration for carbetocin for vaginal delivery based on previously submitted and evaluated PK studies. This information is reviewed below.

4.2. Previously submitted studies providing PK information relating to IM administration

4.2.1. Study CLN 6.3.1

The Clinical Overview provided PK information from a previously submitted Study CLN 6.3.1) supporting the extension of the route of administration to IM for vaginal delivery. This was a PK and dose tolerability study in 25 healthy, non-pregnant female volunteers. The pharmacokinetics of carbetocin were assessed following single IV bolus doses of 20, 100, 200, 400, and 800 µg and single IM doses of 400 and 800 µg. The results of the study have been published (Sweeney et al., 1990) and a copy of the publication was included in the dossier. The published report indicated that the study was undertaken in Canada. The PK results from this study are summarised below in Table 1.

Table 1: PK parameters following carbetocin 400 µg (IV and IM) and 800 µg (IV and IM), study CLN 6.3.1

		Intravenous Injection		Intramuscular Injection	
		400 µg IV N = 6	800 µg IV N = 6	400 µg IM N = 6	800 µg IM N = 6
AUC $_{(0-\infty)}$	Mean ± SD	749.2 ± 131.0	1,370.4 ± 214.9	553.5 ± 132.9	1,107.4 ± 56.5
µg*min/ L	Min-max	539.5-916.9	1,148.8-1,733	403.3-733.7	1,028-1,181.4
C_{max}	Mean ± SD	-	-	6.35 ± 1.39	12.04 ± 1.88
(µg/L)	Min-max			4.1 - 8.1	9.4 - 14.7
T_{max}	Mean ± SD	-	-	20.0 ± 0	28.0 ± 11.0
(min)	Min-max			20 - 20	20 - 40
F	Mean ± SD	-	-	76.0 ± 10.8	83.4 ± 17.6
(%)	Min-max			60.8 - 84.8	59.3 - 102.8

AUC = area under the curve; C_{max} = peak concentration; T_{max} = time to peak concentration; F = percent bioavailability of IM carbetocin.

The pharmacokinetics of carbetocin 100 µg IM have not been investigated. However, the sponsor states that carbetocin doses up to 800 µg IM were generally well tolerated. In addition, the sponsor states that data from Study CLN 6.3.1 suggest dose proportionality for IV as well as for IM administration. Following IM administration of carbetocin 400 and 800 µg, peak concentration (C_{max}) was achieved within 20 to 30 minutes and the absolute bioavailability was approximately 80%.

Comment: There are no PK data relating to the proposed 100 µg IM dose of carbetocin. The sponsor is requested to provide a formal justification for not submitting an absolute bioavailability study for the 100 µg IM dose. The published report (Sweeney et al., 1990) states that increases in heart rate were statistically significant ($p < 0.05$) at 5 minutes after administration of the 400 and 800 µg IM doses, while a significant

decrease in diastolic blood pressure was observed 5 minutes after the 800 µg IM dose. However, the 400 and 800 µg IM dose are 4-fold and 8-fold higher, respectively, than the proposed dose of 100 µg IM.

4.2.2. Study CLN 6.3.7

The Clinical Overview refers to Study CLN 6.3.7 which provided information on transfer of carbetocin from plasma to breast milk following IM administration of carbetocin 70 µg to 5 healthy nursing subjects 6 to 14 weeks postpartum. Information from this study is provided in the currently approved Duratocin PI under *Use in Lactation*.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

The dossier included no new PD studies. The Clinical Overview provided summary PD information supporting the IM route of administration for carbetocin in women delivering vaginally from previously submitted and evaluated PD studies. This information is summarised below.

5.1.1. Studies CLN 6.3.4 (IM) and CLN 6.3.3 (IV)

The original registration application included two studies (CLN 6.3.4 (IM); CLN 6.3.3 (IV)) conducted in 40 postpartum women at 14-22 h following vaginal delivery in order to investigate the effect of several doses of carbetocin on PD endpoints. A total of 23 women were given a single IM injection (Study CLN 6.3.4) and 17 women were given one or more injections through an IV line (Study CLN 6.3.3) until a tetanic uterine contraction occurred. Parameters for evaluation were patient self-reporting and tocographic records. The results for the analysable records are shown below in Table 2.

Table 2: Tocographic activity data (mean ± SD) from Studies CLN 6.3.4 (IM) and CLN 6.3.3 (IV)

Study Drug	Time of onset	Duration of tetany	Total duration
Carbetocin IV	1.2 ± 0.5 minutes	6.9 ± 2.1 minutes	60 ± 18 minutes
Carbetocin IM	1.9 ± 0.6 minutes	11.3 ± 3.0 minutes	119 ± 69 minutes

The Clinical Overview refers to a publication by Hunter et al (1992) which states that carbetocin administered by IM injection has twice the mean (± SD) duration of action of carbetocin administered by IV injection (119 ± 69 versus 60 ± 18 minutes, respectively). However, the Clinical Overview comments that the study did not take into consideration the difference in dose level between IM and IV administration when making the comparison between the two routes of administration. The Clinical Overview notes that the comparison was made between a mean carbetocin dose of 49 µg IM in 8 women (Study CLN 6.3.4) and a mean carbetocin dose of 15 µg IV in 6 women (Study CLN 6.3.3). Therefore, it is not evident that the mode of administration influences the duration of action. The Clinical Overview concludes that a rapid onset of action for the IM route of administration has been shown in Study CLN 6.3.4 (that is, mean ± SD of 1.9 ± 0.6 minutes), which does not represent a delay compared to the IV route of administration observed in Study CLN 6.3.3 (that is, mean ± SD of 1.2 ± 0.5 minutes). Carbetocin is associated with a long duration of action following both the IM and IV routes of

administration. On this basis, the sponsor proposes both IM and IV routes of administration for carbetocin after vaginal delivery.

Comment: The comments made in the Clinical Overview relating to the results for Studies CLN 6.3.3 and CLN 6.3.4 are reasonable, but the mean IM and IV doses used in these studies are notably lower than the 100 µg dose being proposed for IM and IV administration following vaginal delivery. Therefore, it possible that carbetocin 100 µg administered by the IM and IV routes will have longer durations of action based on tocographic activity than those observed in the two studies.

6. Dosage selection for the pivotal studies

The Clinical Overview stated that the primary efficacy parameter for the dose response Studies CLN 6.3.4 and CLN 6.3.3 was the occurrence of tetanic uterine contraction after drug administration. In Study CLN 6.3.4, carbetocin was administered IM to groups of 3-5 women who received doses of 10, 20, 30, 40, 60 and 70 µg. All 23 women treated with carbetocin IM at doses of 10-70 µg experienced sustained uterine contractions at 14-37 h after vaginal delivery. As no difference in uterine contraction in doses was observed, no optimum dose of carbetocin IM was identified. In Study CLN 6.3.3, the effect of carbetocin dose titration on tetanic uterine contraction was assessed following IV administration. In this study, 13 out of the 17 participating women experienced a tetanic uterine contraction after carbetocin IV at doses of 8 µg (n = 2), 10 µg (n = 7), 20 µg (n = 1), 30 µg (n = 1), 50 µg (n = 1) and 100 µg (n = 1). The Clinical Overview comments that the dose titration data from the IM and IV studies have limited relevance to the selection of the proposed carbetocin dose of 100 µg IM or IV following vaginal delivery.

The Clinical Overview states that support for the 100 µg IM dose selected for the 'pivotal Phase III study' in women following vaginal delivery (Boucher et al., 2004) was partly based on the good results from the approved IV dose of carbetocin for elective CS, and partly on the investigator-driven ascending IM dose tolerability study (van Dongen et al., 1998). The objective of *van Dongen et al (1998)* was to determine the maximum tolerated dose (MTD) of carbetocin administered by the IM route for use immediately postpartum. Carbetocin was administered IM to 45 healthy women who delivered vaginally at term. Dosage groups of 15, 30, 50, 75, 125, 150, 175 µg IM were assigned to blocks of 3 women, while 100 µg IM was assigned to 6 women and 200 µg IM to 18 women. MTD was defined as the dose expected to produce dose-limiting adverse events (DLAEs) in 20% of the population. DLAEs did not appear until the 200 µg was reached and based on these findings the MTD was estimated to be 200 µg. As maximum blood loss was greatest at the upper and lower dose levels and lowest in the 70-125 µg dose range, and no drug related serious adverse events were demonstrated until the 125 µg dose, carbetocin 100 µg IM was selected as the optimal therapeutic dose for the 'pivotal Phase III study' (Boucher et al., 2004).

Comment: The dose tolerability study (van Dongen et al., 1998) was undertaken in the Netherlands. The primary goal of the study was to determine the MTD of carbetocin administered by the IM route to women undergoing normal vaginal delivery at term without epidural anaesthesia. The MTD was defined as the dose which was expected to produce dose-limiting adverse events (DLAEs) in 20% of the study population. The DLAEs were evaluated 24 h postpartum and consisted of (1) hypertension (diastolic BP ≥ 120 mmHg) or hypotension due to the study medication, (2) vomiting accompanied by either severe abdominal pain or headache, (3) severe abdominal pain with either tremors or heart rate ≥ 150 bpm, or (4) retained placenta.

DLAEs did not occur until the 200 µg dose, and at this dose 4 out of 18 women (22%) experienced DLAEs (3 cases of retained placenta, 2 cases of hypotension due

to PPH associated with retained placenta). Therefore, based on the results from 45 women tested at 9 dose levels from 15 to 200 µg the MTD (IM) of carbetocin was estimated to be 200 µg. The authors commented that, while 200 µg was the MTD (IM) of carbetocin, the high incidence of retained placenta (22%) and the subsequent high incidence of blood loss ≥ 200 mL (22%) suggest that the optimal IM dose must be lower than 200 µg. The authors suggested that the optimal dose of carbetocin was 100 µg, as the lowest blood loss was recorded in the 70-125 µg range and no drug related AEs were demonstrated until the 125 µg dose. The authors commented that they intended to use the 100 µg dose of carbetocin to prevent PPH in further clinical research. The submitted studies in women following vaginal delivery included in the dossier used carbetocin at a dose of 100 µg IM or IV. The sponsor is requested to justify why a 70 µg dose of carbetocin was not selected for IM administration, given that the lowest blood loss was recorded in the 70-125 µg range and the potential for fewer adverse effects with 70 µg IM compared to 100 µg IM (see Section 12 of this CER).

7. Clinical efficacy

7.1. Vaginal delivery

7.1.1. Submitted studies

The submission included 7 published studies in a total of 1590 women to support the application to extend the indications of carbetocin to include vaginal delivery. Of the 1590 women in the 7 studies, 798 received carbetocin and 792 received an active control (177, oxytocin; 615, Syntometrine).

In each of the 7 studies, single dose carbetocin was compared to single dose active control (oxytocin or Syntometrine) for the active management of the third stage of labour to prevent uterine atony and excessive bleeding following vaginal delivery. There were no studies assessing the efficacy and safety of repeat doses of carbetocin in women needing additional doses of uterotonic agents to control uterine atony and/or excessive bleeding occurring after prophylactic treatment.

The 7 studies included 2 comparing carbetocin 100 µg IM to oxytocin 10 IU or 5 IU IM (Boucher et al., 2004; Maged et al., 2016), 4 comparing carbetocin 100 µg IM to the approved dose of Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM (Leung et al., 2006; Su et al., 2009; Nirmala et al., 2009; Askar et al., 2011), and 1 comparing carbetocin 100 µg IM to a lower non-approved dose of Syntometrine (5 IU oxytocin/0.2 mg ergometrine) IM (Samimi et al., 2013).

The 7 studies submitted to support the extension of indications to women delivering vaginally included 4 studies excluding women at risk of PPH and 3 studies including women at risk of PPH. The 7 studies are tabulated below in Table 3 and evaluated in Section 7.1.2 of this CER.

Table 3: Studies submitted in support of the application to extend the indications of carbetocin to include vaginal delivery, all studies compared single-dose of carbetocin to single-dose of active-control

Study	Objectives	Design	Carbetocin Control	Participants	Efficacy Outcomes
Boucher et al., 2004. Two centres in	Reduce the incidence and severity of PPH in	R, db, ac. Injection after DP.	Carbetocin, 100 µg IM n = 83 Oxytocin 10 IU, single IVI	Vaginal delivery, women with at least 1 risk-factor	Primary: Additional uterotonic agents during the

Study	Objectives	Design	Carbetocin Control	Participants	Efficacy Outcomes
Canada.	women at risk for PPH.		/ 2 h; n = 87.	for PPH.	first 24h after delivery. Secondary: Uterine massage; reduction in Hb and Hct; mean blood loss; PPH (> 500 mL).
Leung et al., 2006. One centre in HK.	Prevention of PPH.	R, db, ac. Injection after AS.	Carbetocin, 100 µg IM; n = 150. Syntometrine (5/0.5)* 1 mL IM; n = 150	Vaginal delivery, excluded women at high risk of PPH.	Primary: Reduction in Hb at 48h after delivery. Secondary: Blood loss; primary PPH; repeat oxytocic injection; blood transfusion; manual removal of placenta; duration of third stage.
Nirmala et al., 2009. One centre in Malaysia.	Prevention of PPH in high risk women.	R, db, ac. Injection after DI.	Carbetocin 100 µg IM; n = 60. Syntometrine (5/0.5)* 1 mL IM; n = 60.	Vaginal delivery, included women at high risk of PPH.	Blood loss over the first postpartum day; PPH (≥ 500 mL); Hb change. No defined primary or secondary outcome measures.
Su et al., 2009. One centre in Singapore.	Prevention of PPH.	R, db, ac. Injection after AS.	Carbetocin 100 µg IM; n = 185. Syntometrine (5/0.5)* 1 mL IM; n = 185.	Vaginal delivery, excluded women with risk-factors for PPH.	Primary: PPH requiring additional uterotonics. Secondary: PPH (≥ 500 mL); severe PPH (≥ 1000 mL); blood transfusion; blood loss; length of hospital stay.
Askar et	Efficacy	R, db, ac.	Carbetocin	Vaginal	Primary:

Study	Objectives	Design	Carbetocin Control	Participants	Efficacy Outcomes
al., 2011. One centre in Kuwait.	and safety in managing third stage of labour in women with low risk-factors for PPH.	Injection after AS.	100 µg IM; n = 120 Syntometrine (5/0.5)* 1 mL IM; n = 120.	delivery, excluded women with high risk-factors for PPH.	PPH requiring additional uterotonics. Secondary: PPH (≥ 500 mL); severe PPH (≥ 1000 mL); blood transfusion; blood loss; Hb changes; urine output during postpartum day 1.
Samimi et al., 2013. One centre in Iran.	Prevention of PPH.	R, db, controlled. Injection after SP.	Carbetocin 100 µg IM; n = 100 Syntometrine (5/0.2) ** 1 mL IM; n = 100.	Vaginal delivery, excluded women with risk-factors for PPH.	Primary: Hb change at 24h after delivery. Secondary: Additional uterotonics. Other: Uterine tonicity and blood pressure over the 60 minutes after delivery.
Maged et al., 2015. Two centres in Egypt.	Prevention of PPK in women with at least 2 risk-factor for PPH.	R, db, ac. Injection after PS.	Carbetocin 100 µg IM; n = 100 Oxytocin 5 IU IM; n = 100.	Vaginal delivery, included women with at least 2 risk-factors for PPH.	Blood loss; PPH (> 500 mL); major PPH (> 1000 mL); additional uterotonics; blood transfusion; change in Hb 24h after delivery. No defined primary or secondary outcomes.

Abbreviations: PPH = postpartum haemorrhage; R = randomised; db = double blind; ac = active controlled; OL = open label; h = h; Hb = haemoglobin; Hct = haematocrit; IM = intramuscular; IV = intravenous; DP = after delivery of the placenta; AS = at/after delivery of the anterior shoulder; DI = after delivery of the infant; SP = after placental separation; PS = after delivery of the posterior shoulder; EP = after expulsion of the placenta. Syntometrine (5/0.5) = 5 IU oxytocin plus 0.5 mg ergometrine; ** Syntometrine (5/0.2) = 5 IU oxytocin plus 0.2 mg ergometrine.

7.1.2. Evaluation of the submitted studies

7.1.2.1. Boucher et al., 2004 carbetocin 100 µg IM versus oxytocin 10 IU IV

Title

Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double blind randomised trial.

Objectives

The objectives of this study were to compare the efficacy of carbetocin administered as a single 100 µg IM dose and oxytocin administered as a single 10 IU IV infusion in reducing the incidence and severity of PPH following vaginal delivery in women at risk for this condition.

Design

The study was a randomised, double blind, active-controlled clinical trial, using a double-dummy method with a placebo-control to maintain the blind. The study was conducted at two Canadian hospitals (Montreal and Ottawa) and took place over a 10 month period. The study was approved by the Internal Review Boards of both hospitals and all participants provided informed consent. The study benefited from a grant from Ferring Inc and medications were provided by Ferring Inc. (Toronto, Canada).

Labour was managed according to the standard of care at each participating centre. After vaginal delivery of the placenta, subjects received a single dose of either carbetocin IM injection and placebo IV infusion **or** an oxytocin IV infusion and placebo IM injection. If uterine tone or the amount of bleeding after the administration of the study drug was judged to be unsatisfactory then additional uterotonic agents were given, uterine massage was performed, or both interventions were used. The administered doses of the additional uterotonic agents were the doses routinely used in clinical practice at each participating institution.

Comment: In this study, single doses of both medications were administered as part of the active management of the third stage of labour following vaginal delivery. The study used normal saline (placebo) to maintain the blind.

Inclusion and exclusion criteria

The study enrolled 164 women aged ≥ 18 years of age with at least 1 risk-factor for PPH. The PPH risk factors included: (i) history of PPH or retained placenta; (ii) grand multiparity (> 5); (iii) uterine over distension related to multiple gestation, fetal macrosomia (fundal height > 40 cm or clinical/ultrasound estimated fetal weight > 4000 g) or polyhydramnios (≥ amniotic fluid pocket > 10 cm); (iv) chorioamnionitis; antepartum haemorrhage (vaginal bleeding requiring medical care after 20 weeks gestational age); (v) induction or augmentation of labour with oxytocin for at least 4 h; (vi) prolonged labour (active phase > 12 h); or (vi) rapid-excessive labour (cervical dilatation ≥ 10 cm/h).

Women younger than 18 years were excluded, as were women who had known or suspected coagulopathy, history of heart disease or cardiac arrhythmia, history or evidence of chronic liver, renal or endocrine disease, or hypersensitivity to study drugs.

Study treatments

The participants were randomised to carbetocin (100 µg) IM plus normal saline (IV) placebo *or* oxytocin (20 IU) IV infusion over 2 h plus normal saline (IM) placebo. Women in this study received a single dose of either treatment administered after delivery of the placenta following vaginal delivery.

Comment: The oxytocin dose used in this study was 10 IU administered by IV infusion over 2 h. The oxytocin PI recommends 5-10 IU by IM injection or 5 IU by slow IV infusion for

the third stage of labour. The carbetocin dose used in this study (100 µg IM) is consistent with the dose being proposed for registration for vaginal delivery.

Efficacy variables and outcomes

The primary efficacy outcome measure was the need for additional uterotonic medication to prevent PPH following vaginal delivery. The number of additional doses of uterotonic medication was recorded as was the time interval between administration of the study drug and additional uterotonic medications

The *secondary efficacy outcome measures* were uterine massage started after placental delivery because of excessive bleeding or inadequate uterine tone, change in haemoglobin concentration and haematocrit over the initial 24 h after delivery, estimated blood loss from the time of study drug administration to the end of delivery, uterine tone, and amount and type of lochia.

Randomisation and blinding methods

Separate randomisation lists using a block size of 4 were prepared for each study site by an independent statistical group. The computer generated randomisation codes were sealed in sequentially numbered envelopes. In order to reduce the risk of randomising women who were likely to require Caesarean delivery randomisation took place when the cervix was 6 cm dilated (multiparous women) or fully dilated (primiparous women). For each study participant, kits containing both the study medication and a placebo were prepared in the hospital pharmacy according to the randomisation schedule to assure 'blinding' of the clinical staff. The clinical staff and the study subjects were blinded to treatment allocation.

Sample size

The sample size was determined using an estimate that 20% of high risk pregnant women would require additional uterotonic medication (primary outcome measure) following vaginal delivery to prevent PPH. With a power of 80% to detect a 15% difference between study groups, 152 patients were required.

Statistical methods

Binary outcomes were analysed using Fisher's exact test or the chi-square test, as appropriate, and the asymptotic 95% CIs were calculated. The significance level was set at $p = 0.05$. Continuous variables were reported as the mean ± 1 standard deviation (SD), analysed using 2-sample t-tests, and variance was tested for homogeneity between the 2 groups. If the variance was not statistically equal, then an appropriate adjustment was applied to account for the two different sample variances.

Comment: The efficacy analysis was not specified to have been undertaken in the intention-to-treat (ITT) population. However, analysis of some of the efficacy outcomes (including the key efficacy outcome of the proportion of women requiring additional uterotonic medication) were undertaken in the number of subjects randomised to each of the two treatment arms, which suggests that the analysis was based on the ITT principle. Analysis of other outcomes were undertaken in a smaller number of subjects than randomised to each treatment group indicating that analysis was not in the ITT population. No information was provided on the reasons for non-inclusion of all randomised subjects in the efficacy analyses involving less than the randomised number of subjects. There was no statistical adjustment for the multiple pairwise comparisons of the secondary efficacy endpoints.

Participant flow

Of the 164 women enrolled in the study, a total of 160 with at least 1 risk-factor for PPH completed the study. Of the 4 women who were enrolled but did not complete the study, 3 were excluded as result of Caesarean birth while the reason for non-completion in 1 woman was not

stated. Of the 160 women who completed the study, 83 were randomised to carbetocin and 77 were randomised to oxytocin.

Major protocol violations/deviations

No information provided.

Baseline data

It was reported that each of the two treatment arms were comparable with respect to maternal age, weight, height, body mass index, vital signs, and haematologic values at entry, as well as for parity, gestational age, and the use of either cervical ripening or epidural anaesthesia. The risks-factors for PPH were comparable in the two treatment arms, with the most common risk-factors in both treatment arms being oxytocin used for augmentation and/or induction of labour.

The characteristics of labour were similar in each treatment arm. The mean ± SD duration of the first, second, and third stages of labour was similar in the two arms, with a total duration of labour of 10.6 ± 7.1 h in the carbetocin arm and 10.1 ± 6.5 h in the oxytocin arm. In women receiving oxytocin for induction or augmentation of labour, the mean ± SD duration of the oxytocin infusion was similar in the carbetocin and oxytocin arms (that is, induction = 8.8 ± 3.8 h versus 8.7 ± 3.5 h, respectively, $p > 0.05$; augmentation = 11.4 ± 7.1 h versus 10.9 ± 4.4 h, respectively, $p < 0.05$).

Comment: The study report indicated that demographic factors and labour characteristics were comparable between the two treatment groups, but the raw data supporting the comparisons were not presented in the published report. In this study anaesthesia was stated to be either regional or by parenteral narcotics, but the number of women receiving the different forms of anaesthesia was not stated. The study report indicated that the use of epidural anaesthesia was comparable between the two treatment arms.

Results for the efficacy outcomes

The key efficacy outcome measures are summarised below in Table 4. The primary outcome measure was the percentage of women requiring additional uterotonic medication.

Table 4: Boucher et al., 2004;Key efficacy outcome measures in the two treatment groups

Efficacy Outcome measures	Carbetocin	Oxytocin	p value
Women requiring additional uterotonic medication, n (%)	14.5% (12/83) (95% CI: 6.9%, 22.0%)	15.6% (12/77) (95% CI: 7.5%, 23.7%)	ns
Women requiring uterine massage, n (%)	43.4% (36/83) (95% CI: 32.7%, 54.0%)	62.3% (48/77) (95% CI: 51.5%, 73.2%)	0.02
Women requiring uterotonic agent and/or massage, n (%)	44.6% (37/83) (95% CI: 33%, 55.3%)	63.6% (49/77) (95% CI: 52.9%, 74.4%)	0.02
Mean ± SD haemoglobin difference (g/L)	-12.8 ± 10.8 (g/L); n = 83	-15.9 ± 11.6 (g/L); n = 73	ns

Efficacy Outcome measures	Carbetocin	Oxytocin	p value
Mean ± SD prenatal and postpartum haemoglobin difference (%)	-10.6 ± 9.3 (%); n = 83	-12.9 ± 9.4 (%); n = 73	ns
N (%) with mean ± SD haematocrit drop of ≥ 10% from baseline	51.2% (42/82)	60.3% (44/73)	ns
Mean ± SD blood loss (mL)	413.3 ± 197.5 (mL); n = 64	410.4 ± 194.1 (mL); n = 67	ns
N (%) of women with estimated blood loss > 500 mL.	15.6% (10/64)	16.4% (11/67)	ns

Source: Boucher et al., 2004; Table 2. Notes: Continuous data reported as mean ± SD; p-value measured by the chi-square test; ns = not statistically significant p > 0.05.

Comment: There was no statistically significant difference between the two treatment arms in the key outcome of the proportion of women requiring additional uterotonic medication. However, the proportion of women requiring additional uterotonic massage was notably greater in the oxytocin arm than in the carbetocin arm and the difference was statistically significant. Outcomes assessing blood loss did not notably differ between the two treatment arms and none of the numerical differences between the arms were statistically significant (that is, haemoglobin reduction, haematocrit reduction, mean estimated blood loss). The percentage of women experiencing a PPH (> 500 mL) was relatively high in both treatment arms (15.6%, carbetocin; 16.4%, oxytocin), and the percentages were similar to the percentages of women requiring additional uterotonic agents in the treatment arms.

Overall comment on the study

This was a good quality study. It showed that there was no significant difference between the percentage of women in either of the two treatment arms requiring additional uterotonic medications (primary outcome measure) or experiencing PPH (> 500 mL). The results adequately demonstrated that carbetocin 100 µg IM and oxytocin 10 IU IV have comparable efficacy as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with at least 1 risk-factor for PPH.

7.1.2.2. Maged et al., 2015 Carbetocin 100 µg IM versus oxytocin 5 IU IM

Title

Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women

Objectives

The objective of this study was to compare the effectiveness and tolerability of carbetocin versus oxytocin for the prevention of postpartum haemorrhage after vaginal delivery in women with at least two risk-factors for atonic PPH.

Design

This study was a prospective, double blind, randomised controlled clinical trial. The study was conducted in 200 pregnant women attending the Kasr Al Ainy and Benisuef maternity hospitals, Egypt, during the period from May 2013 to December 2014. The study report stated that '(a) control group was not included for ethical reasons' (presumably a placebo control group). All participants provided informed consent and the study was approved by local ethics committee

The study included 200 women at high risk of postpartum haemorrhage randomised to carbetocin (n = 100) or oxytocin (n = 100). The study drugs were administered after delivery of the posterior shoulder or after delivery of the second twin in the case of twin births. All participants had a complete history taken, and underwent general, abdominal and obstetric examination. In addition, an ultrasound scan, complete 'blood picture', liver functions and coagulation profile were also undertaken.

Blood pressure (systolic and diastolic) was measured immediately after delivery and then at 30 minutes and 60 minutes after delivery. Possible treatment complications were recorded (that is, nausea, vomiting, tachycardia, flushing, dizziness, headache, shivering, metallic taste, dyspnoea, palpitation and itching).

Inclusion and exclusion criteria

All participants were at 37–40 weeks of gestation with at least two risk factors for developing atonic PPH. Potential participants were approached in the antenatal clinic or early in labour if appropriate. Risk factors included previous PPH, primipara aged > 40 years, BMI > 35 kg/m^2, multiple pregnancy, prolonged labour > 12 h, and ultrasound estimated fetal weight > 4 kg. Participants with placenta previa, coagulopathy, preeclampsia, cardiac, renal, liver diseases, epilepsy, and known hypersensitivity to oxytocin or carbetocin were excluded.

Study treatments

The participants were randomised to single dose carbetocin 100 µg IM or single dose oxytocin 5 IU IM administered at delivery of the posterior shoulder or after delivery of the second twin in the case of twin births.

Comment: The dose of oxytocin (5 IU) IM is consistent with the Australian approved dose for the management of the third stage of labour. The single dose of carbetocin (100 µg) IMI is the proposed dose for vaginal delivery.

Efficacy variables and outcomes

All participants were followed for 24 h after delivery. Uterine tone and amount of bleeding were noted and the need for further uterotonic agents was checked 2 minutes after giving the study drug. Blood loss was estimated by weighing the swabs and using pictorial charts. PPH was defined as bleeding > 500 mL and major PPH was defined as bleeding > 1000 mL. Haemoglobin levels were assessed 24 h after delivery. Systolic and diastolic blood pressure were measured immediately after delivery and then at 30 minutes and 60 minutes after delivery.

Comment: The primary and secondary efficacy outcomes were not explicitly stated. However, as the objective of the study was stated to be prevention of PPH it is considered reasonable to assume that the amount of bleeding was the main efficacy outcome. This is supported by the study abstract which reports the amount of bleeding as the first outcome in the *Results* section.

Randomisation and blinding methods

Participants were randomised 1:1 to the two treatment arms using an automated web-based randomisation system to ensure allocation concealment into two arms. The study was double blind.

Sample size

No information was provided on the method used to select the sample size.

Statistical methods

Comparison of numerical variables between the study groups was done using an independent t-test. The chi-square test was used to compare categorical data, and the exact test was used when the expected frequency was less than 5. Statistically significance was considered when p-values were < 0.05.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the efficacy outcome measures.

Participant flow

No information was provided.

Major protocol violations/deviations

No information was provided.

Baseline data

The baseline characteristics of the two treatment arms were well balanced. The estimated mean age of the women in the study was 33 to 34 years, and the estimated mean SD was 7.5 to 7.6 years. The estimated mean parity was 1 to 2. The estimated mean gestational age was 39 weeks. The most common risk-factors for PPH in the carbetocin and oxytocin arms were prolonged labour > 12 h (62% versus 57%, respectively), history of PPH (54% versus 60%, respectively), and fetal macrosomia > 4000 g (45% versus 50%, respectively). Episiotomy was reported in 26% of women in the carbetocin arm and 22% of women in the oxytocin arm. The duration of each of the three stages of labour did not differ notably between the two treatment arms. The infant birth weight was similar in both treatment arms.

Comment: The methods of analgesia were not stated in this study. There was no information on the number of women receiving regional anaesthesia.

Results for the efficacy outcomes

The results for the efficacy outcomes are summarised below in Table 5.

Table 5: Maged et al., 2015 Efficacy outcomes in the carbetocin (n = 100) and oxytocin (n = 100) treatment arms

	Carbetocin	Oxytocin	*p* value
Amount of bleeding (ml)	337.73 ± 118.77	378 ± 143.2	0.03
PPH (>500 ml)†	4%	16%	0.037
Major PPH (>1000 ml) †	0%	1%	0.316
Need for other uterotonics†	23%	37%	0.031
Need for blood transfusion†	1	2	1
Hb before delivery (g/dl)	11.01 ± 1.3	11.11 ± 1.24	0.581
Hb 24 h after delivery(g/dl)	10.51 ± 1.38	10.13 ± 1.26	0.04
Hb difference (before and after delivery) (g/dl)	0.55 ± 0.35	0.96 ± 0.62	<0.001

*Data are presented as mean ± standard deviation.
†Data are presented as number and percent.

Source: Maged et al., 2015, Table 2.

Comment: The amount of bleeding in the first 24 h following delivery was greater in the oxytocin arm than in the carbetocin arm, and the approximate difference between the two arms of 41 mL was statistically significant. PPH (> 500 mL) occurred 4-fold more frequently in the oxytocin arm than in the carbetocin arm (16% versus 4%, respectively), and the difference between the two arms was statistically significant and is considered to be clinically meaningful. No women in the carbetocin arm experienced severe PPH (> 1000 mL), while 1 (1%) woman in the oxytocin arm experienced a severe PPH. The reduction in the haemoglobin concentration at 24 h after delivery was greater in the oxytocin arm than in the carbetocin arm, and the estimated difference between the two arms of 0.41 g/dL was statistically significant. The need for additional uterotonic agents was reported in a greater proportion of women in the oxytocin arm than in the carbetocin arm (37% versus 23%. respectively), and the difference between the two arms of 14% was statistically significant. The need for blood transfusion was reported infrequently in both treatment arms.

Overall comment on the study

This was a reasonable quality study. The incidence of postpartum haemorrhage (> 500 mL) was notably greater in the oxytocin arm than in the carbetocin arm, as was the amount of blood loss, the reduction in haemoglobin level at 24 h post-delivery and the need for additional uterotonic agents. There was no information on sample size calculations or on participant flow. The results adequately demonstrated that carbetocin 100 µg IM is more efficacious than oxytocin 5 IU IM IV as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with at least 2 risk-factors for PPH.

7.1.2.3. Leung et al 2006 carbetocin 100 µg IM versus Syntometrine (5 IU/0.5 mg) IM

Title

A randomised trial of carbetocin versus Syntometrine in the management of the third stage of labor.

Objectives

The objectives of this study were to compare the efficacy and safety of single doses of carbetocin 100 µg IM and Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM for the management of the third stage of labour in women delivering vaginally, excluding those with high risk-factors for PPH.

Design

This study was a prospective, randomised, controlled and double blind clinical trial. It was conducted from July 2004 to March 2005 at the Prince of Wales Hospital, Hong Kong. Women with a singleton pregnancy achieving vaginal delivery beyond 34-weeks were eligible to be enrolled in the study. Women were randomised to receive a single dose of either carbetocin 100 µg IM or Syntometrine IM on delivery of the anterior shoulder. Administration of the study drug was by an independent midwife. If an oxytocin infusion was in progress it was stopped. The third stage of labour was managed using standard methods. Additional doses of Syntometrine or oxytocin were used if uterine atony was suspected or diagnosed following delivery. The study protocol was approved by the Clinical Research Ethics Committee of the Faculty of Medicine of the Chinese University of Hong Kong. All women were required to give written informed consent at the time of recruitment. The project was supported by Ferring Pharmaceuticals Ltd.

Inclusion and exclusion criteria

Women with a single pregnancy achieving vaginal delivery beyond 34-week gestation were eligible for the study. Exclusion criteria included the presence of contraindications for the use of either Syntometrine or carbetocin, including pre-existing hypertension, preeclampsia, asthma,

cardiac, renal or liver diseases. Women with high risk-factors for primary postpartum haemorrhage such as grand multiparity or presence of uterine fibroids and who required prophylactic oxytocin infusion after delivery were excluded.

Study treatments

Women were randomised to receive a single dose of either carbetocin 100 µg IM or Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM at delivery of the anterior shoulder.

Comment: The dose of Syntometrine used in this study is consistent with the Australian approved dose of this drug for the active management of the third stage of labour (that is, 1 mL IM following expulsion of the placenta). The carbetocin dose used in this study (100 µg) IM is consistent with the dose being proposed for registration for vaginal delivery.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was the drop in haemoglobin level documented by comparing the maternal haemoglobin concentration on admission to the labour ward with that measured 48 h after delivery.

The *secondary efficacy outcome measures* included the visually estimated amount of blood loss during delivery, the incidence of primary PPH (defined as blood loss more than 500 mL) and blood transfusion.

Maternal blood pressure, pulse and temperature were checked immediately after delivery and repeated 30 and 60 minutes after delivery. The duration of the third stage, the incidence of a prolonged third stage (duration longer than 30 minutes), the need for manual removal of the placenta or the need additional uterotonic agents were recorded. The occurrence of nausea, vomiting, flushing, headache, shivering and pain over injection site were recorded by an interview conducted 1 h after delivery.

Randomisation and blinding methods

Randomisation was performed by opening a sealed, consecutively numbered, opaque envelope that contained a computer-generated code prepared before recruitment. Once an eligible woman with informed consent was about to deliver vaginally, an independent midwife opened the envelope and drew up the study drug. The study was double blind.

Sample size

A previous study undertaken by the authors and others showed that the mean (±SD) post-partum haemoglobin concentration change measured 48 h after delivery among women treated with Syntometrine was 1.34 ± 1.26 g/dl. A trial with a power of 90% to detect a difference of 0.5 g/dL in the haemoglobin concentration change with an alpha of 0.05 would require a sample size of 150 in each arm. The study included 150 women randomised to each of the two treatment arms.

Statistical methods

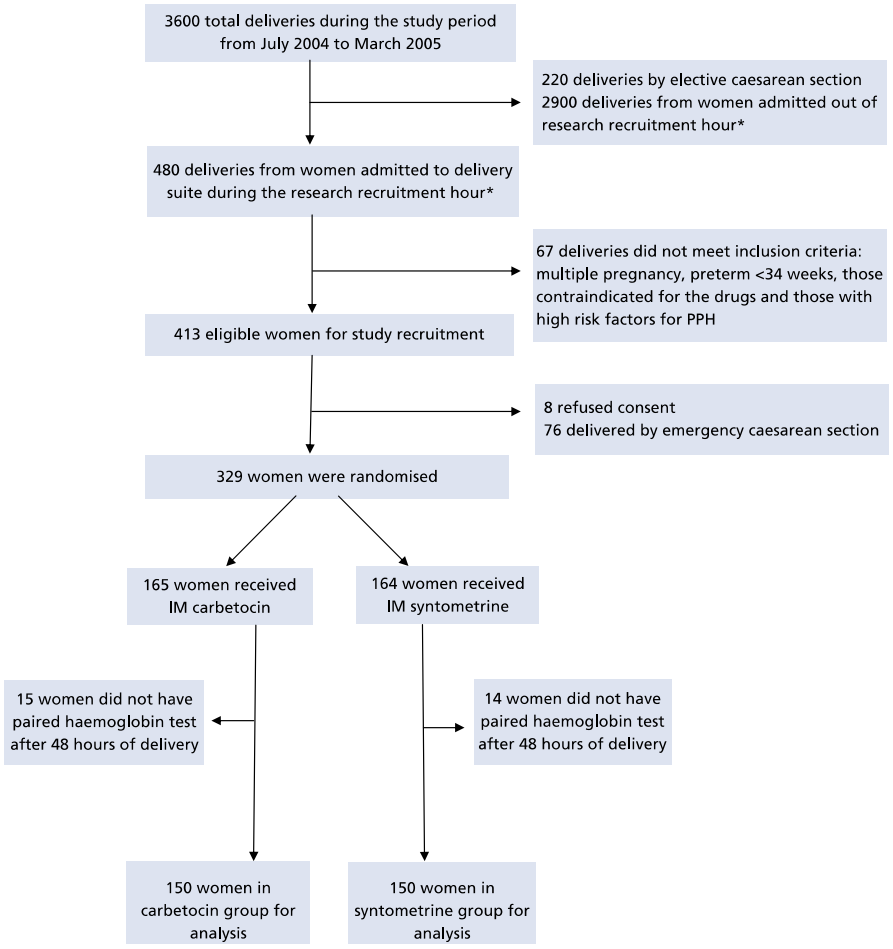
The results for the carbetocin and Syntometrine arms were compared using the chi-square test or Fisher's exact test for categorical data and Student's t-test for continuous data. Where considered appropriate, relative risks (RRs) and 95% CIs were calculated for the outcomes. A p-value of less than 0.05 was considered to be statistically significant.

Comment: Although it is not explicitly stated in the study report it appears that the analysis of the primary efficacy outcome was based on the ITT principle as it included all randomised subjects with paired haemoglobin measurements (that is, on admission and 48 h after delivery). There was no statistical adjustment for multiplicity for the numerous secondary efficacy endpoint pairwise comparisons.

Participant flow

There were a total of 3600 deliveries at the study centre during the study period, and 480 deliveries occurred in women admitted to the delivery suite during the recruitment period. Of these 480 women, 413 were eligible for recruitment while 67 did not satisfy the inclusion and/or exclusion criteria. Of the 413 women eligible for recruitment, 329 were randomised and 84 were not randomised (8 refused consent and 76 underwent emergency CS). Of the 329 randomised women, 165 were randomised to carbetocin and 164 were randomised to Syntometrine. Of the 165 women randomised to carbetocin, 150 were included in the efficacy analysis while 15 were excluded due to the absence of paired haemoglobin concentrations pre- and post-delivery (48 h). Of the 164 women randomised to Syntometrine, 150 were included in the efficacy analysis while 14 were excluded due to the absence of paired haemoglobin concentrations pre- and post-delivery (48 h). The flow chart for participation in the study is provided in Figure 1.

Figure 1: Leung et al., 2006 Flow chart for participating women



Source: Leung et al., 2006, Figure 1. Notes: PPH = post-partum haemorrhage. * 0800 to 1200 hours of each working day.

Major protocol violations/deviations

No information was provided.

Baseline data

The demographic characteristics of the study population were well balanced between the two treatment arms. The mean age of the women in both treatment arms was approximately 28 years, and gestation was approximately 39 weeks in the two arms. Induction of labour was

required in 40% of women in the carbetocin arm and 33% of women in the Syntometrine arm, with augmentation of labour using oxytocin reported in 19% and 20% of women in the two treatment arms, respectively. Epidural anaesthesia was used in 20% of women in the carbetocin arm and 21% of women on the Syntometrine arm.

Results for the efficacy outcomes

The mean (SD) drop in haemoglobin concentration 48 h after delivery was 1.4 (1.1) g/dL in the carbetocin arm and 1.5 (1.3) g/dL in the Syntometrine arm, and the difference between the two arms was not statistically significant (that is, Δ = -0.1 g/dL (95% CI: -0.4, 0.2))). The results in haemoglobin concentrations at 48 h after delivery are summarised below in Table 6, and the results for the secondary efficacy outcomes are summarised below in Table 7.

Table 6: Leung et al., 2006 Haemoglobin concentrations at 48 hours after delivery

	Carbetocin (*n* = 150)	Syntometrine (*n* = 150)	Mean difference	RR	95% CI
Haemoglobin at onset of labour (g/dl)*	11.6 (1.1)	11.8 (1.2)	−0.2	—	−0.5 to 0
Haemoglobin on postpartum day 2 (g/dl)*	10.2 (1.4)	10.4 (1.5)	−0.2	—	−0.5 to 0.2
Mean fall in haemoglobin (g/dl)*	1.4 (1.1)	1.5 (1.3)	−0.1	—	−0.4 to 0.2
Mean percent drop in haemoglobin concentration*	11.6 (9.4)	12.2 (10.3)	−0.6	—	−2.8 to 1.7
Percent drop of haemoglobin**					
>20%	24 (16)	33 (22)	—	0.72	0.3–1.21
>10%	75 (50)	82 (54.7)	—	0.91	0.77–1.90

Source: Leung et al., 2006, Table 2. Notes: * Data presented as mean±SD. ** Data presented as n (%).

Table 7: Leung et al., 2006 Secondary efficacy outcomes

	Carbetocin (*n* = 150)	Syntometrine (*n* = 150)	Mean difference	RR	95% CI
Mean blood loss (ml)*	232 (122)	249 (175)	−17	—	−51 to 18
Primary postpartum haemorrhage**	6 (4)	3 (2)	—	2.00	0.50–8.32
Blood loss ≥ 500 ml**	6 (4)	2 (1.3)	—	3.00	0.61–15.53
Blood loss ≥ 1000 ml**	0	1 (0.7)	—	—	—
Repeat oxytocic injection**	13 (8.7)	10 (6.7)	—	1.30	0.56–3.13
Need of blood transfusion**	5 (3.3)	2 (1.3)	—	2.50	0.49–13.36
Manual removal of placenta**	1 (0.7)	3 (2)	—	0.33	0.03–3.20
Mean duration of third stage* (minutes)	11.6 (17.4)	10.4 (4.2)	1.2	—	−1.7 to 4.1
Duration of third stage (minutes)**					
≤10	128 (85.3)	126 (84)	—	1.02	0.59–2.08
11–30	21 (14)	23 (15.3)	—	0.91	0.47–1.71
>30	1 (0.7)	1 (0.7)	—	1	0.06–16.14

Source: Leung et al., 2006, Table 3. Notes: * Data presented as mean±SD. ** Data presented as n (%).

Comment: There was no clinically meaningful or statistically significant difference between the two treatment arms in the primary efficacy outcome of reduction in haemoglobin concentration from pre-delivery to 48 h post-delivery. The percentage of women experiencing > 10% and > 20% reductions in haemoglobin concentration at 48 h after delivery was lower in the carbetocin arm than in the Syntometrine arm, but the RR for both endpoints was not statistically significant. It was stated in the study report that changes in haemoglobin concentrations were assessed at 48 h after delivery rather than at 24 h after delivery so as to provide for a longer time for equilibrium to be reached.

The mean blood loss was greater in the Syntometrine arm than in the carbetocin arm, but the difference between the two arms was not statistically significant. There were numerical differences between the two treatment arms in the number (%) of women experiencing primary PPH in favour of the Syntometrine arm compared to the carbetocin arm. However, the number of women (%) experiencing primary PPH

was small in both treatment arms and the RR between the two arms was not statistically significant. All cases of primary PPH occurred either immediately or within 1 h post-delivery and while the women were still in the delivery room. One nulliparous woman in the Syntometrine group developed massive postpartum haemorrhage of 2 L after vacuum extraction due to uterine atony and retained cotyledon. There were numerical differences between the two treatment arms for the other secondary efficacy outcomes (repeat oxytocic injection, need for blood transfusion, manual removal of the placenta, mean duration of third stage). However, none of the differences between the two treatment arms for these additional secondary efficacy outcomes are considered to be clinically meaningful, and none of differences between the arms were statistically significant.

Overall comment

This was a good quality study. It showed that there was no marked difference between the two treatment arms in mean reduction in haemoglobin concentrations at 48 h after delivery (primary efficacy outcome). The incidence of primary PPH was small in both treatment arms (4%, carbetocin; 2%, Syntometrine), and although the RR was 2-fold greater in the carbetocin arm than in the Syntometrine arm the result was not statistically significant. The need for repeat oxytocic injection was similar in both treatment arms (8.7%, carbetocin; 6.7%, Syntometrine), and higher than the incidence of primary PPH in both treatment arms. In this study additional doses of oxytocin (IV infusion) were administered if uterine atony was suspected or diagnosed. The results demonstrated that carbetocin 100 µg IM and the approved dose of Syntometrine 1 ml IM have comparable efficacy as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with low-risk of PPH.

7.1.2.4. Nirmala et al., 2009 Carbetocin 100 µg IM versus Syntometrine (5 IU/0.5 mg) IM

Title

Carbetocin versus Syntometrine in prevention of post-partum haemorrhage following vaginal delivery

Objectives

The objective of this study was to compare the efficacy of single dose carbetocin 100 mg IM to single dose Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM in preventing PPH in high risk women following vaginal delivery.

Design

This study was a prospective, randomised, controlled clinical trial. It was undertaken at the National University of Malaysia Hospital, a tertiary hospital in Kuala Lumpur, Malaysia. The study was approved by the Research and Ethics Committee of the participating hospital.

The study included a total of 120 pregnant women (beyond 36 weeks gestation) aged ≥ 18 years with at least one risk-factor for PPH who delivered a viable infant vaginally. The PPH risk factors were a history of blood transfusion or iron sucrose injection pre or post-delivery, a history of retained placenta, grand multiparity (> para 5), twin pregnancy, fetal macrosomia (fundal height 40 cm or clinical ultrasound estimated fetal weight 3.8–4.0 kg), polyhydramnios (more than one amniotic fluid pocket 8.0 cm or AFI 25.0 cm), or induction or augmentation of labor with oxytocin for at least 4 h or prolonged labor (active phase > 12 h).

Baseline blood pressure and pulse rate were recorded on admission to the labour room, and haemoglobin concentrations were measured pre-delivery and repeated on day 1 post-delivery. Labour was managed according to the normal protocol for the participating centre, including active management of the third stage. The study drug was administered IM immediately after delivery of the infant. Preparation and administration of the study drugs were carried out by

midwives who were not involved in the management of the patient except for administration of the study drug. Uterine fundal height and vital signs were assessed at 0, 30 minutes and 60 minutes after administration of the study drug. If uterine tone was not firm or the amount of bleeding was unsatisfactory after administration of the study drug, then an additional oxytocic agent was administered.

Measurement of blood loss by the gravimetric method was started immediately after administration of the study drug. All gauzes, tampons and pads were collected for the first hour following the delivery of the placenta. A digital weighing scale was used and the difference in weight of the material before and after the first h was calculated. A 100 g increase in weight was considered to be equivalent to 100 mL blood. The number of pads used and the amount of lochia were recorded using a pictogram from the end of delivery until day 1 post-delivery.

Any blood transfusion or iron sucrose injection post-partum or incidence of PPH was recorded in the first 24 h after delivery.

Inclusion and exclusion criteria

The study included women aged ≥ 18 years of age who were beyond 36 weeks gestation who delivered a viable infant following vaginal delivery. The women had at least one risk-factor for PPH. Women younger than 18 years old were excluded as were women with history of significant heart disease, hypertension requiring treatment, a history or evidence of liver, renal, vascular disease or endocrine disease (excluding gestational diabetes) or hypersensitivity to oxytocin or carbetocin.

Treatments

Women were randomised to receive a single dose of either carbetocin 100 µg IM or Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM immediately after delivery of the infant.

Comment: The dose of Syntometrine used in this study is consistent with the Australian approved dose of this drug for the active management of the third stage of labour (that is, 1 mL IM following expulsion of the placenta). The carbetocin dose used in this study (100 µg) IM is consistent with the dose being proposed for registration for vaginal delivery.

Efficacy variables and outcomes

Outcome measures assessed in this study included changes in vital signs, amount of intra-partum blood loss, uterine fundal position, addition of another oxytocic agent, side-effects of the drugs, amount of lochia and haemoglobin drop at 24 h post-delivery. The incidences of PPH, blood transfusion or iron sucrose injections were recorded for the first 24 h post-delivery.

Comment: Based on the tabulated results for 'blood parameters' the assessed efficacy outcome measures included estimated blood loss, change in haemoglobin concentration from pre-delivery to post-delivery, and percent drop in haemoglobin concentration. There was no explicit statement concerning which of the efficacy endpoints were primary and which were secondary.

Randomisation and blinding methods

On admission to the labor room, women who fulfilled the eligibility criteria were randomised to receive either carbetocin or Syntometrine by computer-generated randomised codes sealed in sequentially numbered envelopes. Randomisation was undertaken on reaching 6 cm cervical dilatation for multiparous women or full cervical dilatation for primiparous women in order to reduce the risk of randomising women who were likely to require CS. The preparation and administration of the medication was carried out by midwives who were not involved in the management of the patient except for administration of the study drug. When delivery was imminent, the envelope was opened by the midwife in charge of the patient and the numbered vial of the study drug was kept ready for injection during the third stage of labour.

Comment: The randomisation method was satisfactory. It was not explicitly stated whether the study was double blinded. However, it appears from the description of the method of administration of the study drug that the study was double blinded.

Sample size

No information was provided on the method used to select the sample size.

Statistical methods

Fisher's exact test was used to compare categorical variables and Student's t-test was used to compare continuous variables. Statistical significance was defined as $p < 0.05$. Where appropriate, 95% CIs were calculated for the outcome measures.

Comment: It was not stated whether analysis was in the ITT population. However, evaluation appeared to be based on comparison of outcomes in the 60 randomised patients in each treatment arm, which suggests that analysis was based on the principles of ITT.

Participant flow

A total of 120 women with at least one risk factor for PPH completed the study, with 60 women being randomised to each treatment arm. No other information on participant flow was available in the study report.

Major protocol violations/deviations

No information provided.

Baseline data

It was stated that each treatment arm '*was comparable for maternal age, weight, height, body mass index and haematological values at entry, as well as for parity, gestational age, medical disorders and the use of either cervical ripening or epidural analgesia'*. However, no data on these parameters were presented in the study report. The risk factors for PPH were reasonably well balanced between the two treatment arms. The most frequently reported risk factor for PPH in both treatment arms was augmentation of labour for more than 4 h (53%, n = 32, carbetocin versus 60%, n = 36, Syntometrine).[2]

The characteristics of labour were described as being similar in both treatment arms. The duration of the first, second and third stages of labour was similar in the two arms, with the mean total duration of labour being 8 ± 3 h in both treatment arms. There was no significant difference in the mean duration of the oxytocin infusion for induction or augmentation of labour between the carbetocin and Syntometrine arms (5 ± 2 h versus 4 ± 2 h, respectively, $p > 0.05$). Types of perineal tear were similar between the two treatment arms with no cases of cervical tear.

[2] Nirmala et al., 2009 Risk-factors for post-partum haemorrhage (Table 1).

Risk factors	Carbetocin *n* = 60 *n* (%)	Syntometrine *n* = 60 *n* (%)	*P*-value
Grandmultipara	8 (13)	4 (7)	ns
History of retained placenta	3 (5)	1 (2)	ns
History of blood transfusion post-delivery	1 (2)	1 (2)	ns
History of iron sucrose injection pre- or post-delivery	1 (2)	0	ns
Twin pregnancy	4 (7)	2 (3)	ns
Polyhydramnios	0	2 (3)	ns
Fetal macrosomia	1 (2)	2 (3)	ns
Induction of labor	6 (10)	8 (13)	ns
Augmentation of labor more than 4 hours	32 (53)	36 (60)	ns
Prolonged labor 1st stage	4 (7)	4 (7)	ns
Prolonged labor 2nd stage	0	0	–

ns, not significant.

Administration of the study drug within 1 minute of delivery was reported in 42% of women in the carbetocin arm and 33% of women in Syntometrine arm. Administration of the study drug within 2 minutes of delivery was reported in 93% of women in the carbetocin arm and 98% of women in Syntometrine arm. Four (4) women in the carbetocin arm and 1 woman in the Syntometrine arm received treatment between 2 and 3 minutes after delivery due to inadequate staffing. No women received treatment greater than 3 minutes after delivery. Uterine tone increased rapidly after the drug administration, with 95% and 90% of patients in the carbetocin and Syntometrine arms, respectively, having a contracted 20 week size uterus at 5 minutes.

Comment: The study report indicated that women received either regional anaesthesia or parenteral 'narcotics'. The report stated that the two treatment arms were comparable with respect to the use of epidural anaesthesia, but the number of women undergoing this procedure was not stated.

Results for the efficacy outcomes

The results for the 'blood parameters' are summarised below in Table 8.

Table 8: Nirmala et al., 2009 Outcomes for blood parameters

	Carbetocin $n = 60$ Mean ± SD	Syntometrine $n = 60$ Mean SD	P value
Estimated blood loss (mL)	244 ± 114	343 ± 143	$P < 0.001$
Range	78–578	89–870	
Pre-delivery hemoglobin (g/dL)	11.3 ± 1.1	11.4 ± 1.0	ns
Post-delivery hemoglobin (g/dL)	11.0 ± 1.1	11.0 ± 1.0	ns
Hemoglobin difference (g/dL)	0.3 ± 0.2	0.4 ± 0.2	$P < 0.001$
Blood loss (mL)	*n* (%)	*n* (%)	
<100	4 (7)	2 (3)	–
100–199	13 (21)	5 (8)	–
200–299	27 (45)	15 (25)	–
300–399	10 (17)	20 (33)	–
400–499	3 (5)	12 (20)	–
≥500 (PPH)	3 (5)	6 (10)	ns
% of drop in hemoglobin level			
<5%	57 (95)	50 (83)	–
5–10%	3 (5)	9 (15)	–
>10%	0	1 (2)	–

ns, not significant; SD, standard deviation.

Source: Nirmala et al., 2009, Table 4.

No women in the carbetocin arm required a blood transfusion, while one 32 year old woman (Gravida 7, Para 6) in the Syntometrine arm required 2 units of blood following a PPH secondary to uterine atony (blood loss 870 mL; post-delivery haemoglobin fell to 7.8 g/dL from pre-delivery level of 9.0 g/dL).

Oxytocin infusion 40 IU was used as an additional oxytocic in both the carbetocin and the Syntometrine arms. No significant difference was observed between the carbetocin and the Syntometrine arms in the number of women requiring an additional oxytocic agent (3 versus 9, respectively, $p > 0.05$). The mean ± SD time from study drug administration to additional oxytocic drug administration was similar in the carbetocin and the Syntometrine arms (15 ± 8 versus 12 ± 8 minutes, respectively, $p > 0.05$).

No significant difference was observed with regard to the amount of lochia in the 24 h post-partum. No women from either group required admission to the high dependency unit (HDU) or the intensive care unit (ICU), manual removal of the placenta, evacuation of blood clots or haematoma or caesarean hysterectomy.

Comment: The study showed that women at high risk of post-partum haemorrhage who received a single dose of carbetocin (100 µg IM) immediately after vaginal delivery of the infant had notably less blood loss over the 24 h following delivery than women who received a single dose of Syntometrine IM. The mean estimated blood loss over the first 24 h after delivery was notably higher in the Syntometrine arm than in the carbetocin arm, and the difference between the two treatment arms was statistically significant (Δ = 99 mL (95% CI: 52, 145)). The reduction of mean haemoglobin concentration from pre- to post-delivery (24 h) was statistically significantly greater in the Syntometrine arm than in the carbetocin arm, but the difference between the two treatment arms was small and not clinically meaningful (Δ = 0.2 g/dL (95% CI: 0.1, 0.2)). Postpartum haemorrhage (blood loss ≥ 500 mL) was reported more frequently in women in the Syntometrine arm than in the carbetocin arm, but the difference between the two treatment arms was not statistically significant (10%, n = 6 versus 5%, n = 3, respectively, p > 0.05).

Overall comment on the study

This was a reasonable quality study in a relatively small number of participants (60 patients in each of the two treatment arms). The total estimated blood loss over the first postpartum day was greater in the Syntometrine arm than in the carbetocin arm, as was the incidence of PPH (≥ 500 mL). There was no information on the reason for sample size selection. The randomisation method was satisfactory, but there was no explicit statement on whether the study was double blind although the description of randomisation suggests that it was. The results adequately demonstrated that carbetocin 100 µg IM and the approved dose of Syntometrine 1 ml IM have at least comparable efficacy as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with at least 1 risk-factor for PPH.

7.1.2.5. Su et al., 2009 Carbetocin 100 µg IM versus Syntometrine (5 IU/0.5 mg) IM

Title

Carbetocin versus Syntometrine for the third stage of labour following vaginal delivery – a double blind randomised controlled trial.

Objectives

The aim of this study was to test the hypothesis that carbetocin (100 µg) IM is as effective as Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM for the prevention of postpartum haemorrhage for women who undergo vaginal deliveries, but with less adverse effects.

Design

The study was a prospective, double blind, randomised controlled clinical trial. The study recruited healthy pregnant women who were attending antenatal clinics at the National University Hospital, a tertiary hospital in Singapore. A total of 370 women were recruited between January 2005 and April 2008. Women who agreed to participate were required to give written informed consent. The study drugs were administered IM following delivery of the anterior shoulder. The study was stated to have followed Good Clinical Practice guidelines. The study was approved by the National Healthcare Group Domain Specific Review Board and supported by a grant from the National Healthcare Group, Singapore.

Inclusion and exclusion criteria

Women were considered eligible for participation if they were expected to undergo vaginal delivery at or beyond 34 weeks of gestation. Women scheduled for elective CS and women with risk-factors for PPH, such as multiple pregnancies, past history of PPH and history of suspected coagulopathy, were excluded from the study. Other exclusion criteria were women with contraindications for the use of Syntometrine, including history of coronary artery disease or

hypertension, and women with history of hypersensitivity to Syntometrine or carbetocin.

Study treatments

The study treatments were carbetocin 100 µg IM or Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM following delivery of the anterior shoulder.

Comment: The dose of Syntometrine used in this study is consistent with the Australian approved dose of this drug for the active management of the third stage of labour (that is, 1 mL IM following expulsion of the placenta). The carbetocin dose used in this study (100 µg) IM is consistent with the dose being proposed for registration for vaginal delivery.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was postpartum haemorrhage requiring additional uterotonic therapy. The standard criteria for the use of additional uterotonic agents in the study centre were: (a) suboptimal uterine tone; and/or (b) brisk estimated blood loss exceeding 300 mL with or without hypotension (blood pressure <90/60) or tachycardia (pulse rate > 100 beats per minute).

The *secondary efficacy outcome measures* were the incidence of PPH (≥ 500 mL) and the incidence of severe PPH (≥ 1000 mL). The authors stated that clinical estimation of blood loss was not used as the primary outcome as quantitative measurement is 'impractical and difficult to achieve with precision'. Following delivery, uterine tone was monitored, while blood pressure, pulse rate and temperature were monitored every 30 minutes for 2 h after delivery.

Assessment of both the primary and secondary outcomes was performed in the delivery suite, within 2 h after delivery. This was to ensure that any complications related to the delivery or medications had resolved prior to the women being transferred to the postnatal ward. Visual estimation of blood loss was made by both the mid-wife and the obstetrician. The use of additional uterotonic agents, need for manual removal of the placenta, need for blood transfusion and length of hospital stay were recorded. A standard questionnaire assessing adverse effects was completed by the participant and the presence or absence of adverse symptoms was recorded. Participants graded symptoms from very mild to very severe on a five-point visual analogue scale.

Comment: In this study, the need for additional uterotonic agents was selected as the primary outcome measure as the authors considered it to be the most important clinical indicator of postpartum blood loss after delivery. The authors commented that quantitative measurement of postpartum blood loss is impractical and difficult to achieve with precision. In addition, blood loss after delivery comes not only from the placental bed related to inefficient uterine contractions, but also from episiotomy wounds, lacerations and other trauma to the birth canal. On the other hand, the decision to use additional uterotonic agents is based not only on clinical estimation of blood loss but also on diagnosis uterine atony. No changes in haemoglobin concentration from pre- to post-delivery were measured as the authors considered that estimation of postpartum haemoglobin is of low value and may lead to the wrong conclusions.

Randomisation and blinding methods

Randomisation was blocked and stratified by parity. The randomisation list with the allocation of the mode of intervention was forwarded from the Biostatistics Unit to the Department of Pharmacy at the National University Hospital. Both study drugs were packed and coded by the hospital central pharmacy according to the provided randomisation and allocation list. The glass ampoules were masked to make the drugs look identical. The corresponding opaque package containing the allocated drug was kept at the delivery suite. Clinical staff involved in the management of delivery and participants were blinded to the administered study drug. The

medication codes were broken following completion of the trial.

At entry to the delivery suite, subject consent to participate in the study was reconfirmed. Just prior to vaginal delivery, the delivery suite staff checked the registration master list to obtain the trial number for the patient. The corresponding opaque package containing the allocated drug was then administered following delivery of the anterior shoulder. Both medications were administered IM by the nursing staff in the delivery suite.

Sample size

Power calculations were performed. Based on the experience the study centre it was estimated that the need for additional uterotonic agents was around 10–15%. Therefore, the need of additional uterotonic agents of 13% was selected to calculate the sample size. To declare an equivalence of 10% for the need for additional uterotonic agents with 80% power and a two-sided test of 5%, 180 subjects were required in each arm. An additional 10 subjects were recruited to account for possible attrition.

Statistical methods

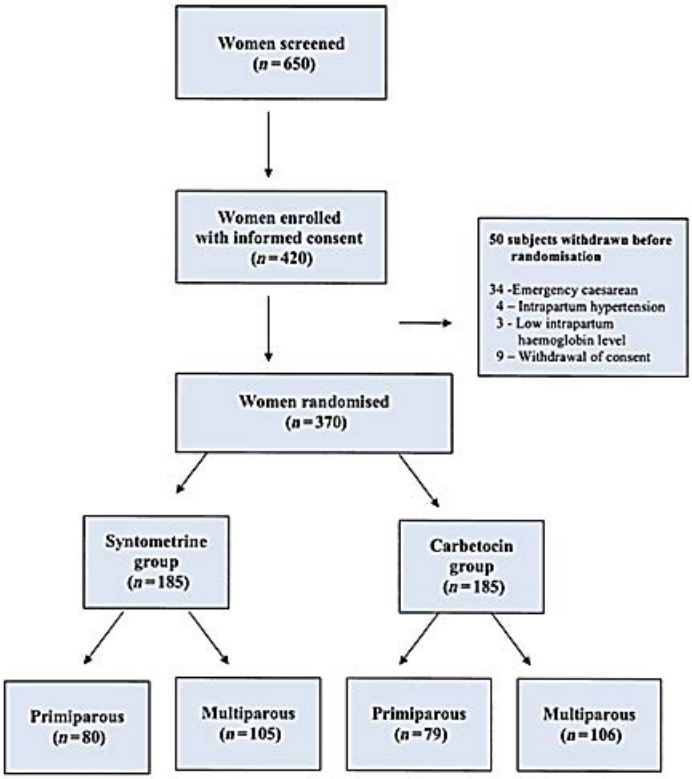
The difference between the two treatment arms in the use of uterotonic agents was assessed using the 2-sample t-test, and the 95% CI was calculated. Differences in quantitative measures between the two groups were analysed using parametric tests when normality and homogeneity assumptions were satisfied otherwise the equivalent non-parametric Mann–Whitney U test was applied. Statistical significance was set at $p < 0.05$.

Comment: In this study it was expressly stated that an ITT analysis had been employed. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy endpoints.

Participant flow

A total of 370 women were recruited between January 2005 and April 2008 and 185 women were randomised to each of the study arms. Informed consent was obtained from 420 participants, and 50 women were withdrawn from the study after informed consent but before randomisation. Of these 50 women, 34 were withdrawn because of emergency CS. The other reasons for withdrawal included intrapartum hypertension and withdrawal of consent. The flow chart for participants in this study is provided in Figure 2.

Figure 2: Su et al., 2009 Flow chart for participating women



Source: Su et al., 2009, Figure 1.

Major protocol violations/deviations

No information provided.

Baseline characteristics

The baseline characteristics of women in the two treatment arms were similar. Of the total population (n = 370), the mean age of the participants was approximately 30 years (range: 17, 47 years). The majority of women in the total population were multiparous (56.9%), the mean gestational age was approximately 39 weeks (range: 34, 42 weeks), and the mean birth weight was 3125 g (range: 1947, 4410). Of the total population (n = 370), normal vaginal delivery occurred in 89.7%, 8.6% required vacuum assistance, and 1.6% required forceps assistance, while manual removal of the placenta was reported in 2.7% and a third/fourth degree perineal tear in 1.9%.

Comment: The methods of analgesia used in this study were not stated. There was no information on the number of women who received regional anaesthesia.

Results for the efficacy outcome measures

The results for the primary and secondary outcome measures are summarised below in Table 9.

Table 9: Su et al., 2009 Primary and secondary outcome measures in the carbetocin and Syntometrine treatment arms

	Carbetocin (*n* = 185)	Syntometrine (*n* = 185)	*P* value	Total (*n* = 370)
Need for additional uterotonics, *n* (%)	25 (13.5%)	31 (16.8%)	0.38	56 (15.1%)
Primiparous	11 (15.1%)	12 (16.4%)	0.81	23 (15.8%)
Multiparous	13 (13.4%)	16 (16.7%)	0.53	29 (15.0%)
PPH (≥500 ml), *n* (%)	3 (1.6%)	3 (1.6%)	1.00	6 (1.6%)
Severe PPH (≥1000 ml), *n* (%)	1 (0.5%)	0 (0.0%)	1.00	1 (0.3%)
Need for blood transfusion, *n* (%)	1 (0.5%)	0 (0.0%)	1.00	1 (0.3%)
Mean blood loss (ml)				
Mean (SD)	217.4 (99.2)	223.1 (76.3)	0.29	220.2 (88.4)
Range	50–1250	100–700		50–1250
Median	200	200		200
Length of hospital stay (days)				
Mean (SD)	1.82 (0.60)	1.81 (0.76)	0.94	1.81 (0.76)
Median	2.00	2.00		

Source: Su et al., 2009, Table 2.

Comment: No significant difference between the two treatment arms was reported for the need for additional uterotonic agents within 2 h of delivery (primary efficacy outcome). The need for additional uterotonic agents was similar in primiparous and multiparous women. The most common therapeutic uterotonic agents used were oxytocin infusions, repeat doses of Syntometrine or bolus doses of ergometrine. The estimated mean blood loss was similar in both treatment arms, and the difference was not statistically significant. A small proportion of women experienced blood loss ≥ 500 mL (1.6% in each treatment arm) and only one woman experienced blood loss ≥ 1000 mL (carbetocin arm). Only one woman required a blood transfusion to manage blood loss (carbetocin arm). The authors comment that the discrepancy between the need for additional uterotonic agents (15.1%, all women) and the incidence of postpartum haemorrhage (1.6%, all women) was because obstetricians 'generally did not wait till blood loss exceeded 500 mL (definition of postpartum haemorrhage) before commencing uterotonics'.

The total number of women needing additional uterotonic agents did not add up to the number of primiparous and multiparous women needing additional uterotonic agents (that is, in the carbetocin arm a total of 25 women were reported to need additional uterotonic agents, including 11 in the primiparous group and 13 in the multiparous group, and in the Syntometrine arm a total of 31 women were reported to need additional uterotonic agents, including 12 in the primiparous group and 16 in the multiparous group). No reference was made to this apparent discrepancy in the report.

Overall comment on the study

This was a good quality study. Overall, the study showed that carbetocin 100 µg IM and Syntometrine IM are comparable as regards the need for additional uterotonic agents, the incidence of postpartum haemorrhage (≥ 500 mL), mean blood loss, need for blood transfusion, and length of hospital stay in women with low-risk of PPH delivering vaginally. The results

adequately demonstrated that carbetocin 100 µg IM and the approved dose of Syntometrine 1 ml IM have comparable efficacy as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with low-risk of PPH.

7.1.2.6. Askar et al., 2011 Carbetocin 100 µg IM versus Syntometrine (5IU /0.5 mg) IM

Title

Carbetocin versus Syntometrine in the management of third stage of labor following vaginal delivery

Objectives

The objective of this study was to compare the efficacy and safety of single IM doses of carbetocin and Syntometrine for the management of the third stage of labour following vaginal delivery in women with low-risk of PPH.

Design

This study was a prospective, double blind, randomised and controlled clinical trial. It included 240 healthy women with viable normal singleton pregnancies achieving normal vaginal delivery at or beyond 37 weeks gestation during the period from May 2009 to December 2009 at TAIBA Hospital in Kuwait. The study was approved by the hospital Ethics Committee, and written informed consent was obtained from eligible women on admission to the labour ward.

Baseline maternal blood pressure, pulse rate, and temperature were recorded on admission to the delivery room. Haemoglobin concentration was measured on admission to the delivery room and repeated 24 h postpartum.

The third stage of labour was actively managed using standard procedures. Oxytocin infusion, if in progress, was stopped. Women received either IM carbetocin or Syntometrine following delivery of the anterior shoulder. Additional doses of uterotonic agents were administered if uterine atony was suspected or diagnosed.

Following delivery, uterine tone was monitored, and blood pressure, pulse rate, and temperature were checked immediately after delivery and repeated every 30 minutes for 2 h after delivery.

Inclusion and exclusion criteria

The study included healthy women with viable normal singleton pregnancies at or beyond 37 weeks. Exclusion criteria included women younger than 18 years of age and those with known or suspected coagulopathy. Other exclusion criteria were contraindications to the use of Syntometrine or carbetocin including pre-existing hypertension, preeclampsia, asthma, cardiac, renal or liver diseases, epilepsy, as well as women with history of hypersensitivity to either study drug. In addition, the study excluded women with high risk-factors for primary postpartum hemorrhage, such as grand multiparity (> para 5) or presence of uterine fibroids, polyhydramnios, twin pregnancy, fetal macrosomia, or severe anaemia. Women with cervical tears or who required prophylactic oxytocin infusion after delivery were also excluded.

Study treatments

Participants received either a single dose of carbetocin 100 µg IM or a single dose of Syntometrine (5 IU oxytocin/0.5 mg ergometrine) IM administered at the delivery of the anterior shoulder.

Comment: The dose of Syntometrine used in this study is consistent with the Australian approved dose of this drug for the active management of the third stage of labour (that is, 1 mL IM following expulsion of the placenta). The carbetocin dose used in this study (100 µg) IM is consistent with the dose being proposed for registration for vaginal delivery.

Randomisation and blinding methods

Randomisation was performed by opening a sealed, consecutively numbered, opaque envelope containing a computer-generated code prepared before recruitment. Clinical staff involved in the management of delivery and participants were blinded to the administered study drug. The medication codes were broken following the completion of the trial.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was postpartum haemorrhage requiring additional uterotonic therapy. The standard criteria for the use of additional uterotonic agents at the study centre were: (a) suboptimal uterine tone; and/or (b) brisk estimated blood loss exceeding 300 mL with or without hypotension (blood pressure < 90/60 mmHg) or tachycardia (pulse rate > 100 beats per minute).

The *secondary efficacy outcome measures* were the incidences of postpartum haemorrhage (≥ 500 mL) and severe postpartum hemorrhage (≥ 1,000 mL).

Measurement of blood loss by the gravimetric method was started immediately after drug administration. All drapes, gauzes, tampons, and pads were collected for the first 2 h following the delivery of the placenta. A digital weighing scale was used. The difference in weight of the material before and after the 2 h collection period was calculated. A 100 g increase in weight was considered to be equivalent to 100 mL blood.

Mean blood pressure (systolic and diastolic) and pulse rate were measured immediately after delivery and at 30 and 60 minutes following delivery. Urine output, blood transfusions and/or iron sucrose injections postpartum were recorded in the first 24 h post-delivery.

Comment: The authors stated that the need for additional uterotonic agents was used as the primary efficacy outcome variable as they considered it to be the most important clinical indicator of postpartum blood loss after delivery. The authors stated that clinical estimation of blood loss was not used as the primary outcome as quantitative measurement of postpartum blood loss is impractical and difficult to achieve with precision.

Sample size

No information was provided on the method used to select the sample size.

Statistical methods

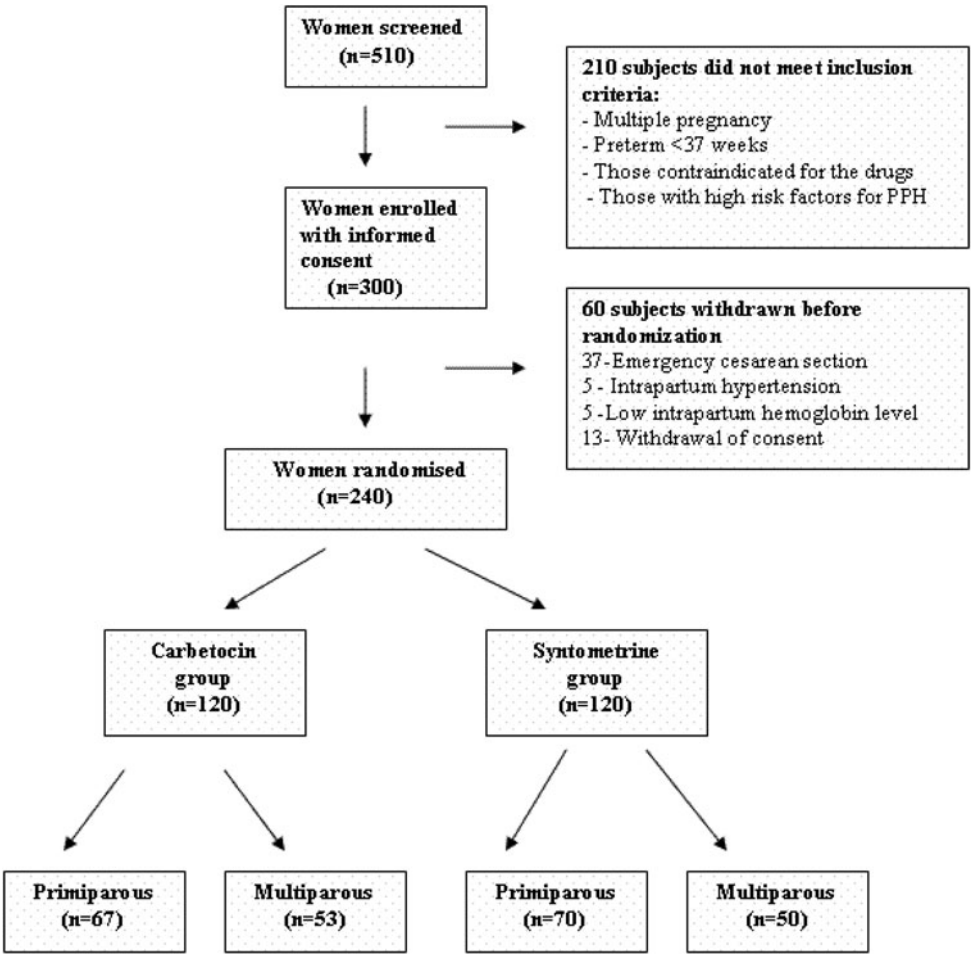
Differences between the carbetocin and Syntometrine arms were compared using Fisher's exact test for categorical data and Student's t-test for continuous data. A p-value of less than 0.05 was considered to be statistically significant, and a p-value of less than 0.01 was considered to be statistically highly significant.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy outcome measures.

Participant flow

A total of 510 women were screened for study entry, including 300 with informed consent who were enrolled and 210 who were not enrolled because of failure to meet the inclusion criteria. Of the 300 enrolled women, 60 were withdrawn prior to randomisation (37 emergency CS; 5 intrapartum hypertension; 5 low intrapartum haemoglobin concentrations; and 13 withdrawal of consent). Therefore, the study included a total of 240 randomised participants, 120 in each of the two treatment arms. All 240 women were reported to have completed the study. The flow chart for participating women is provided in Figure 3.

Figure 3: Askar et al., 2011 Flow chart for participating women



Source: Askar et al., 2011, Figure 1.

Major protocol violations/deviations

No information provided.

Baseline data

The baseline and intrapartum characteristics of the women in the two treatment arms were similar. The mean age of the women in both treatment arms was approximately 28 years, with a mean standard deviation of approximately 5.5 years. The majority of women in both treatment arms were primiparous (56%, carbetocin versus 58%, Syntometrine) and the mean gestational age at delivery in both treatment arms was approximately 39 weeks. Overall, each treatment arm was reported to be comparable with respect to maternal age, weight, height, body mass index, and haematological values at entry, as well as for parity, gestational age, medical disorders, and the use of either labour induction or epidural analgesia. There were no differences in risk-factors for PPH, such as retained placenta and third or fourth degree perineal tears. Labour characteristics were similar in each group. There was no significant difference between the two groups as regards the duration of third stage of labour. There was no significant difference between the two groups as regards the number of patients receiving oxytocin infusion for augmentation of labour.

Comment: In this study the use of epidural anaesthesia was comparable in the two treatment arms (17.5%, carbetocin; 20.0%, Syntometrine).

7.1.2.7. Results for the efficacy outcomes

The primary and secondary outcome measures are summarised below in Table 10.

Table 10: Askar et al. 2011 Primary and secondary outcome measures, peripartum haemoglobin concentration and urine output during postpartum Day 1

Variables	Carbetocin (n = 120)	Syntometrine (n = 120)	P value	Significance
Need for additional uterotonics, *n* (%)				
Primiparous	7 (5.83)	9 (7.5)	0.79 (>0.05)	N.S.
Multiparous	11 (9.16)	12 (10.0)	0.99 (>0.05)	N.S.
Primary PPH (≥500 ml), *n* (%)	2 (1.67)	3 (2.50)	0.99 (>0.05)	N.S.
Severe PPH (≥1,000 ml), *n* (%)	0 (0)	1 (0.83)	0.85 (>0.05)	N.S.
Need for blood transfusion, *n* (%)	0 (0)	1 (0.83)	0.85 (>0.05)	N.S.
Mean blood loss (ml) (mean ± SD)	224.6 ± 110.6	306.1 ± 95.65	<0.0001 (<0.01)	H.S.
Hemoglobin at onset of labor (g/dl)*	11.5 ± 1.3	11.7 ± 1.2	0.21 (>0.05)	N.S.
Hemoglobin on postpartum day 1 (g/dl) (24 h after delivery)	10.9 ± 1.1	10.6 ± 1.2	0.04 (<0.05)	S.
Hemoglobin difference (g/dl) (mean fall in hemoglobin)	0.8 ± 0.2	1.1 ± 0.3	<0.0001 (<0.01)	H.S.
Urine output during postpartum day 1 (ml/h)	48.3 ± 2.7	47.9 ± 2.6	0.24 (>0.05)	N.S.

N.S. non-significant, *SD* standard deviation, *S.* significant, *H.S.* highly significant

Source: Askar et al., 2011, Table 2.

Comment: There was no significant difference in the proportion of women needing additional uterotonic agents during postpartum Day 1, with the incidence being 15% (18/120) in the carbetocin arm and 17.5% (21/120) in the Syntometrine arm, p = 0.72. The proportions of primiparous and multiparous women requiring additional uterotonic agents were similar in both treatment arms, with the incidence in multiparous women requiring additional uterotonic agents being marginally higher than the incidence in primiparous women. The proportion of women experiencing primary postpartum haemorrhage (≥ 500 mL blood loss) was small in both treatment arms and notably less than the proportion of women needing additional uterotonic agents. Only one woman (Syntometrine arm) experienced a severe postpartum haemorrhage (≥ 1000 mL). Mean blood loss during postpartum Day 1 was notably greater in the Syntometrine arm than in the carbetocin arm (approximately 82 mL), and the difference was statistically significant (p < 0.0001). The reduction in mean haemoglobin concentration was statistically significantly greater in the Syntometrine arm than in the carbetocin arm, but the difference between the two treatment arms was small and not clinically meaningful. There were no statistically significant or clinically meaningful differences between the two treatment arms as regards the need for blood transfusion and urine output.

Overall comment on the study

This was a good quality study. Overall, the study showed that carbetocin 100 µg IM and Syntometrine IM were comparable as regards the need for additional uterotonic agents and the incidence of postpartum haemorrhage in women with low-risk of PPH who delivered vaginally. The results adequately demonstrated that carbetocin 100 µg IM and the approved dose of Syntometrine 1 ml IM have comparable efficacy as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with low-risk of PPH.

7.1.2.8. Samimi et al., 2013 Carbetocin 100 µg IM versus Syntometrine (5 IU/0.2 mg) IM

Title

Carbetocin vs. Syntometrine in prevention of postpartum hemorrhage: a double blind randomised control trial.

Objectives

The objective of this study was to compare the efficacy of carbetocin IM to Syntometrine IM for the prevention of PPH.

Design

The study was a double blind, randomised, controlled clinical trial. The study was undertaken at the Shabihkani Maternity Center in Kashan, Iran, from March 2011 to June 2011. The study included 200 women, with 100 women being randomised to each of the two treatment arms. Eligible women provided signed informed consent. The study protocol was approved by the Clinical Research Ethics Committee of Kashan University of Medical Sciences. The study is registered in the Iranian registry of clinical trials. The study was supported in part by a grant from the Kashan University of Medical Sciences, Kashan, and Iran.

The study drug was administered IM after placental separation. If oxytocin infusion was in progress it was discontinued. Maternal blood pressure, pulse rate and uterine tonicity were assessed immediately after administration of the study drug and repeated 30 and 60 minutes later. Uterine tonicity was scored from 0 to 3 (that is, mild, moderate or severe).

Inclusion and Exclusion criteria

The study included women at low-risk of postpartum haemorrhage who delivered vaginally. The exclusion criteria included chronic hypertension, preeclampsia, uterine or cervical rupture, asthma, cardiovascular, renal or liver diseases, grand multiparity, uterine fibroids, and history of PPH.

Study treatments

Patients were randomised to single doses of carbetocin (n = 100) or Syntometrine (n = 100). The carbetocin dose was 100 μg (1 mL) IM and the Syntometrine dose was 1 ml (5 IU oxytocin/0.2 mg ergometrine) IM, administered after placental separation.

Comment: The dose of ergometrine, combined with oxytocin 5 IU in the Syntometrine 1 mL ampoule, was 0.2 mg rather than the Australian approved dose of 0.5 mg. The dose of carbetocin used in the study (100 μg) administered by IM injection is the dose proposed for vaginal delivery.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was the assessment of the haemoglobin concentration on admission to the labour ward compared to the haemoglobin concentration 24 h after delivery. The *secondary efficacy outcome measure* was the requirement for additional uterotonic agents. The criteria for use of additional uterotonic agents were estimated blood loss of more than 500 mL with or without hypotension or tachycardia and poor uterine tonicity. Women were also evaluated for adverse effects of the drugs within 2 h of delivery.

Comment: This study did not include an assessment postpartum blood loss.

Randomisation and blinding methods

Randomisation was performed using a random number table. Both study drugs were coded and packed before recruitment, and stored at the delivery room. The study was double blinded.

Sample size

The authors of the report stated that *'(s)ample size calculations were based on (their) pilot study, which showed that mean and standard deviation haemoglobin level in carbetocin and Syntometrine group was 11.35 ± 1.04 g/dl and 11.79 ± 1.06 g/dl. For 5% level of significance and 80% power it was necessary to recruit 91 women for each trial arm. Considering a dropout rate of 10% the sample size required 100 per group*'.

Comment: The description of sample size calculations in this study was unclear. It is assumed that the haemoglobin levels refer to post-delivery levels in the two treatment arms and that the study was powered on the difference in post-delivery haemoglobin levels in the two treatment arms.

Statistical methods

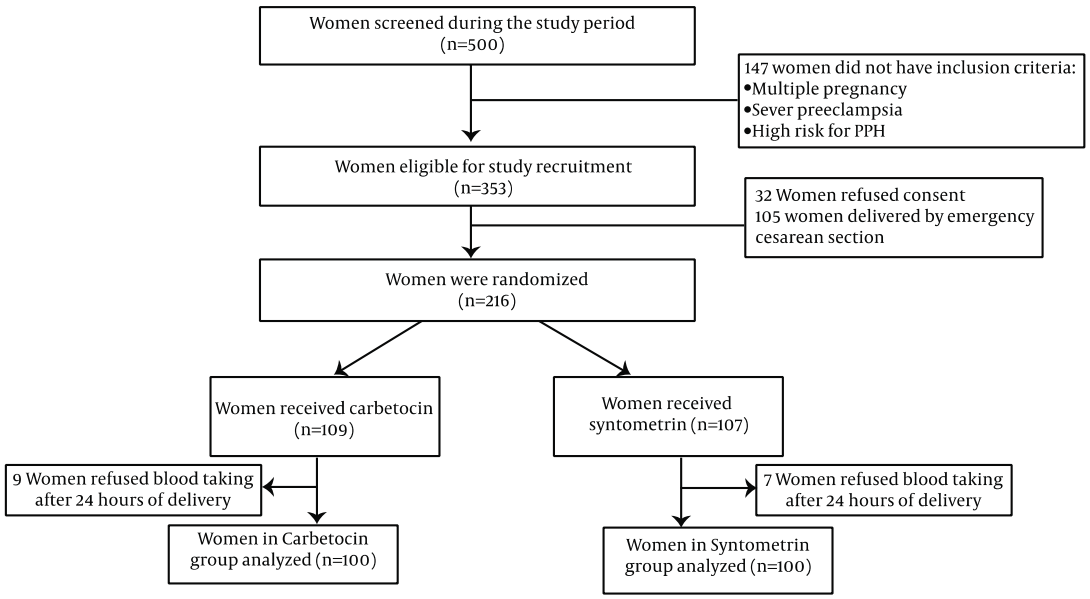
All outcome measures, including the need for additional uterotonic agents, uterine tonicity, blood pressure, pulse rate, fall in haemoglobin and drugs side effects were analysed using chi-square test, Fisher's exact, Student's t-test or logistic regression. The relative risk (RR) and associated 95% CIs were also calculated. A p-value of less than 0.05 was considered statistically significant.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy outcome measures.

Participant flow

There were 500 women screened during the study period, including 353 who were eligible for the study and 147 who were ineligible due to failure to meet the inclusion criteria. Of the 353 eligible women, 216 were randomised, 32 refused consent, and 105 underwent CS. Of the 216 randomised women, 109 were randomised to carbetocin and 100 were analysed (9 refused blood sampling at 24 h after delivery), and 107 were randomised to Syntometrine and 100 were analysed (7 refused blood sampling at 24 h after delivery). The participant flow chart is provided in Figure 4.

Figure 4: Samimi et al., 2013 Study participant flow chart



Source: Samimi et al., 2013, Figure 1.

Major protocol violations/deviations

No information provided.

Baseline data

Baseline and birth characteristics of women in the two treatment arms were well balanced. The mean age of women in this study was approximately 25 years with an approximate standard

deviation of 4 years. The majority of women in the two treatment arms were primiparous. The percentage of women with induced labour and episiotomy were similar in the two treatment arms, while perineal lacerations occurred more commonly in the Syntometrine arm than in the carbetocin arm. The infant birth weights were comparable for the two treatment arms.

Comment: The methods of analgesia were not stated in this study. There was no information on the number of women receiving regional anaesthesia.

Results for the efficacy outcomes

The results for the primary and secondary efficacy outcome measures are summarised below in Table 11.

Table 11: Samimi eta al. 2013 Primary and secondary outcome measures in the carbetocin and Syntometrine treatment arms

Characteristics	Carbetocin (n = 100)	Syntometrine (n = 100)	P-value
Hemoglobin at Onset of Labour (g/dl)[a]	12.12 ± 1.1	13.02 ± 1.2	0.001
Hemoglobin at 24 Hours after Delivery (g/dl)[a]	11.71 ± 1.1	11.98 ± 1.3	0.13
Mean Fall in Hemoglobin (g/dl)[a]	0.41 ± 0.36	1.04 ± 0.78	< 0.001
Percent Fall of Hemoglobin			
> 20%	0 (0)	3 (3)	0.08
> 10%	3 (3)	35 (35)	< 0.001
Need for Additional Uterotonic	1 (1)	11 (11)	0.002
Uterine Tonicity Immediately after Drug Administration[a]	2.11 ± 0.54	1.29 ± 0.47	< 0.001
Uterine Tonicity 30 Minutes after Drug Administration[a]	2.01 ± 0.59	1.68 ± 0.46	< 0.001
Uterine Tonicity 60 Minutes after Drug Administration[a]	2.04 ± 0.63	1.94 ± 0.23	0.14
Mean Systolic Blood Pressure Immediately after Drug Administration[a]	112 ± 91	120 ± 73	< 0.001
Mean Systolic Blood Pressure 30 Minutes after Drug Administration[a]	109 ± 78	115 ± 77	< 0.001
Mean Systolic Blood Pressure 60 Minutes after Drug Administration[a]	111 ± 69	113 ± 85	0.03
Mean Diastolic Blood Pressure Immediately after Drug Administration[a]	71 ± 9	73 ± 8	0.05
Mean Diastolic Blood Pressure 30 Minutes after Drug Administration[a]	70 ± 8	71 ± 7	0.57
Mean Diastolic Blood Pressure 60 Minutes after Drug Administration[a]	71 ± 7	71 ± 7	0.88

[a] Data are presented as Mean ± SD

Source: Samimi et al., 2013, Table 2.

Comments: A limitation of this study was that there was no assessment of the volume of postpartum blood loss or of the proportion of women experiencing postpartum haemorrhage (that is, blood loss ≥ 500 mL). The mean reduction in the haemoglobin level from pre-delivery to 24 h post-delivery, which was the primary efficacy outcome measure, was statistically significantly greater in the Syntometrine arm than in the carbetocin arm. The percentage of women in the two treatment arms with > 10% reduction in haemoglobin level was notably greater in the Syntometrine arm than in the carbetocin arm (35% versus 3%, respectively), and the difference between the arms was statistically significant (RR = 11.6 (95% CI: 3.7, 36.7), p < 0.001). Reduction in haemoglobin level > 20% was reported in no women in the carbetocin arm and 3% of women in the Syntometrine arm. The need for additional uterotonic agents was reported more frequently in the Syntometrine arm than in the carbetocin arm, and the difference was statistically significant and clinically meaningful. Uterine tonicity was notably greater in the carbetocin arm than in the Syntometrine arm immediately after delivery and at 30 minutes after delivery, with similar uterine tonicity in the two arms at 60 minutes after delivery. The results relating to changes in blood pressure are discussed later in this CER.

Overall comment on the study

The quality of this study was reasonable. The study showed that carbetocin was more effective than Syntometrine for the prevention of postpartum haemorrhage, based on a statistically significantly smaller reduction in the haemoglobin level at 24 h post-delivery and a lower incidence of the need for additional uterotonic agents. However, the study included no efficacy outcomes assessing the absolute volume of blood loss post-delivery or the proportion of women experiencing a PPH (that is, blood loss ≥ 500 mL). In addition, the dose of ergometrine in the Syntometrine 1 mL ampoule was stated to be 0.2 mg, which differs from the approved dose of 0.5 mg in the Australian registered Syntometrine 1 mL ampoule approved for use. The description of the sample size calculations in this study was unclear. The results adequately demonstrated that carbetocin 100 µg IM is more efficacious than Syntometrine at a lower than approved dose as regards the prevention of uterine atony and excessive bleeding following vaginal delivery in women with low-risk for PPH.

7.1.3. Evaluator's conclusion on clinical efficacy vaginal delivery: active management of the third stage of labour

The submission included 7 published studies supporting the application to extend the indications of carbetocin to include vaginal delivery. Of the 7 studies, 1 was conducted in Canada, 3 were conducted in Asia (HK, Singapore, Malaysia), 2 were conducted in the middle-east (Kuwait, Iran), and 1 was conducted in North Africa (Egypt). Overall, the 7 published studies were of reasonable quality, with most being of good quality.

The 7 studies included 798 women treated with carbetocin and 792 women treated with an active control (177, oxytocin; 615, Syntometrine). The 7 studies included 4 which excluded women with significant risk-factors for PPH (Leung et al., 2006; Su et al., 2009; Askar et al., 2011, Samimi et al., 2013), and 3 which included women with significant risk-factors for PPH (Boucher et al., 2004; Nirmala et al., 2009; Maged et al., 2016).

In each of the 7 studies, single dose carbetocin 100 µg IM (approved dose) was administered for the active management of the third stage of labour to prevent uterine atony and excessive bleeding following vaginal delivery. In the 2 studies in which oxytocin was the active control, an approved dose of 5 IU IM was used in Maged et al (2015) and an unapproved higher dose of 10 IU IV was used in Boucher et al (2004). The drugs were administered after delivery of the posterior shoulder in Maged et al (2015) and after delivery of the placenta in Boucher et al (2004). In the 5 studies in which Syntometrine was the active control, the dose was the approved dose in 4 studies (Leung et al., 2006; Nirmala et al, 2009; Su et al., 2009; Askar et al., 2011), and lower than the approved dose in 1 study (that is, ergometrine component 0.2 mg/mL rather than 0.5 mg/mL in Samimi et al., 2013). In the 5 carbetocin versus Syntometrine studies the drugs were administered with or after delivery of the anterior shoulder in 3 studies (Leung et al., 2006; Su et al., 2009; Askar et al., 2011), after expulsion of the placenta in 1 study (Samimi et al., 2013), and after delivery of the infant in 1 study (Nirmala et al., 2009).

The anaesthetic methods were not reported in all 7 studies. In Boucher et al (2004), it was stated that anaesthesia was by either parenteral narcotics or by regional administration, but no information on the number of women receiving the different methods of anaesthesia were provided. In Nirmala et al (2009), it was stated that that anaesthesia was by either parenteral narcotics or by regional administration, and that the carbetocin and Syntometrine arms were comparable with respect to the number of women receiving epidural anaesthesia but no numerical values were provided. Epidural anaesthesia in the carbetocin and Syntometrine arms was administered to 20% and 21.3% of women, respectively, in Leung et al (2006), and 17.5% and 20.0% of women, respectively in Askar et al (2011). No information on the method of anaesthesia was provided in Maged et al (2016), Su et al (2006), or Samimi et al (2013).

There were no submitted studies assessing the efficacy of carbetocin for the treatment of postpartum haemorrhage following vaginal delivery, or as an additional uterotonic agent if

needed following the initial administration. The long half-life of carbetocin suggests that the drug might be unsuitable for repeat IM or IV dosing or continuous IV infusion in the postpartum period due to and increased risk of adverse events resulting from accumulation of the drug. Standard uterotonic agents were administered if additional uterotonic therapy was required and data were provided on the incidence of women needing additional uterotonic agents in each of the 7 studies.

The primary efficacy outcome measure differed across the 7 studies, with the primary outcome measure being need for additional uterotonic agents in 3 studies (Leung et al., 2006; Su et al., 2009; Boucher et al., 2004) and reduction in haemoglobin level at 24 or 48 h after delivery in 2 studies (Samimi et al., 2013; Leung et al., 2006). No primary or secondary outcome measures were defined in 2 studies (Nirmala et al., 2009; Maged et al., 2015), but both studies assessed a range of outcome measures. Most studies used a number of efficacy outcome measures to assess blood loss after injection of the study drugs, and in general the results were consistent across the studies.

None of the 7 studies specified PPH (≥ 500 mL) as being the primary efficacy outcome measure. However, information relating to the total volume of blood lost following delivery and the incidence of women with blood loss greater than or equal to 500 mL were reported in 6 of the 7 studies. No information on the volume of blood lost or the incidence of women with blood loss ≥ 500 mL was provided in Samimi et al (2013), but in Samimi et al (2013) the criteria for treatment with uterotonic agents was estimated blood loss > 500 mL. In 2 of the studies in which the need for additional uterotonic agents was defined as the primary outcome measure, the study report stated that this outcome was selected in preference to clinical assessment of blood loss because quantitative measurement of postpartum blood loss is impractical and difficult to achieve with precision (Su et al.,2009; Askar et al., 2011).

The randomisation method was generally well described in nearly all studies, and all studies were double blind in design. Most of the studies included some information on how the sample size was calculated, but detailed data on power were generally not provided. All studies used standard statistical methods to analyse the efficacy outcome measures, with Student's t-test being used for continuous variables and the chi-square or Fisher's exact test being used for categorical variables. Statistical significance for all studies was set at an alpha of 0.05. None of the studies included a statistical adjustment to account for the multiplicity of pairwise testing of the efficacy outcome measures. The efficacy analyses appeared to be based on the ITT principle in all studies, but only 1 study explicitly stated that the data were analysed using the ITT method (Su et al., 2009). None of the studies provided data on major protocol deviations.

In summary, it is considered that the submitted data have satisfactorily established the efficacy of carbetocin 100 µg IM for the active management of the third stage of labour to prevent uterine atony and excessive bleeding following vaginal delivery. The submitted studies showed that the efficacy of carbetocin 100 µg IM was comparable to that of the approved dose of Syntometrine (5 IU oxytocin/0.5 mg ergometrine) 1 mL IM, and to that of oxytocin at both the approved dose (5 IU IM) and higher than the approved dose (10 IU IV). In addition, 1 study showed that carbetocin 100 µg IM was more efficacious than a lower than approved dose of Syntometrine (5 IU oxytocin/0.2 mg ergometrine) 1 mL IM.

7.2. Emergency caesarean section (CS)

7.2.1. Submitted studies

The submission included 3 recently published studies providing efficacy data in a total of 849 women following delivery via emergency CS under regional anaesthesia, including 425 women treated with single dose carbetocin 100 µg IV and 424 women treated with single dose oxytocin 5-20 IU IV (El Behery et., 2016; Razali et al., 2016; Whigham et al, 2016)

The sponsor states that the original application to register carbetocin included safety and efficacy data on a total of 440 women undergoing elective CS under regional anaesthesia. The sponsor states that the 3 new studies in women delivering via emergency CS were submitted to support removal of the statement in the Duratocin PI regarding the lack of data in women at high risk of PPH and in women delivering via CS under general anaesthesia. However, it should be noted that none of the 3 new studies included women delivering via CS under general anaesthesia. The 3 new studies are summarised below in Table 12 and are evaluated in Section 7.2.2 of this clinical evaluation report.

Table 12: Studies submitted in women undergoing emergency caesarean section (CS)

Study	Objectives	Design	Carbetocin Oxytocin	Participants	Efficacy Outcomes
El Behery et al., 2016. Two centres in Egypt.	Efficacy and safety of carbetocin versus oxytocin in obese nulliparous women undergoing emergency CS.	R, db, ac, dd (using RL); drugs	100 µg IV over 2 min, after delivery of the baby, preferably before removal of placenta; n = 90 20 IU/1000 mL RL IV at a rate of 125 mL/h; after delivery of the baby, preferably before removal of placenta; n = 100	Obese nulliparous women (that is, 2 x risk-factors for PPH). Women (n = 28) needing GA were excluded.	Primary: Major PPH (≥ 1000 mL) within 24 h of delivery. Secondary: BP after injection; need for blood transfusion; Hb and Hct drop; need for additional uterotonic agents; uterine tone.
Razali et al., 2016. One centre in Malaysia.	Evaluate the uterotonic effect of carbetocin versus oxytocin in women undergoing emergency CS.	R, db, ac.	100 µg IV; after delivery of the baby; n = 276. 10 IU IV; after delivery of the baby; n = 271.	Women with risk-factors for PPH were included in this study. The study excluded CS under GA.	Primary: Need for additional uterotonic agents on the 24 h after CS. Secondary: type and timing of additional uterotonic agents; estimated blood loss (mean, ≥ 500 mL, ≥ 1000 mL); total operating time; Hb and

Study	Objectives	Design	Carbetocin Oxytocin	Participants	Efficacy Outcomes
					Hct drop.
Whigham et al., 2016. One centre in Australia.	Efficacy of carbetocin versus oxytocin at non-elective CS.	R, db, ac.	100 µg IV; immediately after birth of the baby; n = 59 5 IU IV; immediately after birth of the baby; n = 53.	Primiparous and multiparous. Women were excluded if they required CS under GA.	Primary: Need for additional uterotonic agents. Secondary: Estimated blood loss during surgery, secondary postpartum blood loss, post-operative Hb.

R = randomised; db = double blind; ac = active-controlled; dd = double-dummy; RL = Ringer's lactate; IV = intravenous; h = h; CS = caesarean section; PPK = postpartum haemorrhage; GA = general anaesthesia; HB = haemoglobin; Hct = haematocrit; BP = blood pressure.

7.2.2. Evaluation of the submitted studies

7.2.2.1. El Behery et al, 2016 – carbetocin 100 µg IV versus oxytocin 20 IU IV

Title

Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery.

Objectives

The objective of this study was to compare the effectiveness and safety of carbetocin administered as single IV bolus versus oxytocin administered as a single IV infusion for the prevention of PPH in obese nulliparous women undergoing emergency caesarean delivery.

Design

This study was a randomised, double blind, controlled clinical trial. It was conducted in the Zagazig University maternity hospital and the Suez Canal University Hospital, Egypt, from 1 January 2013 to 31 June 2014. The study included 180 women (90 in each treatment arm) who underwent emergency CS, which was defined as an unplanned caesarean delivery due to an emergency situation in the active phase of labour (for example, failure to progress, obstructed labour and fetal distress). Participants were enrolled in the study after fulfilling the inclusion and the exclusion criteria. All women were obese with a BMI > 30 kg/m^2 calculated at the time of admission to the labour ward. Written informed consent was obtained from eligible women on admission. The study protocol was approved by 'IRP' of Zagazig University hospitals, which is assumed to be the local ethics committee.

Comment: The method of anaesthesia for emergency CS used in this study was not expressly stated. However, as 28 of the initially recruited 280 women were stated to have been excluded from the study due to general anaesthesia it is reasonable to infer that emergency CS was undertaken using regional anaesthesia.

Inclusion and exclusion criteria

Inclusion criteria were obese nulliparous women with a singleton pregnancy with a gestational age of 37 weeks or greater. Exclusion criteria were multigravida and/or malpresentation. Women who delivered vaginally or by elective CS were also excluded.

Study treatment

Patients were randomised to receive either carbetocin 100 µg IV or oxytocin 20 IU IV administered by the anaesthetist after delivery of the infant had been completed and preferably before removal of the placental. As the two drugs were administered differently, a double-dummy system was used to maintain the blind. The two specified protocols were:

- Protocol A: carbetocin 100 µg 1 mL plus Ringer's lactate solution 10 mL administered IV over 2 minutes and Ringer's lactate solution 4 mL in 1000 mL of Ringer's lactate solution administered IV at a rate of 125 mL/h.
- Protocol B: Ringer's lactate solution 11 mL administered IV over 2 minutes and oxytocin 20 IU diluted in Ringer's lactate solution 1000 mL administered IV at a rate of 125 mL/h.

Comment: The carbetocin dose used in this study was consistent with the proposed dose for CS of 100 µg IV as a bolus injection either before or after delivery of the placenta. However, the dose of oxytocin used in this study was notably higher than the approved dose for CS of 5 IU by IV infusion or slow bolus after delivery of the infant.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was the incidence of major primary postpartum haemorrhage defined as blood loss ≥ 1000 mL within 24 h of delivery as per the definition of PPH by the World Health Organisation. The study reported stated that the incidence of blood loss ≥ 1000 mL rather than the incidence of blood loss ≥ 500 mL was selected at the 'clinically relevant amount' because blood loss ≥ 500 mL is '*not uncommon and is not associated with adverse outcomes in the majority of healthy women'*. Blood loss was stated to have been estimated by the surgeon in the 'usual way (visual estimation, number of used swabs and amount of aspirated blood)'.

The *secondary efficacy outcome measures* were blood pressure change immediately after injection, incidence and amount of blood transfusion, haemoglobin and haematocrit from 2 h to 24 h after delivery, the use of additional uterotonic agents, and uterine tone. In this study, the criteria for using additional uterotonic agents were blood loss > 500 mL, with or without hypotension, poor uterine tonicity or tachycardia. The decision to use additional uterotonic agents was at the discretion of the surgeon. The additional uterotonic agents used in this study were oxytocin, methylergometrine, and misoprostol rectal suppositories.

Randomisation and blinding

The randomisation protocol required a designated member of the staff to open a sealed, opaque envelope containing a computer generated code randomising the participants to the carbetocin or oxytocin arm. The codes were broken only after the study was finished and all information had been tabulated and analysed. The study was double blind.

Sample size

The study report stated that for 'a power analysis or 90%' the study needed 90 women in each treatment arm.

Comment: No other information on sample size calculation was provided, other than for 90% power the study needed 90 women in each treatment arm.

Statistical methods

Quantitative data were expressed as means (SD), while qualitative data were expressed as numbers and percentages (%). Student's t-test and ANOVA were used to test significance of difference for quantitative variables and the chi-square test was used to test significance of difference for qualitative variables. A probability value of p value < 0.05 was considered statistically significant.

Comment: The description of the analysis based on quantitative or qualitative variables is unusual. Presumably this means that Student's t-test and ANOVA were used to assess continuous variables and the chi-square test was used to assess categorical variables. The use of Fisher's exact test to analyse categorical variables with small cell numbers was not mentioned. It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy outcome measures.

Participant flow

A total of 280 obese nulliparous women with singleton pregnancy were initially recruited for inclusion, and 100 women were excluded from randomisation (4 had congenital fetal anomalies, 7 had placenta previa, 5 were diabetic, 8 had hypertension, 9 had preeclampsia, 3 had cardiac conditions, 28 needed general anaesthesia, 17 delivered vaginally and 19 delivered by elective CS). Therefore, 180 women were randomised (90 to each of the two treatment arms).

Major protocol violations/deviations

No information provided.

12. Baseline data

The study report stated that there were no statistically significant differences between the two treatment arms as regards, gestational age, BMI, initial haemodynamic or laboratory parameters.

Comment: There appears to be an error in the reporting of the prothrombin time for women in oxytocin arm, where a value of 66 (0.77), no units provided, is given for the difference between patient and control. In addition, no units are provided for the activated partial thromboplastin time and there appears to be an error in the provided p-value for the difference between the two treatment arms for this variable (that is, p value of 30.32 is given). No units were provided for BMI or blood pressure.

Results for the efficacy outcomes

The results for the primary and secondary outcome measures are summarised below in Table 13.

Table 13: El Behery et al, 2016 Primary and secondary outcome measures for the two treatment arms

	Carbetocin ($n = 90$)	Oxytocin ($N = 90$)	p value
Major primary postpartum hemorrhage	2 (2.22)	12 (13.33)	0.03*
Postpartum hemoglobin level, g/dl, mean (SD)	11.14 ± 1.76	10.8 ± 1.68	0.09
Uterine tone			
Soft	2 (2.22)	15 (15.55)	0.03*
Firm	22 (97.78)	75 (86.45)	
Need for additional uterotonics, n (%)	2 (2.22)	64 (71.11)	0.002**
Estimated blood loss	689 ± 580	1027 ± 659	0.002**
Need for blood transfusions, n (%)	0 (0)	14 (15.55)	0.04*
Hemoglobin difference (admission–postpartum), mean (SD), n (%)	1.74 (0.87)	0.94 (0.67)	0.03*
Adverse effect, n (%)	2 (2.22)	4 (4.44)	0.08

N = number.
*$p < 0.5$; **$p < 0.005$.

Source: El Behery et al, 2015, Table 2.

Comment: The incidence of major primary PPH (≥ 1000 mL) was notably greater in the oxytocin arm than in the carbetocin arm (13.3% versus 2.2%), and the difference between the two arms was statistically significant (p = 0.03). The difference between the two treatment arms for the secondary outcome measures consistently favoured the carbetocin arm relative to the oxytocin arm, and the differences were statistically significant. Of particularly note was the markedly higher incidence in the oxytocin arm than in the carbetocin arm of the need for uterotonic agents, the markedly higher mean estimated blood loss blood loss in the oxytocin arm than in the carbetocin arm, and the higher incidence of the need for blood transfusion in the oxytocin arm than in the carbetocin arm. The reporting of the haemoglobin difference (admission-postpartum) was confusing and was inconsistent with the values given for the initial and postpartum haemoglobin levels in the two treatment arms.

Overall comment on the study

The quality of this study was fair. The primary efficacy outcome measure of the incidence of major primary PPH (≥ 1000 mL) was notably greater in the oxytocin arm than in the carbetocin arm, as was the mean estimated blood loss and the need for additional uterotonic agents. The study included no information on the assumptions used to calculate the sample size (that is, no assumed difference between the two treatment arms in the incidence of major primary PPH). The results adequately demonstrated that carbetocin 100 µg IV is more efficacious than oxytocin 20 IU IV as regards the prevention of uterine atony and excessive bleeding following emergency CS under regional anaesthesia in obese nulliparous women.

7.2.2.2. Razali et al., 2016 Carbetocin 100 µg IV versus oxytocin 10 IU IV

Title

Carbetocin compared to oxytocin in emergency cesarean section: a randomised trial.

Objectives

The objective of this study was to evaluate the uterotonic effect of carbetocin compared to oxytocin in emergency caesarean delivery.

Design

This was a randomised, double blind, single-centre study, conducted from December 2008 to September 2012 in a university hospital in Kuala Lumpur, Malaysia. The hospital was stated to have approximately 5000 deliveries per year and a CS rate of about 30%. Written consent was obtained from the participants after the decision for emergency CS was taken. The study was approved by the University of Malaya Medical Center Medical Ethics Committee.

In this study, emergency CS was defined as an unplanned procedure performed after the start of labour. Women who underwent emergency CS under general anaesthesia were excluded from the study. The study drug (carbetocin or oxytocin) was administered as a bolus injection by the anaesthetist after delivery of the baby. The surgeon assessed uterine tone and bleeding intra-operatively and had full discretion on whether additional uterotonic was needed, its mode of administration, dose and duration. The rescue uterotonic regimen in the study centre is oxytocin (40–80 IU in 500 mL isotonic crystalloid solution) administered as an IV infusion over 6 h.

Blood pressure and pulse rate were recorded at 0, 5, 10, 20, 30 and 60 minutes after study drug injection. After skin closure, the surgeon with the anaesthetist estimated the operative blood loss by summing up aspirated losses, surgical field spillage and uptake in surgical gauzes. The duration of surgery was recorded. Standard post CS monitoring was instituted in the recovery area and ward. A normal saline IV infusion at a typical rate of 500 mL every 4 h was routinely maintained post-operatively until full oral intake was established. The need and indication for additional uterotonic agents in the 24 h after CS, further surgery for PPH and blood transfusion before hospital discharge were recorded. Haemoglobin and haematocrit were routinely assessed before and the day after CS.

Inclusion and exclusion criteria

The inclusion criteria were age 18 years, singleton pregnancy, term gestation and decision made for a CS in labour. Emergency CS was defined as an unplanned procedure performed after the start of labour (that is, regular contractions at least every 10 minutes and cervical dilatation ≥ 3 cm). The exclusion criteria included women with known coagulopathy, study drug hypersensitivity, cardiac disease (including dysrhythmia), hypertension, liver, renal or endocrine disease (except gestational diabetes), uterine fibroids or suspicion of placental pathology, cases performed under general anaesthesia or where a transverse lower segment uterine incision was not used.

Study treatments

Participants were randomised (1:1) to either carbetocin 100 μg IV or oxytocin 10 IU IV administered after delivery of the baby.

Comment: The carbetocin dose used in this study was consistent with the proposed dose for CS of 100 μg IV as a bolus injection either before or after delivery of the placenta. The dose of oxytocin used in this study was higher than the approved dose for CS of 5 IU by IV infusion or slow bolus after delivery of the foetus.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was the requirement for additional uterotonic agents in the 24 h after CS.

The *secondary efficacy outcome measures* were the type of additional uterotonic agents, the timing of additional uterotonic agents, the mean estimated blood loss, the incidence of blood loss ≥ 500 mL and ≥ 1000 mL, and the total operating time.

Randomisation and blinding methods

The randomisation sequence was computer generated in a 1:1 ratio in blocks of 4. No stratification was undertaken. Numbered opaque packets containing the allocated study drug were prepared by one of the study authors not involved in trial recruitment. The packets contained either carbetocin 100 μg or oxytocin 10 IU, with both drugs being supplied as 1 mL clear solutions in glass ampoules. The original drug ampoules had their labels covered with an opaque white sticker to sustain blinding to both surgeon and anaesthetist. The numbered packets were kept in the operating theatre and assigned in sequence to participants. The study was double blind.

Sample size

The primary outcome in this study was the requirement for additional uterotonic agents in the 24 h after CS. The assumptions for the sample size calculation were based on the results of previous clinical trial that compared carbetocin to oxytocin in elective caesarean delivery and showed that additional uterotonic agents were required in 4.7% of women in the carbetocin arm and 10.1% of women in the oxytocin arm (Dansereau et al., 1999). For the higher risk emergency CS cases included in current the study, doubling in the additional uterotonic rates to 9.4% and 20.2% was assumed by the authors. Therefore, taking into account an alpha of 0.05, 90% power, a 1:1 recruitment ratio and applying Fisher's exact test, 243 subjects were required in each arm. The recruitment target was increased by 20% to account for post-randomisation drop-outs and then rounded up to the target recruitment of 300 in each arm.

Statistical methods

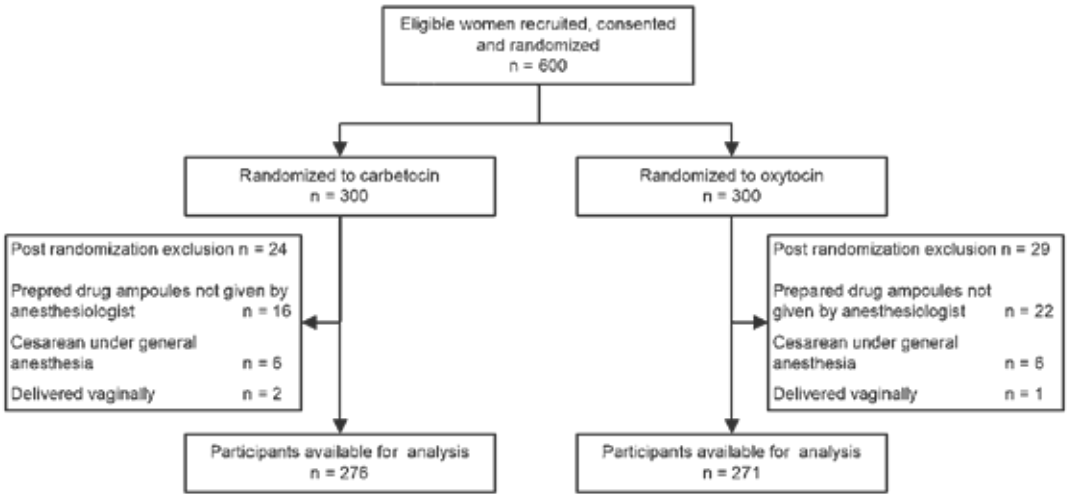
Independent sample t-test was applied to compare mean values. Pearson chi-square test was used for analysis of categorical variables, and Fisher's exact test was used when a cell size was less than 5. A repeated measure ANOVA was applied to compare the series of blood pressure and pulse readings assessed over time following administration of the study drugs. All tests were 2-sided and significance level was set at $p < 0.05$.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy outcome measures.

Participant flow

A total of 600 women were enrolled as planned and 300 women were randomised to each of the two treatment arms. There were 24 women in the carbetocin arm who were excluded post randomisation (24 prepared drug ampoules not given by the anaesthetist; 6 CS under general anaesthetic; 2 delivered vaginally). There were 29 women in the oxytocin arm who were excluded post randomisation (22 prepared drug ampoules not given by the anaesthetist; 6 CS under general anaesthetic; 1 delivered vaginally). There were 276 women available for analysis in the carbetocin arm and 271 women in the oxytocin arm. The flow chart for participation of women in this study is provided in Figure 5.

Figure 5: Razali et al., 2016 Participant flow chart



Source: Razali et al, 2016, Figure 1.

Major protocol violations/deviations

No information provided.

Baseline data

The baseline characteristics of the women in the two treatment arms were similar. The mean (SD) age of the women in the two treatment arms was 29.5 (4.6) years in the carbetocin arm and 29.7 (4.30) years in the oxytocin arm. The majority of women in both treatment arms had not delivered by CS previously, and median parity was 0 in both treatment arms with a range of 0-4 in the carbetocin arm and 0-5 in the oxytocin arm. Risk-factors for PPH were present in 51.8% of women in the carbetocin arm and 48.7% of women in the oxytocin arm, with the most frequently reported risk-factors in both treatment arms being labour induction/augmentation in 43.5% and 43.2% of women in the two arms, respectively. The two most frequent indications for CS in the carbetocin and oxytocin arms were 'non reassuring fetal status' (49.5% versus 48.2%, respectively) and 'failure to progress during pregnancy' (35.2% versus 33.9%, respectively).

Results for the efficacy outcomes

The results for the efficacy outcomes are summarised below in Table 14.

Table 14: Razali et al., 2016 Primary and secondary outcome measures in the two treatment arms

	Carbetocin n=276	Oxytocin n=271	*P* value	RR (95% confidence interval)	NNTb[a] (95% CI)
Primary outcome					
Additional uterotonic	107 (38.8)	155 (57.2)	*P*<0.001	0.68 (0.57–0.81)	6 (3.8–9.8)
Secondary outcome					
Type of additional uterotonics					
Oxytocin infusion only	91 (33.0)	143 (52.8)	*P*<0.001	0.6 (0.51–0.76)	
Other uterotonics[b]	16 (5.8)	12 (4.4)	*P*=0.47	1.3 (0.63–2.71)	
Timing of additional uterotonics					
Intraoperatively	105 (98.1)	152 (98.1)	*P*=1.0		
After skin closure	0 (0.0)	2 (1.3)			
In recovery room	0 (0.0)	1 (0.6)			
In postnatal ward	2 (1.9)	0 (0.0)			
Estimated blood loss (ml)					
Mean (SD)	458 (258)	446 (281)	*P*=0.6		
Blood loss ≥500 ml	107 (39)	12 (36)	*P*=0.47	1.1 (0.9–1.3)	
Blood loss >1000 ml	15 (5.4)	10 (3.7)	*P*=0.33	1.5 (0.7–3.2)	
Total operating time (min)					
Mean (SD)	45.9 (16)	44.5 (13)	*P*=0.26		
Hemoglobin (g/dL)					
Mean fall (SD)	1.2 (0.98)	1.3 (1.07)	*P*=0.18		
Hematocrit					
Mean Fall (SD)	0.03 (0.03)	0.03 (0.02)	*P*=0.61		
Adverse outcome					
Blood transfusion	6 (2.2)	10 (3.7)	*P*=0.30	0.6 (0.22–1.6)	
Additional surgical intervention	0 (0.0)	1 (0.4)			
Cardiac arrhythmias	1 (0.4)	0 (0.0)			

Data expressed as mean ± standard deviation, median [interquartile range] or number (%).
[a] Number need to treat to benefit with carbetocin compared with oxytocin.
[b] Includes carboprost (intramuscular or intramyometrial), gameprost (rectal).

Source: Razali et al (2016), Table 2.

Comment: The need for additional uterotonic agents (primary efficacy outcome measure) was notably higher in women in the oxytocin arm compared to the carbetocin arm (57.2% versus 38.8%, respectively), and the difference was statistically significant ($p < 0.001$). The need for additional uterotonic agents was reported in 32% fewer women in the carbetocin arm than in the oxytocin arm (RR = 0.68 (95% CI: 0.57, 0.81). Of the women needing additional uterotonic agents, 98% of women in both treatment arms received the agent in the intraoperative period.

In 89% (234/262) of participants who were administered additional uterotonic agents, a rescue 40–80 IU oxytocin infusion over 6 h was the only additional

uterotonic agent needed. The need for rescue with the additional uterotonic regimen was higher in the oxytocin arm than in the carbetocin arm (33.0% versus 52.8%), and the difference between the two treatment arms was statistically significant ($p < 0.001$). The need for third line uterotonic agents was higher in the carbetocin arm than in the oxytocin arm (5.8% versus 4.4%, respectively), and the difference between the two treatment arms was not statistically significant. In a post hoc analysis including only those women who required additional uterotonic agents, the incidence of women requiring third line agents was statistically significantly greater in the carbetocin arm than in the oxytocin arm (15.0% (16/107) versus 7.7% (12/155), respectively, $p = 0.06$). The study authors comment that '*third line agents were usually given to recalcitrant cases of uterine atony*'.

The estimated mean blood loss was similar in the two treatment arms, as was the incidence of women with blood loss ≥ 500 mL and ≥ 1000 mL, and none of the differences between the two arms were statistically significant for these three variables. The mean fall following delivery in the haemoglobin concentration and the haematocrit was similar in the two treatment arms, and the difference between the treatment arms was not statistically significant for either of the two variables. The incidence of women requiring blood transfusions did not significantly differ between the two treatment arms.

Overall comment on the study

This was a good quality study. The study found a significant reduction in the use of additional uterotonic agents in the carbetocin arm compared to the oxytocin arm in women undergoing emergency CS, but no significant difference between the two arms as regards the secondary efficacy outcome measures relating to the volume of blood loss. The study was adequately powered to assess the difference between the two treatment arms as regards the primary outcome of the need for additional uterotonic agents in women undergoing emergency CS. The study was not powered to detect a statistically significant difference between the two treatment arms in the secondary efficacy outcome measures, but the differences between the arms for these outcomes are unlikely to be clinically meaningful. The results adequately demonstrated that carbetocin 100 µg IV is more efficacious than oxytocin 10 IU IV as regards the prevention of uterine atony and excessive bleeding following emergency CS under regional anaesthesia in women with and without risk-factors for PPH.

It is noted that, while the sample size was calculated on the assumption that there would be a doubling in the rates of the need for additional uterotonic agents in the carbetocin arm of 9.4% to 20.2% in the oxytocin arm, the observed rates were substantially higher in both treatment arms (38.8% versus 57.2%, respectively). This might be due to the study having a lower threshold for the use of additional uterotonic agents than the study from which the assumed rates were derived. The authors comment that their '*findings might not be generalizable to practices where the threshold for the use of an additional uterotonic during emergency cesarean section is higher resulting in delayed intra-operative oxytocin infusion'*.

7.2.2.3. Whigham et al., 2016 Carbetocin 100 µg IV versus oxytocin 5 IU IV

Title

Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double blind, randomised trial

Objective

The objective of this study was to compare the efficacy of carbetocin to oxytocin given at non-elective caesarean section.

Design

The study was a randomised, double blind, controlled clinical trial. The study was performed at the Frankston Hospital, a secondary level teaching hospital in Victoria, Australia, with approximately 2600 deliveries per year. Recruitment and randomisation took place between 28 August 2012 and 3 February 2013. Women who were eligible to take part in the study were approached for consent in the antenatal clinic and on the labour ward. The trial was registered with the Australia and New Zealand clinical trials registry. Ethics Committee approval was granted by the Peninsula Health Human Resources and Ethics Team. The project was awarded the Peninsula Health Grant for Health Research.

Inclusion and exclusion criteria

The study recruited women undergoing emergency CS at Frankston Hospital. Women were approached to participate in this study when they presented to the birth suite for a planned induction of labour, or when they were in early labour or in active labour but had an epidural anaesthetic. Women who were in the active phase of labour with no epidural were not approached, as they were considered to be in too much discomfort to provide informed consent.

Women with multiple gestation, placental abruption or who were under 37 weeks of gestation were excluded from the study. In addition, women who had a general anaesthetic for their CS were also excluded, given that 'carbetocin is licensed for use in Australia with regional analgesia only'.

Study treatments

In this study women were randomised to a single dose of carbetocin 100 µg IV or a single dose of carbetocin 5 IU IV. The study drugs were administered immediately after the birth of the baby.

Comment: The carbetocin dose used in this study was consistent with the approved dose for CS of 100 µg IV as a bolus injection either before or after delivery of the placenta. The dose of oxytocin used in this study was consistent with the approved dose for CS of 5 IU by IV infusion or slow bolus after delivery of the foetus.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was the need for additional uterotonic agents. The *secondary efficacy outcomes measures* included estimated blood loss during surgery, secondary post-partum blood loss and post-operative haemoglobin concentration.

At the time the decision to perform a CS was made, information was collected on parity, age, gestation, body mass index, indication for caesarean section, pre-operative haemoglobin concentration, and cervical dilatation

Randomisation and blinding methods

The randomisation sequence was computer generated by the hospital pharmacy. The pharmacy used a study label which included study title, number and expiry date to cover the trade label. Participants, anaesthetists and operating obstetricians were blinded to the intervention drug. Recruited women were randomised on entering the operating theatre, when the next sequential ampoule was taken out of the fridge. The randomisation was revealed to the investigators once recruitment was completed and analysis was to begin.

Sample size

The sample size calculation was based on results reported in the Bristol study conducted in women undergoing elective or emergency CS (Attilakos et al. 2010). This study found that 45.5% of women in the oxytocin group required additional uterotonic agents. Assuming that only 26% women in the carbetocin group require additional uterotonic agents, 58 participants in each group provided 80% power to detect the difference with two-sided alpha of 0.05.

Statistical methods

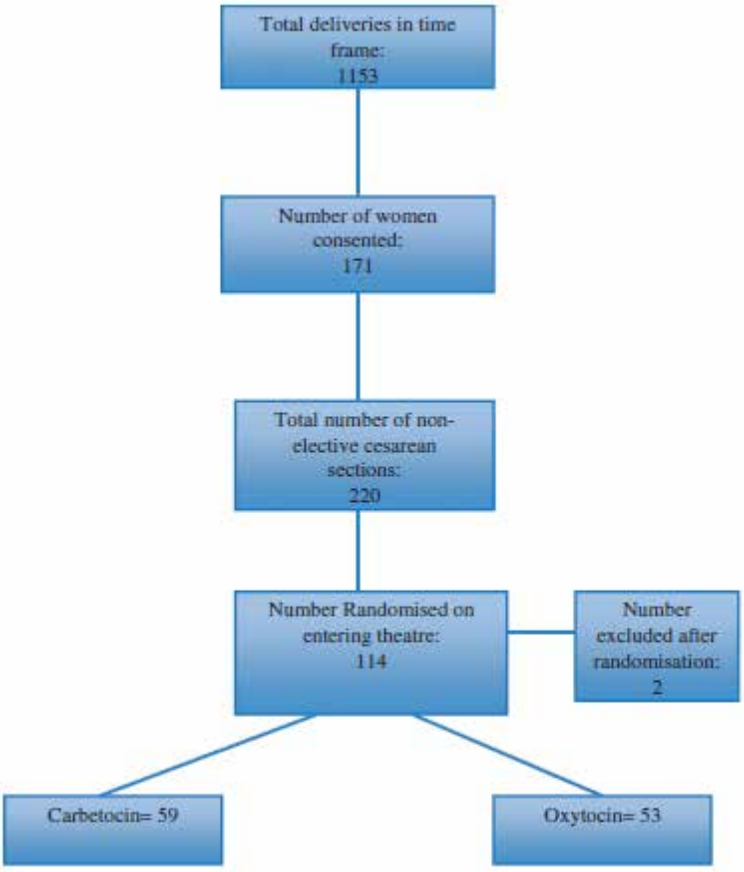
The need for additional uterotonic agents, uterine massage and blood transfusion were analysed using Fisher's exact test. Estimated blood loss, age and weight were analysed using Student's t-test.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy outcome measures.

Participant flow

A total of 220 non-elective caeserean sections were performed during the period of the study (that is, 28 August 2012 to 3 February 2013). In total, 171 women gave consent to participate in the study and 114 women went on to have a non-elective CS. Of the 114 women included in the study, 59 were randomised to carbetocin, 53 were randomised to oxytocin, and 2 were excluded as they underwent CS under general anaesthetic. The participant flow chart is provided in Figure 6.

Figure 6: Whigham et al., 2016 Participant flow chart



Source: Whigham et al., 2016, Figure 1

Comment: The number of women randomised to the oxytocin arm (n = 53) was lower than the planned number (n = 58) used to calculate power of the study (i.e. n = 58 in each treatment arm).

Major protocol violations/deviations

No information provided.

Baseline data

There were no significant differences between the two groups as regards baseline demographics and clinical factors, and the variables were reasonably well balanced between the two treatment arms. The mean (SD) age of the women in the carbetocin and oxytocin arms was 28.3 (5.9) years and 28.9 (5.8) years, respectively, and the majority of women in both treatment arms were nulliparous. Median cervical dilatation was 4 cm in both treatment arms, and the interquartile range was 1-7 cm in the carbetocin arm and 2-6 cm in the oxytocin arm. The main reasons for CS in both treatment arms were failure to progress and fetal distress. Emergency CS was performed under regional anaesthesia (spinal or epidural).

Comment: In the table in the study report summarising *Demographics and clinical factors (Table 1),* the number of women receiving regional anaesthesia in the oxytocin arm (n = 52) does not equal the number of women randomised to this treatment arm (n = 53). No comment on this discrepancy was identified in the study report.

Results for the efficacy outcomes

The results for the primary and secondary efficacy outcome measures are summarised below in Table 15.

Table 15: Whigham et al, 2016 – Primary and secondary efficacy outcome measures in both treatment arms.

	Carbetocin 100 IV (n = 59)	Oxytocin 5 IU (n = 53)	Statistics
Additional uterotonics, n (%)	13 (22.0%)	7 (13.2%)	p = 0.323
Estimated blood loss mL, mean	586 mL	561 mL	p = 0.591
Blood loss ≥ 1000 mL in theatre, women	6 women (10.2%)	5 women (9.4%)	-
Blood loss ≥ 1000 mL (total) in 24 h	7 women (11.9%)	8 women (15.1%)	-
Haemoglobin drop g/dL, mean	1.76 g/dL	1.82 g/dL	p = 0.784
Blood transfusion, women	1 woman (1.7%)	1 woman (1.9%)	-

Source: Whigham et al (2016), Tables 2 and 3.

Comment: There were no statistically significant differences between the two treatment arms in the primary efficacy outcome measure (need for additional uterotonic agents) or the secondary efficacy outcome measures (estimated mean blood loss and haemoglobin drop following CS). In addition, the incidence of women with estimated blood loss ≥ 1000 mL in theatre, estimated blood loss ≥ 1000 mL in the first 24 h (including in theatre), and need for blood transfusion were comparable between the two treatment arms.

Overall comment on the study

This was a good quality study undertaken in a relatively small number of women in an Australian setting. The efficacy data were clearly described and were clinically relevant, which

allowed for a clinically meaningful comparison between the two treatment arms to be undertaken. One of the main strengths of the study was that it used the approved dose of oxytocin for emergency CS under regional anaesthesia. The main limitation of the study was the absence of comparative adverse event data for the two treatment arms, including the effects of treatment on blood pressure and pulse rate over the first 60 minutes following administration.

The incidence of women requiring additional uterotonic agents was greater in the carbetocin arm than in the oxytocin arm (22.0% versus 13.2%, respectively), but the difference between the two arms was not statistically significant. The study was powered on a sample size of 58 in each treatment to detect a statistically significant difference between the arms of 0.05 (two-sided alpha) based on an incidence of additional uterotonic agents of 45.5% in the oxytocin arm and 26% in the carbetocin arm. In this study, the observed incidence rates for the use of additional uterotonic agents in each of the treatment arms was approximately half those used to calculate the sample size. In addition, the number of women in the oxytocin arm (n = 53) was lower than the number on which the power calculations were made (n = 58).

The notably lower incidence rate of the need for additional uterotonic agents in both treatment arms than assumed when powering the study and the smaller number of patients in the carbetocin arm than planned might have resulted in the study being underpowered to detect the smaller difference between treatment arms observed in the study than assumed. However, the observed absolute difference in the incidence between the two treatment arms was 8.8%, which suggests that the difference between the two treatment arms as regards the need for additional uterotonic agents is of doubtful clinically significance. There was no statistically significant difference between the two treatment arms in the mean estimated blood loss or the mean haemoglobin drop following CS, and the observed differences are considered to be clinically insignificant. In addition, the results for women with blood loss of ≥ 1000 mL in theatre and in the first 24 h after delivery were comparable. Overall, it is considered that the observed numerical differences between the two treatment arms in the efficacy outcome measures are unlikely to be clinically significant.

Of note, the authors of the study concluded '*that there are no benefits to the use of carbetocin over oxytocin in emergency caesarean section' and 'suggest 5 units of oxytocin by slow intravenous injection should continue to be used at non-elective caesarean deliveries'*.

7.2.3. Evaluator's conclusion on clinical efficacy Emergency CS

The submission included 3 recently published studies (2016) in women delivering via emergency CS under regional anaesthesia. Of these 3 studies, 1 was conducted in Egypt (El Behery et al., 2016), 1 was conducted in Malaysia (Razali et al., 2016) and 1 was conducted in Australia (Whigham et al., 2016). Two of the studies (Razali et al., 2016 and Whigham et al., 2016) are considered to be of good quality while one is considered to be of fair quality (El Behery et al., 2016).

The sponsor states that the studies were submitted to support the administration of carbetocin to women at high risk of PPH and in women delivering via CS performed under general anaesthesia. However, in the 3 studies conducted in women delivering by emergency CS the procedure was performed under regional anaesthesia in Razali et al (2016) and Whigham et al (2016), while in El Behery et al (2016) it can be inferred that regional anaesthesia was used as patients delivering under general anaesthesia were excluded from the study. The 3 studies included women undergoing emergency CS who were at risk of PPH.

The 3 studies included efficacy data on 425 women treated with single dose carbetocin 100 µg IV and 414 women treated with single dose oxytocin 5-20 IU IV following delivery of the infant via emergency CS. In each of the 3 studies, carbetocin was administered at a dose of 100 µg IV, which is the approved dose for CS under regional anaesthesia. In 1 of the 3 studies (Whigham et al., 2016), oxytocin was administered at a dose of 5 IU IV, which is the approved dose for CS. In 2

of the 3 studies, oxytocin was administered at a higher dose than the approved dose for CS (10 IU IV in Razali et al., 2016 and 20 IU IV in El Behery et al., 2016).

In Razali et al (2016) and Whigham et al (2016), the primary efficacy outcome measure was the need for additional uterotonic agents and in El Behery et al (2016) the primary efficacy outcome measure was the incidence of major postpartum haemorrhage (≥ 1000 mL). In El Behery et al (2016) the results for all efficacy outcome measures statistically significantly favoured the carbetocin arm compared to the oxytocin arm. In Razali et al (2016) the incidence of the need for additional uterotonic agents was statistically significantly greater in the oxytocin arm than in the carbetocin arm, but the results for all secondary outcome measures did not significantly differ between the two arms. In Whigham et al (2016) there were no statistically significant differences between the carbetocin and the oxytocin arms for all efficacy outcome measures.

It is considered that the results of the three studies have adequately demonstrated that carbetocin 100 µg IV and oxytocin 5-20 IU IV are comparable as regards the prevention of uterine atony and excessive bleeding following emergency CS under regional anaesthesia in women with risk-factors for PPH.

7.3. High-risk of postpartum haemorrhage

7.3.1. Studies with evaluable efficacy data

The submission included 3 studies assessing the efficacy and safety of carbetocin in women at high risk of PPH (Reyes, 2011; Reyes et al., 2011; Fahmy et al., 2016). The sponsor stated that these studies were submitted to support the removal of the statement in the Duratocin PI regarding the lack of data in patients at high risk of PPH and in patients delivered via CS under general anaesthesia. The 3 studies compared carbetocin to oxytocin and the women delivered either vaginally or by CS (stated to be under general anaesthesia in 1 study). The high risk factors were twin delivery in 1 study, grand multiparity (≥ 5 births) in 1 study, and severe preeclampsia in 1 study. The 3 studies are summarised below in Table 16 and are evaluated in Section 7.3.2 of this clinical evaluation report (Reyes, 2011; Reyes et al, 2011; Fahmy et al, 2016).

Table 16: Studies in women at high risk of postpartum haemorrhage delivering vaginally or via caesarean section

Study	Objectives	Design	Carbetocin Oxytocin	Participants	Efficacy Outcome Measures
Fahmy et al., 2016. One centre in Egypt.	Effect on haemodynamics, uterine contraction, and blood loss in women delivering twins via CS under GA.	R, db, ac. CSD under GA.	100 µg IV (DI); n = 30. CSD under GA. 20 IU IV (DI); n = 30. CSD under GA.	Healthy young women with twin pregnancies.	Primary: Need for additional uterotonic agent (methergine) due to poor uterine contractions. Secondary: Need for decrease in isoflurane concentration from 1% to 0.5%; need

Study	Objectives	Design	Carbetocin Oxytocin	Participants	Efficacy Outcome Measures
					for blood transfusion; blood loss.
Reyes et al., 2011. One centre in Panama.	Prevention of PPH in women with severe preeclampsia.	R, db, ac. dd. VD and CSD (not stated whether under GA or RA).	100 µg IV (DP); n = 26. VD (n = 14), CSD (n = 12). 20 IU IV (DP); n = 29. VD (n = 16); CSD (n = 14).	Women at high risk of PPH due to severe preeclampsia.	Primary: PPH requiring use of additional uterotonic agents. Secondary: Hb concentration after delivery; oliguria; haemodynamic status.
Reyes, 2011. One centre in Panama.	Prevention of PPH in grand multiparous women (> 5 births).	R, db, ac. VD.	100 µg IV (EP); n = 45. 20 IU IV (EP); n = 90.	Women at high risk of PPH due to grand multiparity (> 5 births)	Primary: therapeutic failure (defined as use of additional uterotonic agents); manual exploration of the uterine cavity; blood transfusion Secondary: milk letdown; milk supplements.

Abbreviations: PPH = postpartum haemorrhage; R = randomised; OL = open label; db = double blind; ac = active controlled; dd = double-dummy to maintain the blind. VD = vaginal delivery; CS =caeserean section; GA = general anaesthetic; RA = regional anaesthesia; CSD = caeserean section delivery; Hb = haemoglobin IV = intravenous; (DP) = after delivery of the placenta; (DI) = after delivery of the infant.

7.3.2. Evaluation of the submitted studies

7.3.2.1. Reyes, 2011 Carbetocin 100 µg IV versus oxytocin 20 IU IV Vaginal delivery

Title

Carbetocin versus oxytocin for the prevention of postpartum haemorrhage in grand multiparous patients: a randomised controlled trial.

Objective

The objective of the study was to compare the effectiveness and tolerability of carbetocin to oxytocin for the prevention of postpartum bleeding in grand multiparous women (≥ 5 births) following vaginal delivery of singleton pregnancies (≥ 28 weeks gestation).

Design

The study was a prospective, randomised, open label controlled clinical trial. The study was conducted in Saint Thomas Maternity Hospital, Panama City, Panama. Over the study period from August 2008 to August 2009, 135 women who met the eligibility criteria were recruited. The third stage of labour was actively managed. Oxytocin was stopped if it had been used to augment labour. Women requiring CS were excluded from the study. The study drugs were administered after expulsion of the placenta. In the event of suspected or clinically evident uterine atony, the use of additional uterotonic agents was permitted (misoprostol 1000 μg administered rectally). The use of additional uterotonic agents was noted and recorded as a therapeutic failure of the study drug. Informed consent was obtained from the participating women at the time of admission to the labour ward. The study was approved by the Research Studies Committee of the study centre.

Comment: This study was open label in design. The study was published in Spanish and an English translation was submitted by the sponsor.

Inclusion and exclusion criteria

The inclusion criteria were grand multiparous women (≥ 5 births) with singleton pregnancies (≥ 28 weeks) delivering vaginally. The exclusion criteria included known allergy to carbetocin, clotting disorders, or unknown parity.

Study treatments

Women randomised to the carbetocin arm received a single dose of carbetocin (100 μg; 1 mL) diluted in 10 mL of Ringer-lactate administered IV in not less than 1 minute. Women randomised to oxytocin received a 20 IU dose by continuous IV infusion (20 IU/1000 ML of Ringer-lactate administered at a rate of 100 mL/h).

Comment: The IV dose of carbetocin (100 μg) used in this study is consistent with the proposed IV dose for women delivering vaginally (100 μg (1 mL) administered IV as a bolus injection or slowly over 1 minute). The IV dose of oxytocin used in this study (20 IU) was greater than the dose approved for the routine management of the third stage of labour following vaginal delivery (that is, 5 IU by slow IV bolus).

Efficacy variables and outcomes

The *primary efficacy outcome measures* were the incidence of postpartum haemorrhage despite preventive treatment (therapeutic failure), the need to perform manual 'explorations' of the uterus, and the need for blood transfusion. The *secondary efficacy outcome measures* included milk let-down in the immediate postnatal period and the need to supplement breast feeding.

Comment: The efficacy outcome measures did not include an assessment of postpartum haemorrhage (that is, no measurement of total blood loss, no assessment of the incidence blood loss ≥ 500 mL, no assessment of the change in haemoglobin level from pre- to post-delivery.

Randomisation and blinding methods

No information was provided on the randomisation method. The study was open label.

Comment: The study was described as being randomised. However, no information on the randomisation method was provided. It was stated that randomisation to the two treatment arms was 1:2 (45 carbetocin, 90 oxytocin), but no reason for this randomisation ratio was provided.

Sample size

No information was provided on the method used to select the sample size.

Statistical methods

The differences between the two treatment arms for categorical data were analysed using the chi-square test or Fisher's exact test. Where appropriate, the relative risk (RR) and associated 95% CI were also calculated. A p-value of less than 0.05 was considered statistically significant.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the efficacy outcome measures.

Participant flow

There were 12,906 births (10,022 vaginal and 2,827 caesarean) recorded during the period of the trial. Of the total births, 574 (4.3%) corresponded to grand multiparous patients, of whom 451 (78.6%) gave birth vaginally. Of these 451 patients, 135 patients were recruited into the study (45 carbetocin and 90 oxytocin). The majority of the 451 eligible patients were not recruited due to technical problems, including lack of informed consent, assisted deliveries, or very advanced cervical dilatation on arrival in the labour ward.

Major protocol violations/deviations

No information provided.

Baseline data

The baseline characteristics of the two treatment arms were reasonably well balanced between the two treatment arms. The mean±SD age of the women in the carbetocin arm was 33.0±5.2 years and 31.6±5.5 years in women in the oxytocin arm, with mean gestational age being greater than 36 weeks in both arms and mean parity being 7 in both treatment arms. Augmentation of labour was reported more frequently in women in the oxytocin arm than in the carbetocin arm (66% versus 76%, respectively), while the mean duration of labour was longer in the oxytocin arm than in the carbetocin arm (254 versus 193 minutes, respectively).

Comment: The methods of analgesia used in this study in women delivering vaginally were not stated.

Results for the efficacy outcomes

As regards the *primary efficacy outcome measures*, the study showed that therapeutic failure (use of additional uterotonics) occurred in 3 (3.3%) women in the oxytocin arm and no women in the carbetocin arm ($p = 0.29$), manual exploration of the uterus was undertaken in 33 (36.7%) women in the oxytocin arm and 2 (4.4%) women in the carbetocin arm (RR = 0.12 (95% CI: 0.03, 0.48) $p < 0.05$), and blood transfusion was needed by no women in the oxytocin arm and 1 (2.2%) woman in the carbetocin arm ($p = 0.33$).

As regards *the secondary efficacy outcome measures,* milk let-down was reported in 88 (97.8%) women in the oxytocin arm and 45 (100%) women in the carbetocin arm, and the need to administer milk supplements to the newborn was reported in 2 (4.4%) and 4 (4.4%) women in the two arms, respectively. The difference between the two treatment arms was not statistically significant for either of the two secondary efficacy outcomes measures.

Comment: The main difference between the two treatment arms as regards the primary efficacy outcome measures was the notably higher incidence of manual exploration of the uterus in the oxytocin arm than in the carbetocin arm. The differences between the two treatment arms in the proportion of women requiring additional uterotonic agents and the proportion of women needing blood transfusions are considered to be not clinically significant. There were no meaningful differences

between the two treatment arms as regards the secondary efficacy outcome measures of milk let-down and the need for milk supplements in the new born.

Overall comment on the study

This was reasonable quality study in women at high risk of PPH (grand multiparity). The efficacy outcome measures in this study did not include information on the incidence of PPH in the two treatment arms, information on the volume of blood loss post-delivery, or assessment of the change in haemoglobin level from pre- to post-delivery. In addition, the oxytocin dose used in this study (20 IU administered by IV infusion) was notably greater than the Australian approved IV dose for the active management or the third stage of labour (that is, 5 IU by slow IV bolus). Other limitations in this study included: (i) imbalance in participant numbers between the two treatment arms, with no reasons being provided for selecting the randomisation ratio of 1:2 to carbetocin or oxytocin; (ii) no information on the method of randomisation; (iii) no information on selection of the sample size; and (iv) an open label rather than double blind design. The results provide reasonable evidence that carbetocin 100 µg IV and oxytocin 20 IU IV is comparable as regards the prevention of uterine atony following vaginal delivery grand multiparous women.

7.3.2.2. Reyes et al., 2011 Carbetocin 100 µg IV versus oxytocin 20 IU IV Vaginal or CS

Title

Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: a double blind randomised controlled trial.

Objectives

The objective of this study was to compare oxytocin to carbetocin for the routine prevention of postpartum haemorrhage in women with severe preeclampsia.

Design

The study was a randomised, double blind, controlled clinical trial. The study was conducted in Saint Thomas Maternity Hospital, Panama City, Panama. Women with singleton pregnancies of more than 28 weeks gestation with severe preeclampsia were eligible for the study. Written informed consent was obtained at an early stage of labour by one of the investigators. The study was approved by the Saint Thomas Hospital's Institutional Ethics Review Committee.

Participants were randomised to receive either carbetocin IV or oxytocin IV administered after the delivery of the placenta following vaginal birth or CS. Women with uterine atony following administration of the study drugs (determined by physical examination and continuous postpartum bleeding) were considered to be a therapeutic failure, and additional uterotonic agents were administered to these women (oxytocin and/or prostaglandin, at the discretion of the attending physician). The numbers of women needing manual removal of the placenta or blood transfusion were also recorded.

Standard laboratory assessments (haemoglobin, haematocrit, platelets, and renal and liver function tests) were performed in every patient on admission and postpartum. Vital signs (blood pressure, heart rate, respiratory rate) and diuresis were measured every h until at least 12 h after delivery.

All patients were in a 'stable condition' before randomisation (that is, no evidence of maternal haemodynamic instability or fetal distress), and conduct of labour followed national Panamanian standards for the management of hypertensive disorders of pregnancy. No woman needed additional treatment for their symptoms or developed antepartum complications that required admission to the intensive care unit. All patients were evaluated hourly and received magnesium sulphate to prevent eclampsia during labour and for a minimum of 12 h postpartum.

Comment: The study was referred to in the report as a pilot study.

Inclusion and exclusion criteria

Women with singleton pregnancies of more than 28 weeks gestation admitted to the study centre with severe preeclampsia were eligible for the study. Exclusion criteria were the HELLP syndrome, blood dyscrasia, and multiple pregnancy. The HELLP syndrome is a life threatening pregnancy complication usually considered to be a variant of preeclampsia. The HELLP syndrome is named for its characteristics of H (haemolysis), EL (elevated liver enzymes) and LP (low platelet count).

Study treatments

Patients were randomised to carbetocin 100 µg IV or oxytocin 20 IU IV administered after the delivery of the placenta following vaginal birth or CS. In order to maintain the double blind, a double-dummy masking method was used with Ringer's lactate solution. The two study protocols were:

- Protocol A (carbetocin + placebo): carbetocin 100 µg + Ringer's lactate solution 10 mL administered IV over 2 minutes, and Ringer's lactate solution 4 mL in 1000 mL administered IV at a rate of 125 mL/h
- Protocol B (oxytocin + placebo): Ringer's lactate solution 11 mL administer IV over 2 minutes, and oxytocin 20 U diluted in 1000 mL of Ringer's lactate solution administered IV at a rate of 125 mL/h

Comment: The dose of carbetocin (100 mg IV) used in this study is consistent with the dose proposed for approval. The dose of oxytocin used in this study (20 IU IV) is higher than the approved IV dose (5 IU) for vaginal delivery or CS.

Efficacy variables and outcomes

The *primary efficacy outcome measure* was the development of postpartum haemorrhage needing additional uterotonic agents.

The *secondary efficacy outcome measures* were haemoglobin concentration after delivery, oliguria (< 0.5 mL/kg/h), and haemodynamic status (mean arterial pressure and heart rate). Patients were asked about milk letdown, breastfeeding, and lactational failure.

Comment*:* There was no information on the amount of postpartum blood loss that would trigger administration of additional uterotonic agents. However, it was stated that additional uterotonic agents were administered in cases of uterine atony and continuous postpartum bleeding. There was no information on the volume of blood loss postpartum (that is, mean estimated loss, proportion of women with postpartum haemorrhage ≥ 500 mL or ≥ 1000 mL).

Randomisation and blinding methods

The randomisation protocol required a designated member of the staff to open a sealed, opaque envelope containing a computer generated code randomising the patient to one of the two treatment arms. The codes were broken only after the study was completed and all study information tabulated and analysed. The study was double blind. A double-dummy method using Ringer's lactate (IV bolus or IV infusion) was used to maintain the blind.

Sample size

No information was provided on the method used to select the sample size.

Statistical methods

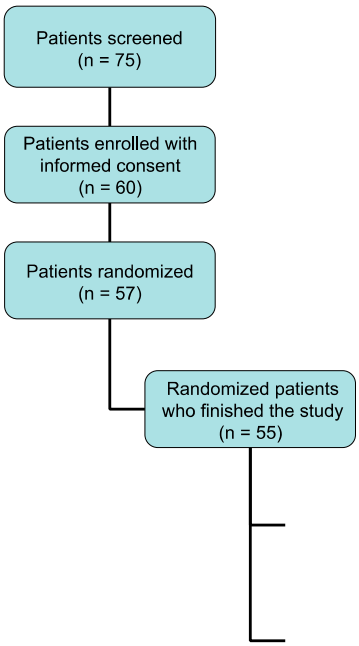
Differences in continuous variables were analysed using the Mann-Whitney U test and non-continuous variables were analysed using the chi-square test. Statistical significance was set at $p < 0.05$.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the secondary efficacy outcome measures.

Participant flow

A total of 75 women were screened, and 60 women met the required inclusion criteria. These 60 women were recruited from July 2010 to September 2010 (30 were randomised to receive carbetocin and 30 to receive oxytocin). Informed consent was obtained from the 60 participants, but 5 women were excluded before the end of the study (2 developed HELLP syndrome, 1 had an undiagnosed twin pregnancy, 1 received the assigned study drug before the extraction of the placenta, and in 1 the medication ampoule broke before use). The participant flow chart is presented in Figure 7.

Figure 7: Reyes et al., 2011 Participant flow chart



Source: Reyes et al., 2011, Figure on page 1101.

Major protocol violations/deviations

No information was provided.

Baseline data

The baseline characteristics of women in the two study arms were similar. The mean age of the women in both treatment arms was 27 years and the mean parity was approximately 2 in both arms. The associated symptoms of preeclampsia (persistent headache, visual symptoms, epigastric pain) were reported in 38.5% (n = 10) of women in the carbetocin arm and 55.5% (n = 16) of women in the oxytocin arm. The arterial blood pressure on admission was comparable

between the two treatment arms, as was the prothrombin time and the activated partial thromboplastin time.

The characteristics of labour in the two treatment arms were generally comparable, although the first stage of labour was 55 minutes longer in women in the carbetocin arm than in the oxytocin arm. Delivery was by CS in 53.8% (n = 14) of women in the carbetocin arm and 55.2% (n = 16) of women in the oxytocin arm, and vaginal in 46.2% (n = 12) and 44.8% (n = 13) of the women in the two arms, respectively.

Comment: There was no information in the study on whether CS was performed under general or regional anaesthesia. There was no information on the methods of anaesthesia used in women delivering vaginally.

Results for the efficacy outcomes

The results for the primary and secondary efficacy outcome measures are summarised below in Table 17.

Table 17: Reyes et al., 2011 Primary and secondary outcome measures in the two treatment arms

	Carbetocin n = 26	Oxytocin n = 29	*P*
Need for additional uterotonics, n (%)	0 (0)	1 (3.4)	0.50
Need for blood transfusions, n (%)	0 (0)	3 (10.3)	0.13
Need for instrumental curettage of the uterine cavity, n (%)	2 (8)	4 (13.8)	0.41
Postpartum hemoglobin level, g/dL, mean (SD)	10.8 (1.68)	11.14 (1.76)	0.56
Hemoglobin difference (admission–postpartum), mean (SD)	1.24 (0.87)	1.41 (1.12)	0.81
Oliguria, n (%)	6 (23.1)	9 (31.0)	0.26

Source: Reyes et al., 2011, Table 2.

Comment: There were no statistically significant or clinically meaningful differences between the two treatment arms in the primary and secondary efficacy outcome measures.

Overall comment on the study

This was a reasonable quality study in a small number of women with severe preeclampsia. No information was provided on either sample size calculations or the power of the study. However, the study was identified in the report as a pilot study, which might account for sample size and power calculations not being undertaken. There was no information on the amount of postpartum blood loss in women in this study, or on the amount of postpartum blood loss needed to trigger the use of additional uterotonic agents. The results for the primary and secondary efficacy outcome measures did not identify statistically significant or clinically meaningful differences between the two treatment arms. The results provide reasonable evidence that carbetocin 100 µg IV and oxytocin 20 IU IV is comparable as regards the prevention of uterine atony following vaginal delivery in grand multiparous women.

7.3.2.3. Fahmy et al., 2016 Carbetocin 100 µg IV versus oxytocin20 IU IV CS (GA)

Title

Comparative study between effect of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients undergoing cesarean section.

Objectives

The aim of the study was to compare the effects of carbetocin and oxytocin on haemodynamics, uterine contraction and blood loss in women delivering twins via elective CS under general anesthesia using isoflurane.

Design

This was a randomised, double blind, controlled clinical trial. It was undertaken in women with twin pregnancies scheduled for elective CS at the Ain Shams University Hospital, Cairo, Egypt, between November 2012 and June 2013. Written informed consent was obtained from the women. The study was approved by the study centre's ethics committee.

Standard pre-operative assessment was undertaken for women undergoing the procedure. All patients delivered via elective CS under general anesthesia. The procedure involved pre-oxygenation with 100% oxygen for 4 minutes then induction with thiopentone sodium IV 4 to 7 mg/kg and cisatracurium 0.5 mg/kg to facilitate endotracheal intubation. Anaesthesia was maintained with isoflurane and intermittent doses of cisatracurium. Lactated Ringer's solution was infused (10-15 mg/kg), but the rate was not provided. At the end of the procedure, muscle relaxation was reversed with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine.

In all patients, heart rate, mean arterial blood pressure, uterine contraction score (0 (atony) to 4 (very good)), and amount of blood loss (estimated by counting the number of swabs soaked with blood and the amount of aspirated blood) were monitored. If the uterine contraction score was less than 3 (that is, less than good) after 5 minutes, isoflurane concentration was decreased from 1% to 0.5%. If uterine contraction was still unsatisfactory following reduction in isoflurane concentration then additional uterotonic agents were administered as necessary (that is, methergine 0.4 mg; route not stated). Blood transfusions were administered to women who lost more than 1200 mL of blood.

Comment: The inhalational anaesthetic Isoflurane is associated with reduction in uterine tone, which is a risk-factor for PPH. One of the efficacy outcome measures in this study was reduction in isoflurane concentration from 1% to 0.5%, which was undertaken in order to increase uterine tone in women not responding favourably to the study drugs (that is, no increase in uterine tone).

Inclusion and exclusion criteria

The study included women with twin pregnancies, American Society of Anaesthesiologists (ASA) physical status 1 (that is, normal healthy patient), and aged 28-36 years who were scheduled for elective CS. Exclusion criteria included women with hypertension, preeclampsia, cardiac, respiratory, renal or liver disease, pre-existing bleeding disorders and women taking therapeutic anticoagulants or who were hypersensitivity to carbetocin or oxytocin. Women with preoperative haemoglobin less than 9.5 gm% were also excluded from the study as were women expecting more than two infants.

Study treatments

Randomisation was to carbetocin 100 µg IV in 10 mL of normal saline (n = 30) or oxytocin 20 IU in 10 mL of normal saline (n = 30), with both drugs being administered over 1 minute after delivery of the infants.

Comment: The dose of carbetocin (100 µg IV) used in this study is consistent with the proposed dose for CS under general anaesthesia. The dose of oxytocin (20 IU IV) used in this study is greater than the approved dose for women delivering by CS (that is, 5 IU IV).

Efficacy variables and outcomes

The *primary outcome measure* was not explicitly stated. However, as the study was stated to be powered on the difference in the proportion of women needing an additional uterotonic agent it can be reasonably inferred that this is the primary efficacy outcome measure. The additional uterotonic agent used in this study was methergine 0.4 mg (route not stated).

The *additional efficacy outcome measures* were the number of patients who required blood transfusions, uterine tone, reduction in the isoflurane concentration from 1% to 0.5%, and estimated blood loss.

Randomisation and blinding

Randomisation was performed using a computer-generated program. Both drugs were prepared preoperatively and coded so that the working investigator and the obstetrician were blinded to the study drug. The study was double blind.

Sample size

The study report stated that power calculations were based on former studies which revealed that in order to detect a statistically significant difference between the proportions of women who require additional methergine of 0.4 mg, a sample size of 26 women per treatment arm was required. To compensate for dropouts and missing data, the sample size was increased to 30 patients per treatment arm. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05.

Comment: The 'former' studies used to calculate the power of the current study were not referenced. The proportions of women needed to 'reveal' a statistically significant difference between the two treatment arms requiring additional methergine 0.4 mg were not stated. Reporting of power calculations is considered to be incomplete.

Statistical methods

Student's t-test was used to analyse the parametric data, and discrete (categorical) variables were analysed using the chi-square test, non-parametric data were compared using the Mann–Whitney test, and p values < 0.05 were considered to be statistically significant.

Comment: It was not stated whether the analysis was undertaken in the ITT population. However, analysis of efficacy was undertaken in all randomised women in both treatment arms, which suggests that the analysis was based on ITT principles. There was no statistical adjustment for the multiple pairwise assessments of the efficacy outcome measures.

Participant flow

A total of 60 women were enrolled and randomised to the carbetocin 100 µg IV arm (n = 30) or the oxytocin 20 IU IV arm (n = 30).

Comment: No information on participant flow was provided, apart from the number of women enrolled and randomised.

Major protocol violations/deviations

No information provided.

Baseline data

There were no significant difference differences between the two treatment arms with respect to age, BMI, pre-operative haemoglobin concentration, parity, previous CS, birth weight and duration of anesthesia. The mean ages of the women were 25.4 years in the carbetocin arm and 24.5 years in the oxytocin arm, the mean respective parities were 3 (range: 2-4) and 4 (range: 3-5).

Results for the efficacy outcomes

The results for the main efficacy outcome measures are summarised below in Table 18.

Table 18: Fahmy et al., 2016 Efficacy outcome measures in the carbetocin and oxytocin arms

Time	Group C (n = 30)	Group O (n = 30)	p-Value
Number of patients with reduced isoflurane concentration	5(16.7%)	15(50%)	< 0.001
Number of patients who need methergine	4(13.3%)	15(50%) one dose 10(33.3%) 2 doses	< 0.001
Number of patients who need blood transfusion	1(3.33%)	4(13.3%)	< 0.001
Blood loss (ml)	437 ± 45	721 ± 50	< 0.001

Group C: Those who received carbetocin.
Group O: Those who received oxytocin.
Data are presented as number and percentage of patients or mean (SD).

Source: Fahmy et al., 2016, Table 5.

The median (range) uterine contraction scores at both 2 minutes and 2 h after administration of the study drugs were significantly lower in the carbetocin arm than in the oxytocin arm (2 (range: 2-3)) versus 2 ((range: 1-2)), respectively, at both time-points, p < 0.001).

Overall comment on the study

This was a reasonable quality pilot study in a small number of women with twin pregnancies undergoing elective CS under general anaesthetic. The primary outcome measures favoured women in the carbetocin arm compared to the women in the oxytocin arm, and the differences between the two arms were statistically significant and clinically meaningful. The reporting of the assumptions on which the sample size was based was incomplete. The results of this study provide reasonable evidence supporting the superiority of carbetocin 100 µg IV compared to oxytocin 20 IU IV as regards prevention of uterine atony and excessive bleeding in women with high risk of PPH (twin pregnancy) following emergency CS under general anaesthesia

7.3.3. Evaluator's conclusion on clinical efficacy women at high-risk of postpartum haemorrhage delivering vaginally of via CS under GA

The submission included 3 published studies considered to be of reasonable quality in women at high risk of PPH delivering either vaginally or via CS. Of these 3 studies, 2 were conducted in Panama (Reyes, 2011; Reyes et al., 2011) and 1 was conducted in Egypt (Fahmy et al., 2016).

The sponsor states that studies were submitted to support administration of carbetocin to women at high risk of PPH and to women delivering via CS under general anaesthesia. The high risk factors for PPH and the methods of delivery in the 3 studies were twin pregnancy in women delivered via CS under GA (Fahmy et al, 2016), grand multiparity (≥ 5 births) in women delivered vaginally (Reyes, 2011), and severe preeclampsia in women delivered either vaginally or via CS, but not stated whether CS was under general or regional anaesthesia (Reyes et al., 2011).

The primary efficacy outcome measure in each of the 3 studies was the need for additional uterotonic agents. In none of the 3 studies was the incidence of postpartum blood loss ≥ 500 mL or ≥ 1000 mL assessed, and in only 1 of the 3 studies was blood loss estimated (Fahmy et al., 2016) or change in postpartum haemoglobin concentration measured (Reyes et al., 2011)

The 3 studies compared carbetocin 100 µg IV in a total of 101 women to oxytocin 20 IU IV in a total of 149 women. The dose of carbetocin (100 µg IV) used in the 3 studies was consistent with that being proposed for registration. However, the dose of oxytocin (20 IU IV) used in the 3 studies was notably higher than the approved IV dose (5 IU IV) for vaginal delivery and for delivery via CS.

The primary efficacy outcome measure in each of the 3 studies was the need for additional uterotonic agents, but the trigger for initiating treatment was different across the studies. In Fahmy et al (2016), if the uterine contraction score was less than 3 (that is, score 2 = sufficient; score 1 = poor; or score 0 = atony) at 5 minutes after administration of the study drug then the inhaled isoflurane concentration was reduced from 1% to 0.5%, and if uterine contraction was still unsatisfactory then additional uterotonic agents were administered (that is, methergine 0.4 mg; route of administration not stated). In Reyes et al (2011), the primary outcome was the development of postpartum haemorrhage requiring the use of additional uterotonic agents (oxytocin or prostaglandins), but the volume of blood loss needed to trigger the use of additional uterotonic agents was not specified. In Reyes (2011), additional uterotonic agents (misoprostol, rectal) were administered in the event of suspected or clinically 'evidenced' uterine atony.

In Fahmy et al (2016), the incidence of women needing one dose of an additional uterotonic agent was significantly greater in the oxytocin arm compared to the oxytocin arm. In Reyes et al (2011), only 1 woman required an additional uterotonic agent (oxytocin arm), and in Reyes (2011) only 3 women required additional uterotonic agents (all in the oxytocin arm).

In Fahmy et al (2016), the secondary outcome measures all favoured women in the carbetocin arm compared to the oxytocin arm, while in Reyes et al (2011) and Reyes (2011) the secondary efficacy outcome measures generally did not differ significantly between the two arms.

Overall, it is considered that the 3 studies provide reasonable support for the use of carbetocin in women at high risk of PPH delivering vaginally or by CS under general or regional anaesthesia. The 3 studies suggest that the effects of carbetocin 100 µg IV and oxytocin 20 IU IV are comparable with regard to the prevention of uterine atony and excessive blood loss in women at high risk of PPH delivering vaginally or by CS under general or regional anaesthesia.

7.4. Analyses performed across trials: pooled and meta-analyses

7.4.1. Studies with evaluable data

The submission included two high quality meta-analyses in women who received carbetocin or oxytocin following CS or vaginal delivery and in women who received carbetocin or Syntometrine following vaginal delivery. The studies included in the two meta-analyses are summarised below in Table 19, and those studies which have been separately evaluated in this clinical evaluation report and were included in the meta-analyses have been flagged.

Table 19: Comparison of the studies submitted in the two meta-analyses (Jin et al., 2015 and Su et al., 2012) and the studies included in the dossier and evaluated separately

Study	Jin et al., 2015	Su et al., 2012	Comparison	Dossier
Askar et al., 2011	✔	✔	C versus S; VD	✔
Attilakos et al., 2010	✔	✔	C versus O; CS	✖
Barton and Jackson, 1996	✖	✔	C versus P; CS	✖
Borruto et al., 2009	✔	✔	C versus O; CS	✖
Boucher et al., 1998	✔	✔	C versus O; CS	✖

Study	Jin et al., 2015	Su et al., 2012	Comparison	Dossier
Boucher et al., 2004	✔	✔	C versus O; VD	✔
Dansereau et al., 1999	✔	✔	C versus O; CS	✖
Del Angel-Garcia et al., 2006	✖	✔	C versus O; VD	✖
Elgafor El Sharkwy et al., 2013	✔	✖	C versus S; CS	✖
Leung et al., 2006	✔	✔	C versus S; VD	✔
Moerti et al., 2011	✔	✖	C versus O; CS	✖
Nirmala et al., 2009	✔	✔	C versus S; VD	✔
Reyes et al., 2011	✔	✖	C versus O; CS/VD	✔
Su et al., 2009	✔	✔	C versus S; VD	✔

Notes: ✔ = included in the meta-analysis and separately evaluated; ✖ = not included in the meta-analysis and not separately evaluated; C versus S = carbetocin versus Syntometrine; C versus O = carbetocin versus oxytocin; C versus P = carbetocin versus placebo; VD = vaginal delivery; CS = caesarean section.

Comment: In Jin et al (2015), 12 randomised controlled trials were included in the study and in Su et al (2012), 11 randomised controlled trials were included in the study. The two meta-analyses shared 9 studies. Both studies included the same 4 studies comparing carbetocin to Syntometrine in women following vaginal delivery and all 4 of these studies were included in the dossier and evaluated separately in this clinical evaluation report. Not surprisingly, the results for the two meta-analyses of the 4 studies comparing carbetocin to Syntometrine in women following vaginal delivery were similar, with small numerical differences between the two analyses being reported for some efficacy outcomes due to minor differences in the inclusion criteria between the two studies. Similarly, the results for the two meta-analyses for the comparisons between carbetocin and oxytocin were similar. Both meta-analyses have been reviewed below in Sections 7.4.2 and 7.4.3.

7.4.2. Jin et al., 2015 Meta-analysis and systematic review

Title

Carbetocin for the prevention of postpartum haemorrhage: a systematic review and meta-analysis of randomised controlled trials.

Objectives

The objective of this meta-analysis was to compare the efficacy and safety profile of carbetocin to other uterotonic agents for the prevention of postpartum haemorrhage.

Methods

The report states that the systematic review and meta-analysis was conducted in accordance with PRISMA guidelines. The authors searched the medical databases PubMed, Web of Science, Scopus and EBSCOhost for relevant randomised controlled trials (RCTs). The analysis included all identified randomised controlled studies that compared carbetocin to other uterotonic agents for the prevention of PPH in women who underwent CS or vaginal delivery.

The selection process retrieved 38 references in PubMed, 73 in Scopus, 40 in Web of Science and 13 in EBSCOhost. Of the 164 identified references, 147 did not match the selection criteria based on the review of their titles and abstracts conducted by two of the authors. These two authors then independently reviewed the full texts of the remaining 17 references to determine eligibility for inclusion in the analysis. Five studies were excluded from analysis after evaluation of the full study report. The most common reason for exclusion from the analysis was non-randomised controlled trial. Finally, 12 studies were deemed to be eligible for inclusion in the analysis. Any disagreements about results were resolved by consensus or arbitration by a third reviewer. The risk of bias for each study was critically assessed using the recommended approach in the Cochrane Handbook for Systematic Reviews of Interventions.

Statistical analysis

Dichotomous data were tested by calculating the relative risks (RR) with 95% CIs. The means (SD) of continuous variables were used to derive a weighted mean difference (WMD). RR and WMD from individual studies were meta-analysed using a fixed effects model or random effects model for analysis if significant heterogeneity was observed (that is, $I^2 > 50$ %). Heterogeneity was investigated graphically using forest plots and statistically using the I^2 statistic to quantify heterogeneity between studies. If pooled estimated effects were shown to be heterogeneous, sub-group analysis was to be conducted to investigate possible sources of heterogeneity. The meta-analysis compared the outcome measures of carbetocin versus other uterotonic agent in women following cesarean or vaginal delivery. Statistical analyses were performed using REVMAN 5.0 (Cochrane Collaboration, Oxford, UK).

Studies included in the analyses

The systematic review identified 12 randomised controlled trials involving 2975 participants, published from 1998 to 2013.

There were 8 studies comparing carbetocin to oxytocin (6 in women who underwent CS, 1 in women following vaginal delivery, and 1 in women undergoing vaginal delivery or CS.) The carbetocin dose in these 8 studies was single dose 100 µg via IV bolus, while the dose and route of oxytocin administration varied across the studies (total dose 5 IU to 32.5 IU). Out of the 8 studies comparing carbetocin to oxytocin, 3 recruited participants undergoing CS with at least 1 risk-factor for PPH (for example, preeclampsia, previous PPH, gestational diabetes, fetal macrosomia, previous CS), while 2 enrolled women with or without risk-factors for PPH.

There were 4 studies comparing carbetocin 100 µg IM to a standard dose of Syntometrine (5 IU oxytocin and 0.5 mg ergometrine) 1 mL IMI in women undergoing vaginal delivery. Of the 4 studies, 3 involved women with no risk-factors for PPH and 1 was conducted in women with risk-factors for PPH, including a history of blood transfusion or retained placenta, grand multiparity, twin pregnancy, fetal macrosomia, polyhydramnios or prolonged labour.

In the 5 studies comparing carbetocin to Syntometrine or oxytocin in women undergoing vaginal delivery the same definition for PPH was used (that is, estimated blood loss in excess of 500 mL following a vaginal birth). In the 6 studies evaluating the efficacy and safety of carbetocin compared to oxytocin in women following CS, no single clear definition of PPH was used.

Quality assessment of the included studies

Overall, the authors considered that the methodology of each of the included studies was of good quality. Both random sequence generation and adequate allocation concealment were performed in 8 studies, while 3 studies did not clearly describe the method of randomisation and 3 studies used a block randomisation of 2 resulting in allocation concealment being less effective. Blinding was fully conducted in 11 studies. Attrition and selective reporting bias was specified in detail in 6 studies. The authors comments that other sources of bias were mainly because the projects 'benefited from pharmaceutical companies'.

Outcome measures

The *primary outcome measure* in 11 of the 12 studies was the need for additional therapeutic uterotonic agents, with perioperative blood loss being the primary outcome measure in 1 of the 12 studies. The need for additional uterotonic agents was used as the primary outcome variable as it was considered to be the most important clinical indicator of postpartum blood loss after delivery, with the decision to administer additional uterotonic agents being determined by the obstetrician based not only on clinical estimation of blood loss but also on the clinical assessment of uterine atony. *Secondary outcome measures* varied across studies, but mainly included the incidence of PPH and/or severe PPH, the incidence of blood transfusion, estimated blood loss, uterine massage and adverse effects.

Efficacy outcomes – caesarian section (CS) - carbetocin versus oxytocin

The results for the pooled data from the studies comparing carbetocin to oxytocin following CS are summarised below in Table 20.

Table 20: Jin et al., 2015 Pooled efficacy outcome data from the 8 studies comparing carbetocin to oxytocin following caesarean section

Outcome measure	Studies (N)	C (n/N)	O (n/N)	Relative Risk	95% CI	Hetero-geneity (p)
Therapeutic uterotonics	5 (1553)	106/776	157/777	0.68	(0.55, 0.84)	0.38
PPH (≥ 500 mL)	4 (1195)	23/596	35/599	0.66	(0.42, 1.06)	0.60
Severe PPH (≥ 1000 mL)	2 (432)	9/215	10/217	0.91	(0.39, 2.15)	0.49
Uterine massage	2 (739)	29/369	54/370	0.54	(0.31, 0.96)	0.17
Blood transfusion	2 (757)	5/378	9/379	0.56	(0.19, 1.65)	0.36

C=Carbetocin; O=oxytocin; N = number of subjects; Source: Jin et al, 2015. 5 studies (n = 1553) (Elgafor El Sharkwy, 2013; Attilakos et al, 2010; Borruto et al., 2009; Dansereau et al, 1999; Boucher et al., 1998); 4 studies (n = 1195) (Attilakos et al, 2010; Borruto et al., 2009; Dansereau et al., 1999; Boucher et al., 1998); 2 studies (n = 432) (Attilakos et al, 2010; Boucher et al., 1998); 2 studies (n = 739) (Borruto et al., 2009; Dansereau et al., 1999); 2 studies (n = 757) (Elgafor El Sharkwy, 2013; Attilakos et al, 2010).

The study also included an assessment of estimates for weighted mean differences (WMDs) in blood loss and haemoglobin concentration changes in the pooled data for the carbetocin and the oxytocin groups in women undergoing CS. The estimated WMD in blood loss for the comparison

between the carbetocin arm (n = 407) and the oxytocin arm (n = 407) was -43.19 mL (95% CI: -105.76, 19.37), and the estimated WMD in haemoglobin concentration (units not stated) between the carbetocin arm (n = 723) and the oxytocin arm (n = 725) was 0.01 (95% CI: -0.1, 0.12). The differences between the two treatment groups for both outcome measures were not statistically significant.

Efficacy outcomes vaginal delivery Carbetocin versus oxytocin

The efficacy outcome measures comparing carbetocin to oxytocin in women following vaginal delivery are summarised below in Table 21. It should be noted that the results were based on data from only 1 study (Boucher et al, 2004).

Table 21: Jin et al., 2015 Efficacy outcome from studies comparing carbetocin to oxytocin following vaginal delivery

Outcome measure	Studies (N)	C (n/N)	O (n/N)	Relative Risk	95% CI	Hetero-geneity (p)
Therapeutic uterotonics	1 (160)	12/83	12/77	0.93	(0.44, 1.94)	NA
PPH (≥ 500 mL)	1 (131)	10/64	11/67	0.95	(0.43, 2.09)	NA
Uterine massage	1 (160)	36/83	48/77	0.70	(0.51, 0.94)	NA

C=Carbetocin; O=oxytocin; N = number; Source: Jin et al., 2015. One study (Boucher et al., 2004).

There were no statistically significant differences between the two treatment groups in the weighted mean differences for estimated blood loss, haemoglobin changes and haematocrit changes.

Efficacy outcomes – carbetocin versus Syntometrine - vaginal delivery

The results for the pooled data from the studies comparing carbetocin 100 µg IM to Syntometrine 1 mL IM following vaginal delivery are summarised below in Table 22.

Table 22: Jin et al., 2015 Pooled efficacy outcome data following vaginal delivery from studies comparing carbetocin to Syntometrine

Outcome measure	Studies (N)	C (n/N)	S (n/N)	Relative Risk	95% CI	Hetero-geneity (p)
Therapeutic uterotonics	4 (1030)	59/515	71/515	0.83	(0.60, 1.15)	0.35
PPH (≥ 500 mL)	4 (1030)	14/515	15/515	0.93	(0.46, 1.91)	0.54
Severe PPH (≥ 1000 mL)	3 (910)	1/455	2/445	0.71	(0.14, 3.61)	0.55
Blood transfusion	3 (910)	6/455	3/455	1.75	(0.52, 5.93)	0.51

C=Carbetocin; S=Syntometrine; N = number of subjects; Source: Jin et al., 2015, adapted from Table 3. 4 studies (n = 1030) (Leung et al., 2006; Askar et al., 2011; Nirmala et al., 2009; Su et al., 2009); 3 studies (n = 910) (Leung et al., 2006; Askar et al., 2011; Su et al., 2009)

Conclusion of the study authors on their meta-analysis

The authors stated that their meta-analysis showed that carbetocin was associated with a significantly reduced need for subsequent interventions with additional uterotonic agent and uterine massage compared to oxytocin in women who underwent CS. However, with respect to PPH, severe PPH, mean estimated blood loss, haemoglobin level changes and the incidence of blood transfusion, their analysis failed to detect a significant difference. Furthermore, the meta-analysis showed none of the reported adverse effects to be significantly different for the comparison between the carbetocin and oxytocin groups in women undergoing CS or vaginal delivery.

In addition, the authors stated that the estimated effects of studies comparing carbetocin and Syntometrine in women following vaginal delivery showed no statistically significant difference with respect to the risk of PPH, severe PPH and the need for additional uterotonic agent. However, women who received carbetocin experienced significantly fewer adverse effects and less blood loss than women who received Syntometrine.

The authors concluded that carbetocin is associated with a similar low incidence of adverse effects to oxytocin and is at least as effective as Syntometrine and may become an alternative uterotonic agent for the prevention of postpartum haemorrhage. The authors recommended that further studies should be conducted to determine the safety and efficacy profile of carbetocin in women with cardiac disorders and to analyse the cost-effectiveness and minimum effective dose of carbetocin.

Evaluator's comment on the efficacy data reported in the study

The methodology used in this study was high quality. There was a statistically significant reduction in the need for additional uterotonic agents of 32% in the carbetocin group relative to the oxytocin group in women undergoing CS (RR = 0.68 (95% CI: 0.55, 0.84); pooled data from 4 studies), and a statistically significant reduction of 46% in the need for uterine massage in the carbetocin arm relative to the oxytocin arm (RR = 0.54 (95% CI: 0.31, 0.96); pooled data from 2 studies). There was no difference between the carbetocin and oxytocin groups in the pooled CS studies in the incidence of PPH (≥ 500 mL), the incidence of severe PPH (≥ 1000 mL), or the need for blood transfusion.

There were no statistically significant differences between the carbetocin and oxytocin groups for the outcome measures of the need for additional uterotonic agents, the incidence of PPH, or need for uterine massage between the carbetocin and oxytocin groups in women following vaginal delivery. However, the results for the comparison between carbetocin and oxytocin following vaginal delivery were reported for only 1 study. There were no statistically significant differences between the carbetocin and Syntometrine groups in the need for additional uterotonic agents, the incidence of PPH (≥ 500 mL), the incidence of severe PPH (≥ 1000 mL), or the need for blood transfusion in women following vaginal delivery.

It was noted that the labeling of Figures 2 and 3 in the body of the study report was incorrect and the identification of the pooled studies contributing to the data in supplementary Tables S3 and S4 was incomplete.

7.4.3. Su et al, 2012 Meta-analysis and systematic review Cochrane database

Title

Carbetocin for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews 2012, Issue 4.

Objectives

The primary objective of the study was to determine whether carbetocin is as effective as conventional uterotonic agents (that is, oxytocin, Syntometrine) for the prevention of PPH.

The secondary objectives were to determine the best route of administration and the optimal dose of carbetocin to prevent PPH.

Methods

The search for eligible studies was extensive and the search strategy included all relevant databases such as Central (Cochrane library), Medline (Ovid), and Embase (Dialog Datastar). The search strategy included studies in women undergoing either vaginal delivery or CS. The interventions included (1) carbetocin versus other uterotonic agents at any route or doses, and (2) carbetocin versus placebo or no treatment. A total of 11 randomised controlled trials, involving 2635 women were identified from the searches and included in the analysis.

Statistical analysis

The statistical analysis was carried out using the Review Manager software (that is, RevMan 2011). A fixed-effect meta-analysis for combining data was used where it was considered reasonable to assume that the trials were estimating the same underlying treatment effect. Statistical heterogeneity was assessed using T^2, I^2 and Chi^2 statistics. Heterogeneity was considered substantial if I^2 was greater than 30% and either T^2 was greater than zero or there was a low p value (< 0.10) in the Chi^2 test for heterogeneity. If clinical heterogeneity was sufficient to expect that the treatment effects differed for the trials, or if substantial statistical heterogeneity was detected, then a random-effects meta-analysis was used to produce an overall summary if an average treatment effect across trials was considered to be clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects. If the average treatment effect was not clinically meaningful, then trials were not combined. For random-effects analyses, the results were presented as the average treatment effect with 95% CI, and the estimates of T^2 and I^2. Subgroup analysis comparing high risk versus low-risk pregnancy for PPH was carried out for carbetocin versus Syntometrine in women following vaginal delivery.

Included studies

A total of 11 RCTs involving 2635 women were identified.

There were 6 trials comparing carbetocin to oxytocin: 4 trials were conducted in women undergoing CS (Attilakos 2010; Borruto 2009; Boucher 1998; Dansereau 1999); 1 trial was conducted in women following vaginal delivery (Boucher 2004); and in 1 trial the method of delivery was not clear. Carbetocin 100 µg IV was administered in all 6 trials, but the dose of oxytocin varied across the trials.

There were 4 trials comparing carbetocin to Syntometrine in women following vaginal delivery (Askar 2011; Leung 2006; Nirmala 2009; Su 2009). Three of the trials (Askar 2011; Leung 2006; Su 2009) were conducted in women with no risk factor for PPH, while one trial (Nirmala 2009) was conducted in women with risk factors for PPH. There was 1 trial comparing the use of carbetocin with placebo following vaginal delivery (Barton 1996).

Comment: The dose of carbetocin used across the trials was 100 µg. However, the dosage of oxytocin varied across the trials: that is, 32.5 IU over 16 h in the trial by Boucher 1998; 5 IU oxytocin IV bolus followed by 20 units oxytocin over 8 h in Dansereau 1999; 10 IU oxytocin infusion over 2 h in Borruto 2009 and 5 IU oxytocin as IV bolus in Attilakos 2010. Trials that used oxytocin doses greater than those approved in Australia had the potential to bias efficacy towards oxytocin and safety towards carbetocin. No discussion relating to this matter could be identified in the meta-analysis.

One trial reported in abstract form compared the use of carbetocin and placebo (normal saline) following CS (Barton 1996). PPH was not reported as an outcome measure in this trial. The primary outcome measure was the use of additional uterotonic agents, which was reported in 12.9% (8/62) of women in the carbetocin arm and 71.9% (41/57) of women in the placebo arm (HR = 0.18 (95% CI: 0.09, 0.35)). Uterine tone was reported to be significantly increased for 20 minutes following drug administration ($p < 0.05$) in carbetocin-treated women compared to placebo-treated women, but no differences in fundal position or lochia between the two groups were reported. However, no numerical results for the duration of uterine tone were presented in the abstract. It should be noted that results relating to the use of additional uterotonic agents were not included in the meta-analysis comparing carbetocin to oxytocin for this endpoint but were reported separately (Analysis 4.1 of the meta-analysis). Therefore, the results of this placebo controlled trial cannot bias the efficacy results towards carbetocin in the pooled data comparing the need for additional uterotonic agents in patients treated with carbetocin or oxytocin.

Quality of the studies

In assessing the quality of the studies the following features were considered by the authors: (a) method of randomisation; (b) method of allocation concealment; (c) blinding of participants, surgeons and outcome assessors; (d) completeness of follow up; and (e) use of intention-to-treat analysis. High quality trials were defined as those in which treatment allocation had been concealed, outcome assessment had been blinded, and ITT analysis had been used to handle dropouts and withdrawals.

The authors considered that all 4 trials comparing carbetocin to Syntometrine were of high methodological quality, with computer generated randomisation and adequate concealment allocation. ITT analyses were performed for 3 of the 4 studies. The author's considered that for the 6 trials comparing carbetocin and oxytocin, adequate randomisation was conducted for 3 out of the 6 trials, while allocation concealment was adequate for 2 out of the 6 studies. None of the 6 trials did an ITT analysis when analysing the effectiveness of oxytocin and carbetocin.

Comment: Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions.* Discrepancies were resolved through discussion and through consultation with the third reviewer. Explicit judgements were made about whether individual studies were at high risk of bias. The methods used to assess bias for each of the individual studies are considered to be satisfactory. The authors did not assess publication bias. The authors stated that in future updates to the review if there are 10 or more studies in the meta-analysis then they will investigate reporting biases (such as publication bias) using formal assessment of funnel plots and other appropriate methods.

Outcome measures

The *primary outcome maternal measures* were: (1) severe PPH, including measured or clinically estimated blood loss of ≥ 1000 mL or as defined by trial authors, irrespective of the mode of delivery; and (2) maternal death or severe morbidity (for example, major surgery, organ failure, intensive care unit admission, hyperpyrexia or as defined by trial authors).

The *secondary outcome maternal measures* were: (1) any PPH (measured or clinically estimated blood loss of ≥ 500 mL, or as defined by trial authors), irrespective of the mode of delivery; (2) manual removal of the placenta; (3) blood transfusion; (4) use of therapeutic (that is, additional) uterotonic agents; (5) additional treatment for PPH (uterine tamponade, X-ray embolisation); (6) side effects reported either individually or as a composite where appropriate (elevation of blood pressure, vomiting, nausea, shivering, hyperpyrexia, headache, chest pain,

shortness of breath, diarrhoea); (7) postnatal anaemia (defined by the trial authors, absolute or relative drop in Hb); (8) thromboembolic events; and (9) cost.

The *secondary neonatal outcome measures* were: (1) admission to neonatal intensive care unit; (2) respiratory distress; (3) jaundice requiring phototherapy; and (4) not breastfed at discharge.

Comment: The primary and secondary efficacy outcome measures used to assess treatment were extensive. The most appropriate outcomes for the purposes of the current submission are considered to be severe PPH (> 1000 mL), PPH > 500 mL, need for additional uterotonic agents, post-natal reduction in haemoglobin concentration, and need for blood transfusion.

Results for efficacy outcome measures carbetocin versus oxytocin

The results for the studies with estimated data are summarised below in Table 23 (CS) and Table 24 (vaginal delivery). The summarised efficacy outcome measures are considered to be clinically relevant for assessing the effects of the study drugs on PPH, and are representative of the efficacy outcome measures assessed in the studies submitted by the sponsor and evaluated separately in this clinical evaluation report.

Caesarian section carbetocin versus oxytocin

The results for the efficacy outcome measures of clinical interest in the two treatment groups in women undergoing CS are summarised below in Table 23.

Table 23: Su et al., 2012 Efficacy outcome measures carbetocin versus oxytocin following CS

Outcome measures	Studies (N)	C (n/N)	O (n/N)	Relative Risk	95% CI	Hetero-geneity Chi^2 (p); I^2 %
Severe PPH (> 1000 mL)*	2 (432)	9/215	10/217	0.91	(0.39, 2.15)	0.49; 0%
PPH (> 500 mL)*	4 (1195)	23/597	35/598	0.66	(0.42, 1.06)	0.60; 0%
Additional uterotonic agents	4 (1173)	80/586	126/587	0.64	(0.51, 0.81)	0.31; 17%
Need for blood transfusion	1 (377)	4/188	5/189	0.80	(0.22, 2.95)	NA
	Studies (subjects)	Carbetocin (outcome, n)	O (outcome, n)	Mean difference (Δ) (95% CI)		Hetero-geneity Chi^2 (p); I^2 %
Mean (SD) blood loss mL	1 (616)	159 (92) mL	188 (115) mL	Δ = -29.0	(-3.2, 25.2)	NA
		(n = 29)	(n = 28)			
Mean (SD) Hb difference g/dl	1 (635)	- 7.5 (10)	- 8.3 (10)	Δ = 0.80	(-.76, 2.36)	NA

Outcome measures	Studies (N)	C (n/N)	O (n/N)	Relative Risk	95% CI	Hetero-geneity Chi² (p); I² %
		(n = 417)	(n = 318)			

C=Carbetocin; O=oxytocin; N = number of subjects; * Severe PPH and PPH also included events defined by the trial authors. NA = not applicable (heterogeneity not estimable due to the analysis including 1 study only).

Comment: The primary efficacy outcome measure (incidence of severe PPH) was assessed in 2 studies in women undergoing CS, and the relative risk for the comparison between the two treatment groups for this outcome was not statistically significant. Of the 5 other clinically relevant efficacy outcomes, the difference in the need for additional uterotonic agents was statistically significantly lower in women in the carbetocin group compared to the oxytocin group, while the differences in PPH, need for blood transfusion, mean blood loss and mean Hb difference did not significantly differ between the two treatment groups. It is noted that need for blood transfusion, mean blood loss and mean Hb difference were each assessed in 1 study only.

Vaginal delivery carbetocin versus oxytocin

The results for the efficacy outcome measures of clinical interest in the two treatment groups in women following vaginal delivery assessed in the 1 study with data (Boucher et al., 2004) are summarised below in Table 24.

Table 24: Su et al. 2012 Efficacy outcome measures carbetocin versus oxytocin following vaginal delivery

Outcome measures Boucher et al (2004)	Studies (N)	C (n/N)	O (n/N)	Relative Risk	95% CI
PPH (> 500 mL)*	1 (131)	10/64	11/67	0.95	(0.43, 2.09)
Additional uterotonic agents	1 (160)	12/83	12/77	0.93	(0.44, 1.94)
	Studies (subjects)	Carbetocin (outcome, n)	Oxytocin (outcome, n)	Mean difference (Δ) (95% CI)	
Mean (SD) blood loss mL	1 (160)	413 (198)	410 (194)	Δ = 3.3	(-57.4, 64.0)
		(n = 83)	(n = 77)		
Mean (SD) Hb difference g/dl	1 (160)	-12.8 (10.8)	-15.9 (11.6)	Δ = 3.10	(-0.38, 6.58)
		(n = 83)	(n = 77)		

C=Carbetocin; O=oxytocin; N = number of subjects; * PPH also included events defined by the trial authors.

Comment: The data comparing the two treatment groups in women delivering vaginally were derived from 1 study (Boucher et al., 2004). The results showed no statistically significant differences between the two treatment groups for the incidence of PPH,

need for additional uterotonic agents, mean difference in estimated blood loss, and mean difference in haemoglobin concentration.

Results for efficacy outcome measures: carbetocin versus Syntometrine following vaginal delivery

The results for the studies with the relevant data are summarised below in Table 25. The summarised efficacy outcome measures are considered to be clinically relevant for assessing the effects of the study drugs on PPH in women following vaginal delivery, and are representative of the efficacy outcome measures assessed in the studies submitted by the sponsor and evaluated separately in this clinical evaluation report.

Table 25: Su et al., 2012 Efficacy outcome measures carbetocin versus Syntometrine following vaginal delivery

	Studies (N)	C (n/N)	O (n/N)	Relative Risk	95% CI	Hetero-geneity Chi² (p); I² %
Severe PPH (> 1000 mL)	3 (910)	1/455	3/445	0.50	(0.09, 2.72)	0.83; 0%
PPH (> 500 mL)	4 (1030)	14/515	14/515	1.00	(0.48, 2.07)	0.38; 3%
Additional uterotonic agents	4 (1030)	59/515	71/515	0.83	(0.60, 1.15)	0.35; 9%
Need for blood transfusion	3 (910)	6/455	3/455	1.75	(0.52, 5.93)	0.51; 0%
	Studies (N)	**C (outcome, n)**	**O (outcome, n)**	**Mean difference (Δ) (95% CI)**		**Heteroge neity Chi² (p); I² %**
Mean (SD) blood loss mL	4 (1030)	217-244 mL	223-343 mL	Δ = -48.8	(-94.8, -2.9)	p < 0.00001; 90%
		(n = 515)	(n = 515)			

C=Carbetocin; O=oxytocin; N = number of subjects;

Comment: There were no statistically significant differences between the two treatment groups in the incidence of severe PPH, the incidence of PPH, the need for additional uterotonic agents or the need for blood transfusion. However, the mean estimated blood loss was approximately 48 mL lower in the carbetocin group than in the Syntometrine group, and the difference between the two groups was statistically significant. There was significant heterogeneity in the mean blood loss trials, which the authors speculate might be due to the different methods used to assess blood loss across the trials. In Askar et al (2011) and Nirmala et al (2009), measurement of blood loss was performed by the gravimetric method, whereas in Leung et al (2006) and Su et al (2009), the amount of blood loss was by visual estimation.

Subgroup analysis between carbetocin and syntometrine

The meta-analysis included a comparative subgroup assessment of the effects of the risk of PPH on efficacy outcome measures between women in the carbetocin and Syntometrine groups. However, of the 4 studies comparing carbetocin to Syntometrine there was only 1 study in women with risk-factors for PPH (Nirmala et al., 2009) compared to 3 studies without risk-factors for PPH (Leung et al., 2006; Su et al., 2009; Askar et al., 2011). The imbalance between study numbers available for pooling in women with and without risk-factors for PPH is considered to be a significant limitation of the subgroup analysis. The results of the subgroup analysis have not been reviewed in this CER as it is considered no significant weight can be given to the comparison due to the imbalance in the number of relevant pooled studies between women with and without risk factors for PPH.

Conclusion of the study authors on their meta-analysis

The authors conclude that for women who undergo CS, carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, but there is no difference in the incidence of postpartum haemorrhage between the two treatment arms. Carbetocin is associated with less blood loss compared to Syntometrine in the prevention of PPH for women who have vaginal deliveries and is associated with significantly fewer adverse effects. Further research is needed to analyse the cost-effectiveness of carbetocin as an uterotonic agent.

Overall comment on the study

This was a high quality meta-analysis. The main conclusions relating to the efficacy outcome measures were: (1) the use of carbetocin resulted in a statistically significant reduction in the need for additional uterotonic agents compared to oxytocin in women who underwent CS (RR = 0.62 (95% CI: 0.44, 0.88); 4 trials, 1173 women); (2) there were no statistically significant differences between the carbetocin and oxytocin groups in the risk of PPH (> 500 mL), risk of severe PPH (> 1000 mL), mean estimated blood loss, mean reduction in haemoglobin and need for blood transfusion in women following CS or vaginal delivery; (3) mean blood loss was statistically significantly lower in the carbetocin group compared to the Syntometrine group in women following vaginal delivery (Δ = -48.84 mL (95% CI: -94.82, -2.85; 4 trials, 1030 women), but there was significant heterogeneity between the trials; (4) there were no statistically significant differences between the carbetocin and Syntometrine groups in the risk of PPH (> 500 mL), risk of severe PPH (> 1000 mL), need for additional uterotonic agents and need for blood transfusion in women following vaginal delivery.

8. Clinical safety

8.1. Vaginal delivery

8.1.1. Studies with evaluable safety data

- Evaluable safety data were provided in each of the 7 studies submitted to support carbetocin for the prevention of uterine atony and excessive bleeding in women delivering vaginally, irrespective of whether or not the women had risk-factors for PPH. Carbetocin (100 µg IM) was compared to oxytocin (5 IU IM or 10 IU IV) in 2 of the 7 studies and to Syntometrine IM in 5 studies of the 7 studies (5 IU oxytocin/0.5 mg ergometrine (4 studies) or 5 IU oxytocin/ergometrine 0.2 mg (1 study)). The safety data for each of the 7 studies are summarised below.
- The 7 studies included a total of 1590 women, including 798 who received carbetocin and 792 who received an active control (177, oxytocin; 615, Syntometrine). The 7 studies

included 4 which excluded women with risk-factors for PPH (Leung et al., 2006; Su et al., 2009; Askar et al., 2011, Samimi et al., 2013), and 3 which included women with risk-factors for PPH (Boucher et al., 2004; Nirmala et al., 2009; Maged et al., 2016).

- In each of the 7 studies the study drugs were administered as a single dose regimen for the active management of the third stage of labour. In each of the 7 studies, additional uterotonic agents were administered as needed to prevent uterine atony or control blood loss. Carbetocin versus oxytocin, and in each of the studies the majority of women did not require additional uterotonic agents.
- The safety data for each of the 7 studies are summarised below.

8.1.1.1. Boucher et al., 2004

In Boucher et al (2004), the safety of carbetocin 100 µg IM (n = 83) and oxytocin 10 IU IV 2-h infusion (n = 77) were compared following vaginal delivery in women with at least 1 risk factor for PPH. The incidence of adverse events reported by at least 5% of women in either treatment arm is summarised below in Table 26. The mean blood pressure, heart rate and respiratory rate for the two treatment arms assessed over 24 h after injection are summarised below in Figure 8.

Comment: In general, there were no marked differences in the safety profiles of the two drugs. Adverse events were reported in 51.8% (n = 43) of women in the carbetocin arm and 54.5% in the oxytocin arm. Adverse events by preferred term reported in ≥ 10% of women in either treatment arm (carbetocin versus oxytocin, respectively) were headache (7.2% versus 14%), and leucocytosis (7.2% versus 10.4%). Vital signs (SBP, DBP, HR, RR) were measured in both treatment arms at regular intervals up to 300 minutes after administration and then at 24 h after treatment. No notable differences between the two treatment arms in vital signs were observed at any time-points after administration through to 24 h.

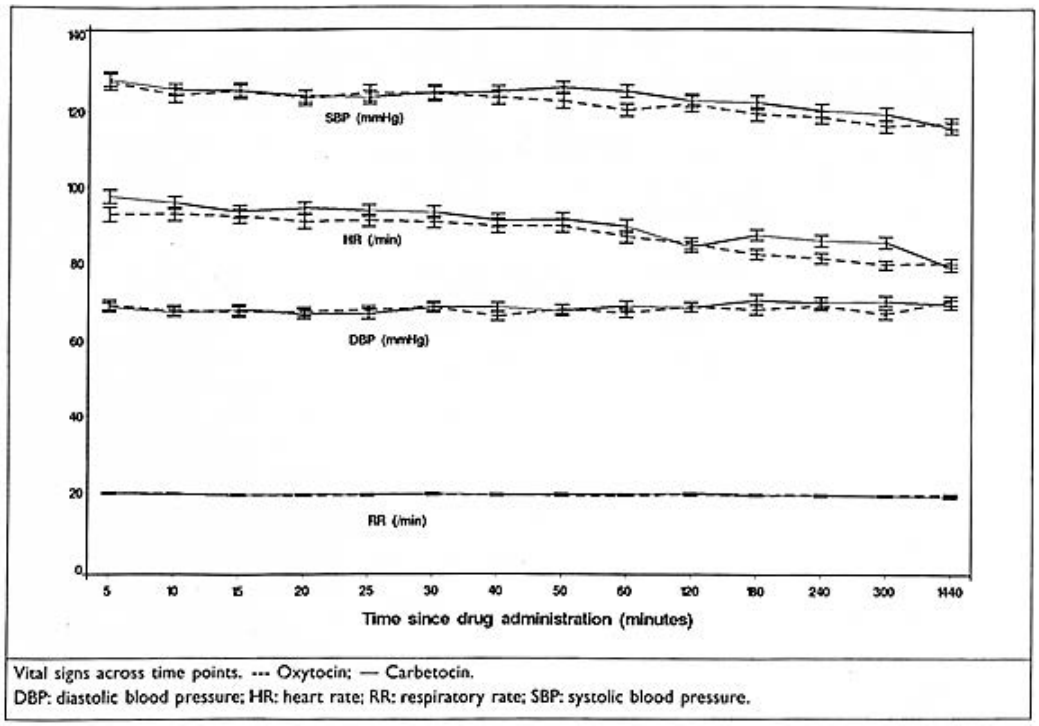
Table 26: Boucher et al., 2004 Incidence of adverse events reported by at least 5% of women in either of the carbetocin or oxytocin treatment arms

Body System* Preferred Term	Carbetocin (N = 83) n (%)	Oxytocin (N = 77) n (%)
Women reporting at least 1 adverse event	43 (51.8)	42 (54.5)
Body as a whole	20 (24.1)	22 (28.6)
Headache	6 (7.2)	11 (14.3)
Chills	8 (9.6)	7 (9.1)
Abdominal pain	5 (6.0)	0
Nervous	12 (14.5)	9 (11.7)
Dizziness	7 (8.4)	6 (7.8)
Tremor	5 (6.0)	4 (5.2)
Cardiovascular	8 (9.6)	11 (14.3)
Vasodilatation	6 (7.2)	5 (6.5)
Hemic/lymphatic	9 (10.8)	10 (13.0)
Leukocytosis	6 (7.2)	8 (10.4)
Digestive	7 (8.4)	10 (13.0)
Nausea	5 (6.0)	7 (9.1)
Vomiting	0	6 (7.8)
Urogenital	7 (8.4)	5 (6.5)
Skin/appendages	0	5 (6.5)
Pruritis	0	4 (5.2)

*Coded using COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms).

Source: Boucher et al., 2004, Table 3.

Figure 8: Boucher et al., 2004 Vital signs assessed in the carbetocin and oxytocin treatment arms over the 24 h from injection following vaginal delivery



Vital signs across time points. --- Oxytocin; — Carbetocin.
DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure.

Source: Boucher et al., 2004, Figure on page 486.

8.1.1.2. Maged et al., 2015

In Maged et al (2015), the safety of carbetocin 100 IM (n = 100) and oxytocin 5 IU IM (n = 100) were compared following vaginal delivery in women with at least 2 risk-factors for PPH. All participants were followed for 24 h. Systolic and diastolic blood pressures were measured immediately after delivery and then at 30 and 60 minutes after delivery. Possible complications including nausea, vomiting, tachycardia, flushing, dizziness, headache, shivering, metallic taste, dyspnoea, palpitation and itching were recorded. The adverse effects are summarised below in Table 27 and the blood pressure results are summarised below in Table 28.

Table 27: Maged et al., 2015 Adverse effects in the two treatment arms

	Carbetocin ($n = 100$)	Oxytocin ($n = 100$)	p value
Nausea	3	1	0.621
Vomiting	2	0	0.497
Tachycardia (h >100 b/min)	10	2	0.017
Flushing	1	0	1
Dizziness	2	0	0.497
Headache	5	2	0.445
Shivering	2	0	0.497
Anemia	29	27	0.753
Metallic taste	1	0	1
Dyspnea	1	0	1
Palpitations	2	1	1
Itching	1	0	1

*Data are presented as number and percent.

Source: Maged et al., 2015, Table 4.

Table 28: Maged et al., 2015 Blood pressure results in the carbetocin and oxytocin treatment arms

		Carbetocin	oxytocin	*p* value
Systolic blood pressure (mmHg)	Immediately after delivery	110.25 ± 6.39	117.51 ± 9.71	<0.001
	30 min after delivery	108.06 ± 6.64	115.19 ± 10.28	<0.001
	60 min after delivery	112.57 ± 6.67	118.42 ± 9.49	<0.001
Diastolic blood pressure (mmHg)	immediately after delivery	73.38 ± 3.7	76.67 ± 4.73	<0.001
	30 min after delivery	74.22 ± 3.78	80.7 ± 10.89	<0.001
	60 min after delivery	74.87 ± 3.8	76.96 ± 4.89	0.001

*Data are presented as mean ± SD.

Source: Maged et al., 2015, Table 3.

Comment: The incidence of women experiencing adverse effects was similar in the two treatment arms, apart from a higher incidence of tachycardia (> 100 bpm) in the carbetocin arm than in the oxytocin arm. However, systolic and diastolic blood pressure levels were both statistically significantly higher at all time-points in the oxytocin arm than in the carbetocin arm. Overall, the results suggest that the safety profiles of carbetocin and oxytocin are comparable.

8.1.2. Carbetocin versus Syntometrine

8.1.2.1. Leung et al., 2006

In Leung et al (2006), the safety of carbetocin 100 µg IM (n = 150) and Syntometrine (oxytocin 5 IU/ergometrine 0.5 mg) (n = 150) were compared following vaginal delivery in women undergoing uncomplicated vaginal delivery. The occurrence of nausea, vomiting, flushing, headache, shivering and pain over injection site were recorded by an interview conducted 1 h after delivery. Maternal blood pressure, pulse and temperature were checked immediately after delivery and repeated 30 and 60 minutes later. The adverse effect profiles of the two treatment arms are summarised below in Table 29.

Table 29: Leung et al., 2006 Adverse effects in the carbetocin and Syntometrine treatment arms

	Carbetocin (*n* = 150)	Syntometrine (*n* = 150)	Mean difference	RR	95% CI
Nausea*	2 (1.3)	11 (7.3)	—	0.18	0.04–0.78
Vomiting*	1 (0.7)	10 (6.7)	—	0.10	0.01–0.74
Facial flushing*	0	3 (2)	—	—	—
Headache*	1 (0.7)	2 (1.3)	—	0.50	0.05–5.54
Shivering*	2 (1.3)	6 (4)	—	0.33	0.06–1.63
Pain over injection site*	0	1 (0.7)	—	—	—
Tachycardia (pulse ≥ 100 beats per minute) within 60 minutes postdelivery*	32 (21.3)	19 (12.7)	—	1.68	1.03–3.57
Mean systolic blood pressure immediately after delivery**	113.7 (11.6)	116.7 (12.9)	−3.0	—	−5.7 to −0.2
Mean diastolic blood pressure immediately after delivery**	63.4 (9.2)	67.2 (9.4)	−3.8	—	−6.0 to −1.7
Mean systolic blood pressure 30 minutes after delivery**	112.9 (10.3)	118.1 (11.6)	−5.2	—	−7.8 to −2.8
Mean diastolic blood pressure 30 minutes after delivery**	64.5 (8.4)	68.1 (10.0)	−3.6	—	−5.7 to −1.5
Mean systolic blood pressure 60 minutes after delivery**	113.3 (10.5)	117.1 (11.9)	−3.8	—	−6.4 to −1.3
Mean diastolic blood pressure 60 minutes after delivery**	64.7 (8.7)	67.9 (8.8)	−3.2	—	−5.2 to −1.2
Hypertension (blood pressure ≥ 140/90 mmHg)*					
Immediately after delivery	2 (1.3)	4 (2.7)	—	0.5	0.09–2.74
30 minutes after delivery	0	8 (5.3)***	—	—	—
60 minutes after delivery	0	6 (4)****	—	—	—

Source: Leung et al., 2006, Table 5. Notes: * Data are presented as n (%). ** Data are presented as mean (SD). *** P = 0.01 by Fisher's exact test. **** P = 0.05 by Fisher's exact test.

Comment: Nausea and vomiting occurred significantly less frequently in the carbetocin arm than in the Syntometrine arm, while there were no clinically meaningful differences

between the two treatment arms in facial flushing, headache, shivering or pain over the injection site. Tachycardia (pulse ≥ 100 beats/minute) within 30 minutes post-delivery occurred significantly more frequently in the carbetocin arm (21.3%) than in Syntometrine arm (12.7%), with a RR of 1.68 (95% CI: 1.03, 3.57). Mean systolic and diastolic blood pressure immediately after delivery and 30 and 60 minutes after delivery were lower in the carbetocin arm than in the Syntometrine arm, and while the differences were statistically significant they are considered to be not clinically meaningful. The incidence of hypertension (BP > 140/90 mmHg), was similar in the two treatment arms immediately after delivery, but significantly greater in the Syntometrine arm than in the carbetocin arm at 30 and 60 minutes after delivery. Overall, it is considered that the data demonstrated that the adverse event profile of carbetocin was superior to that of Syntometrine.

8.1.2.2. Nirmala et al., 2009

In Nirmala et al (2009), the safety or carbetocin 100 µg IM (n = 60) and Syntometrine (oxytocin 5 IU/ergometrine 0.5 mg) (n = 160) were compared following vaginal delivery in women at high risk of PPH. Uterine fundal height and vital signs were monitored in the labour ward at 0, 30 minutes and 60 minutes after administration of the study drug. Increases in systolic or diastolic pressure equal to or greater than 30 mmHg or 20 mmHg, respectively, were considered to be significant. Women were monitored for side effects of the study drug in the first 24 h after delivery and were questioned about the presence of side effects after drug administration in the recovery room and in the postnatal ward. Women were also specifically monitored for signs of flushing, sweating, tremor and vomiting. Other symptoms volunteered by the women or signs observed by the attending clinicians were also recorded. The frequency of adverse events reported in the two treatment arms are summarised below in Table 30.

Table 30: Nirmala et al., 2009 Adverse events in the carbetocin and Syntometrine treatment arms

	Carbetocin *n* (%)	Syntometrine *n* (%)	*P* value
Abdominal pain	1 (2)	3 (5)	ns
Back pain	0	1 (2)	ns
Headache	2 (3)	1 (2)	ns
Nausea	0	1 (2)	ns
Feeling of warmth	0	0	–
Metallic taste	0	0	–
Other symptoms	0	0	–
Flushing	0	0	–
Sweating	0	0	–
Tremors	0	0	–
Vomiting	0	2 (3)	ns
Other signs	0	0	–

Source: Nirmala et al., 2009, Table 3.

Vital signs were monitored at 0, 30 and 60 minutes after study drug administration. In both treatment arms, changes in mean systolic and diastolic blood pressure and heart rate were similar throughout the study period and no statistically significant differences were reported (see Table 31, below). There was no significant difference in the number of patients with hypertension between the two treatment arms (n = 7, 12%, carbetocin versus n = 9, 15%, Syntometrine, p > 0.05).

Table 31: Nirmala et al., 2009 Vital signs in the carbetocin and Syntometrine treatment arms

	Carbetocin *n* = 60 Mean ± SD	Syntometrine *n* = 60 Mean ± SD	*P*-value
Systolic blood pressure on admission = baseline (mmHg)	120 ± 57	120 ± 58	ns
Increase in systolic blood pressure at 30 min from baseline (mmHg)	7 ± 4	7 ± 5	ns
Increase in systolic blood pressure at 60 min from baseline (mmHg)	7 ± 4	7 ± 4	ns
Diastolic blood pressure on admission = baseline (mmHg)	73 ± 38	76 ± 36	ns
Increase in diastolic blood pressure at 30 min from baseline (mmHg)	1 ± 2	1 ± 1	ns
Increase in diastolic blood pressure at 60 min from baseline (mmHg)	1 ± 2	1 ± 2	ns
Pulse rate on admission = baseline (bpm)	84 ± 5	86 ± 5	ns
Increase in pulse rate at 30 min from baseline (bpm)	2 ± 2	1 ± 3	ns
Increase in pulse rate at 60 min from baseline (bpm)	3 ± 2	2 ± 3	ns

ns, not significant; SD, standard deviation.

Source: Nirmala et al., 2009, Table 2.

Comment: There were no significant differences between the two treatment arms in the frequency of the reported adverse events. In addition, there were no notable differences between the two treatment arms in the change in systolic or diastolic blood pressure or pulse rate over the first 60 minutes after delivery. The incidence of hypertension (level not defined) was marginally higher in women in the Syntometrine arm than in the carbetocin, but the difference was not statistically significant.

8.1.2.3. Su et al; 2009

In Su et al (2009), the safety of carbetocin 100 µg IM (n = 185) and Syntometrine (5 IU oxytocin/0.5 mg ergometrine) (n = 185) were compared following vaginal delivery in women considered not to be at low-risk of PPH. Each participant was required to complete a standard questionnaire assessing adverse effects and graded the effect from very mild to very severe on a 5-point visual analogue scale. Assessment was performed in the delivery suite within 2 h after delivery to ensure that any complications relating to the delivery or medications had resolved prior to the women being transferred to the postnatal ward. The adverse effects reported by the women in both treatment arms are summarised below in Table 32.

Table 32: Su et al., 2009 Adverse effects in the carbetocin and Syntometrine treatment arms

	Carbetocin (*n* = 185)	Syntometrine (*n* = 185)	*P* value	RR (95% CI)
Nausea				
Yes	11 (5.9%)	46 (24.9%)	<0.001	4.2 (2.2–7.8)
Moderate to very severe	2 (1.1%)	25 (13.5%)	<0.001	12.5 (3.0–52.6)
Vomiting				
Yes	7 (3.8%)	30 (16.2%)	<0.001	4.3 (1.9–9.5)
Moderate to very severe	1 (0.5%)	18 (9.7%)	<0.001	17.8 (2.4–142.8)
Headache	15 (8.1%)	18 (9.7%)	0.58	
Retching	2 (1.1%)	14 (7.6%)	0.002	7.0 (1.6–30.3)
Flushing	7 (3.8%)	10 (5.4%)	0.46	
Tremor	11 (5.9%)	26 (14.1%)	0.01	2.4 (1.2–4.7)
Chest pain	6 (3.2%)	3 (1.6%)	0.34	
Dyspnoea	5 (2.7%)	6 (3.2%)	0.77	
Pruritus	16 (8.6%)	12 (6.5%)	0.43	
Sweating	5 (2.7%)	15 (8.1%)	0.02	3.0 (1.1–8.1)
Anxiety	9 (4.9%)	10 (5.4%)	0.82	
Dizzy	21 (11.4%)	28 (15.1%)	0.28	
Warmth	11 (5.9%)	14 (7.6%)	0.53	
Uterine pain	21 (11.4%)	37 (20.0%)	0.002	7.0 (1.6–30.3)

Source: Su et al., 2009, Table 3.

Comment: Overall, the data demonstrated that the adverse effect profile of carbetocin was superior to that of Syntometrine. Both nausea and vomiting were reported notably less frequently in the carbetocin arm than in the Syntometrine arm, as were tremor, sweating and uterine pain. Vital signs were stated to have been collected but no results were provided.

8.1.2.4. Askar et al., 2011

In Askar et al (2011), the safety of carbetocin 100 µg IM (n = 120) and Syntometrine (5 IU oxytocin/0.5 mg ergometrine) (n = 120) were compared following vaginal delivery in women considered not to be at increased risk of PPH. The occurrence of nausea, vomiting, flushing, headache, and abdominal pain were recorded by an interview conducted 2 h after delivery in the postnatal ward. Any other symptoms volunteered by the participating women or signs observed by the attending clinicians were also recorded in the first 24 h post-delivery. The adverse effects profile of both treatment arms are summarised below in Table 33.

Table 33: Askar et al., 2011 Adverse effects in the carbetocin and Syntometrine treatment arms

Variables	Carbetocin ($n = 120$)	Syntometrine ($n = 120$)	P value	Significance
Nausea	4 (3.33)	13 (10.38)	0.04 (<0.05)	S.
Vomiting	3 (2.5)	12 (10)	0.03 (<0.05)	S.
Headache	1 (0.83)	2 (1.66)	0.99 (>0.05)	N.S.
Flushing	1 (0.83)	4 (3.33)	0.36 (>0.05)	N.S.
Abdominal pain	1 (0.83)	2 (1.66)	0.99 (>0.05)	N.S.
Increase in diastolic blood pressure at 60 min from baseline (mmHg)*	2.6 ± 1.0	3.5 ± 1.6	<0.0001 (<0.01)	H.S.
Pulse rate immediately after delivery = baseline (bpm)*	83.7 ± 6.5	84.9 ± 5.8	0.13 (>0.05)	N.S.
Increase in pulse rate at 30 min from baseline (bpm)*	2.2 ± 1.0	2.3 ± 1.1	0.46 (>0.05)	N.S.
Increase in pulse rate at 60 min from baseline (bpm)*	2.8 ± 1.3	3.1 ± 1.4	0.08 (>0.05)	N.S.
Hypertension (blood pressure >140/90 mmHg)**				
Immediately after delivery	2 (1.66)	4 (3.33)	0.68 (>0.05)	N.S.
30 min after delivery	0 (0)	8 (6.66)***	0.006 (<0.01)	H.S.
60 min after delivery	0 (0)	7 (5.83)****	0.014 (<0.05)	S.

N.S. non-significant, *SD* standard deviation, *S.* significant, *H.S.* highly significant

*Data are presented as n (%)

**Data are presented as Mean ± SD

***$P < 0.01$ by Fisher's exact test

****$P < 0.05$ by Fisher's exact test

Source: Askar et al., 2011, Table 3.

Comment: Overall, the data demonstrated that the adverse effect profile of carbetocin was superior to that of Syntometrine. Nausea and vomiting both occurred notably more frequently in the carbetocin arm than in the Syntometrine arm, and the difference between the two treatment arms was statistically significant for both events. The incidence of headache, flushing and abdominal pain was low in both treatment arms, and did not significantly differ between the arms. There was a notable increase in the proportion of women with hypertension (> 140/90 mmHg) at both 30 and 60 minutes after delivery in the Syntometrine arm compared to the carbetocin arm, and the difference between the two treatment arms at both time-points was statistically significant. Of note, no women in the carbetocin arm had hypertension (> 140/90 mmHg) at either 30 or 60 minutes after delivery.

8.1.2.5. Samimi et al., 2013

In Samimi et al (2013), the safety of carbetocin 100 µg IMI (n = 100) and Syntometrine (5 IU oxytocin/0.2 mg ergometrine) IMI (n = 100) were compared following vaginal delivery in women considered not to be at increased risk of PPH. Blood pressure and pulse rate were measured immediately after administration and repeated at 30 and 60 minutes. The adverse effects in the two treatment arms are summarised below in Table 34.

Table 34: Samimi et al., 2013 Adverse effects in the two treatment arms

Characteristics	Carbetocin (n = 100)	Syntometrine (n = 100)	P-value
Nausea	2%	3%	0.65
Vomiting	1%	0%	0.5
Chill	0%	1%	0.5
Abdominal Pain	1%	0%	0.5
Hypotension (BP < 90 / 60 mmHg)	0%	2%	0.49
Tachycardia (Pulse ≥ 100 Beats per Minute) Immediately After Delivery	13%	5%	0.04

Source: Samimi et al., 2013, Table 3.

Comment: The dose of the ergometrine component of Syntometrine was lower than the dose of the ergometrine component of approved Syntometrine (that is, 0.2 versus 0.5 mg, respectively). The only significant difference in the adverse effects reported in the two treatment arms was a greater incidence of tachycardia (≥ 100 bpm) immediately after delivery in the carbetocin arm than in the Syntometrine arm. All other adverse effects were reported infrequently in both treatment arms and in a similar proportion of women in the two arms.

8.1.3. Evaluator's conclusion on clinical safety vaginal delivery

In the 2 studies comparing carbetocin to oxytocin (Boucher et al., 2004; Maged et al., 2016) the safety profile of carbetocin (n = 183) was similar to the safety profile of oxytocin (n = 177) following single dose administration of both study drugs for the active management of the third stage of labour in women delivering vaginally. In each of the 2 studies, the participating women had at least 1 risk-factor for PPH.

In the 4 studies comparing carbetocin (n = 515) to the approved dose of Syntometrine (n = 515), the safety profile of carbetocin was superior to the safety profile of Syntometrine following vaginal delivery in both the 3 studies excluding women at risk of PPH (Leung et al., 2006; Su et al., 2009; Askar et al., 2011) and the 1 study including women at high risk of PPH (Nirmala et al., 2009). The incidence of nausea and vomiting was notably lower in women treated with carbetocin compared to women treatment with Syntometrine, while the incidence of increased systolic and diastolic blood pressure and hypertension was notably higher in women treated with Syntometrine compared to women treated with carbetocin. In the 1 study comparing carbetocin to a lower than approved dose of Syntometrine in women with risk factors for PPH the safety profiles of the two treatment arms were comparable (Samimi et al., 2013).

Of note, tachycardia (> 100 bpm) was reported in 3 of the 7 studies in women who received carbetocin (Maged et al., 2015; Samimi et al., 2013; Leung et al, 2006), but was not reported in the other 4 studies.

8.2. Emergency caesarean section (SC)

8.2.1. Studies with evaluable safety data

The submission included 3 studies in women delivering via emergency CS performed under regional anaesthesia. Two of the studies include safety data (El Behery et al., 2016; Razali et al., 2016), while one of the studies included no safety data (Whigham et al, 2016). In total, there were safety data for 366 women treated with carbetocin 100 µg IV and 361 women treated with oxytocin 10-20 IU IV. In each of the 3 studies, women received a single dose regimen of either carbetocin or oxytocin after delivery of the infant or removal of the placenta.

8.2.2. El Behery et al., 2016

In El Behery et al (2016), the safety of carbetocin 100 µg IV (n = 90) and oxytocin 20 IU IV (n = 90) were compared in obese nulliparous women undergoing emergency CS under regional anaesthesia. The study drugs were administered after delivery of the infant had been completed and preferably before removal of the placenta. The adverse effects reported in this study are summarised below in Table 35.

Table 35: El Behery et al., 2016 Adverse effects in the carbetocin and oxytocin treatment arms

	Carbetocin group ($n = 90$)	Oxytocin group ($n = 90$)	p value
Headache	23 (57.5%)	30 (75%)	0.09 (NS)
Nausea and vomiting	3 (7.5%)	23 (57.5%)	<0.001*
Sweating	1 (2.5%)	27 (67.5%)	<0.001*
Palpitation	0 (0%)	0 (0%)	–
Fever	8 (20%)	0 (0%)	0.003*

NS, no statistically significant difference.
*Statistically significant difference.

Source: El Behery et al., 2016.

Comment: Headache was the most commonly reported adverse effect in both treatment arms, and was reported notably more frequently in the oxytocin arm than in the carbetocin arm. Other adverse effects reported notably more frequently in the oxytocin arm than in the carbetocin arm were nausea and vomiting, and sweating. Fever was reported notably more frequently in the carbetocin arm than in the oxytocin arm. Of note, palpitations were not reported in either treatment arm. The study report stated that blood pressure after injection was a secondary outcome, but no results for blood pressure changes could be identified in the report. In this study, 2.2% (n = 2) of women in the carbetocin arm needed additional uterotonic agents (oxytocin, methylergometrine, or misoprostol rectal suppositories) compared to 71.1% (n = 64) of women in the oxytocin arm. Therefore, it is possible that the notably increased incidence of adverse effects in the oxytocin arm compared to the carbetocin arm might be due, at least in part, to the higher use of additional uterotonic agents in women in the oxytocin arm.

8.2.3. Razali et al., 2016

In Razali et al (2016), the safety of carbetocin 100 µg IV (n = 276) and oxytocin IV (n = 271) were compared in women undergoing emergency CS under regional anaesthesia. In this study, the need for blood transfusion was reported as an adverse outcome and was reported in 2.2% (n = 6) of women in the carbetocin arm and 3.7% (n = 10) of women in the oxytocin arm, p = 0.30. Other adverse outcomes reported in this study in women in the carbetocin and oxytocin arms were additional surgical intervention in 0% (n = 1) and 0.4% (n = 1), respectively, and cardiac arrhythmias in 0.4% (n = 1) and 0% (n = 0), respectively. One woman in the oxytocin arm had a hysterectomy due to 'massive' postpartum blood loss of 2500 mL secondary to uterine atony. One woman who received carbetocin had a self-limited intraoperative episode of ventricular tachycardia which lasted for less than 1 minute. Hypotension was noted 30 minutes after carbetocin and IV ephedrine was given as part of her treatment to correct this condition. This participant had an uneventful post cesarean recovery. The results for the changes in blood pressure and pulse rate over the 60 minutes following administration of the study drugs are summarised below in Table 36.

In this study, 38.8% of women in the carbetocin arm needed additional uterotonic agents compared to 57.2% of women in the oxytocin arm. In those women requiring additional uterotonic agents, 98% of women in both treatment arms received treatment in the intraoperative period. Of the 107 women in the carbetocin arm needing additional uterotonic agents, 85% (n = 91) required a single oxytocin infusion (40-80 IU over 6 h) and 15% (n = 16) required additional third line uterotonic agents (carboprost IM or intramyometrial; gameprost rectal). Of the 155 women in the oxytocin arm needing additional uterotonic agents, 92%

required a single oxytocin infusion (40-80 IU over 6 h) and 8% required additional third line uterotonic agents (carboprost IM or intramyometrial; gameprost rectal).

Table 36: Razali et al., 2016 Blood pressure and pulse rate changes over the 60 minutes following administration of carbetocin and Syntometrine

		Time (min)					
		0	5	10	20	30	60
Carbetocin	Systolic BP	112.4 (15.1)	111.2 (15.7)	109.7 (14.8)	110.42 (14.9)	109.7 (16.3)	114.1 (17.0)
	Diastolic BP	66.0 (13.6)	63.23 (12.4)	62.4 (12.3)	61.9 (11.9)	62.7 (12.2)	65.8 (11.5)
	Pulse	92.1 (16.7)	92.8 (15.8)	92.4 (16.8)	91.6 (16.3)	90.2 (17.2)	85.3 (17.7)
Oxytocin	Systolic BP	116.0 (16.6)	113.9 (16.6)	113.1 (16.5)	111.3 (14.7)	112.3 (15.5)	113.7 (16.5)
	Diastolic BP	67.2 (13.4)	64.4 (12.3)	63.7 (12.4)	63.0 (12.0)	64.2 (11.4)	66.8 (12.4)
	Pulse	94.2 (17.1)	92.5 (18.5)	91.9 (18.1)	92.2 (16.8)	90.0 (16.3)	88.0 (40.30)

Data expressed as mean ± standard deviation.

Source: Razali et al., 2016, Table 3.

Comment: The study included limited information on adverse outcomes experienced by women in the two treatment arms. The available adverse outcome data showed no significant difference between the two treatment arms. The mean systolic blood pressure over the first 60 minutes following administration was marginally higher in the oxytocin arm than in the carbetocin arm, and the difference between the two arms was statistically significant based on repeated measurement ANOVA (p = 0.03). There were no significant differences between the two treatment arms as regards the diastolic blood pressure and pulse rate over the first 60 minutes following administration. The difference in the frequency of use of additional uterotonic agents in this study is unlikely to be a confounder in interpretation of the safety data.

8.2.4. Evaluator's conclusion on clinical safety emergency CS

The reported safety data in women undergoing CS in the submitted studies were limited. This is probably a reflection of the difficulty in separating the adverse effects of the single dose regimens of the study drugs from the risks of emergency CS under regional anaesthesia. In the 2 submitted studies with evaluable safety data, 336 women were exposed carbetocin 100 mg IV and 361 women were exposed to oxytocin 10-20 IU IV (El Behery et al, 2016; Razali et al, 2016).

In El Behery et al (2016), headache, nausea and vomiting, and sweating were reported more frequently in women in the oxytocin arm, fever was reported more commonly in the carbetocin arm and there were no reports of palpitations in either treatment arm. It is possible that comparison of the adverse effects in this study have been confounded by the markedly increased use of additional uterotonic agents in the oxytocin arm compared to the carbetocin arm. Systematic assessment of changes in blood pressure and heart rate following administration of the study drugs was not reported in this study.

In Razali et al (2016), adverse outcomes of blood transfusion, additional surgical interventions and cardiac arrhythmias were reported infrequently in the carbetocin and oxytocin arms, and the small numerical differences between the two arms are clinically insignificant. In this study, mean systolic blood pressure over the first 60 minutes was marginally higher in the oxytocin arm than in the carbetocin arm, and although the difference between the two arms was statistically significant it is considered to be clinically insignificant. There were no significant differences between the two treatment arms in mean diastolic blood pressure or heart rate over the first 60 minutes following administration of the study drugs. The difference between the

two treatment arms in the use of additional uterotonic agents is considered unlikely to have significantly confounded the interpretation of the safety data in this study.

8.3. High risk of PPH vaginal and CS delivery

8.3.1. Studies with evaluable safety data

The submission included 3 studies in women at high risk of PPH (Reyes, 2011; Reyes et al, 2011; Fahmy et al., 2016). In these 3 studies, a total of 101 women were randomised to treatment with carbetocin 100 µg IV and a total of 149 women were randomised to treatment with oxytocin 20 IU IV. Of the 250 women in the studies, 165 delivered vaginally and 85 delivered by CS. Of the 85 women delivered by CS, 60 underwent CS under general anaesthesia while 25 underwent CS for which the method of anaesthesia was not specified. The high risk factors for PPH were severe preeclampsia in 55 women delivering vaginally (n = 30) or by CS (n = 25) (Reyes et al, 2011), twin birth in 60 women delivered by CS under general anaesthesia (Fahmy et al, 2016), and grand multiparity (≥ 5 births) in 135 women delivering vaginally (Reyes, 2011).

8.3.2. Reyes et al., 2011

In *Reyes et al. 2011,* safety data were available for 55 women with severe preeclampsia delivering either vaginally (n = 30) or by CS (n = 25) and randomised to treatment with carbetocin 100 µg IV (n = 26) or oxytocin 20 IU IV (n = 29) administered immediately after delivery of the placenta. No information was provided on the method of anaesthesia used for CS. There was no significant difference between the two treatment arms in the incidence of women needing additional uterotonic agents (0%, carbetocin versus 3.4%, oxytocin). Symptoms were reported only if they were not present before study entry and if they appeared immediately after administration of the study drug. If a symptom persisted for more than 24 h, it was concluded that it was unlikely to be caused by the drug used, and the symptom was not considered an adverse effect. The adverse effects in the two treatment arms are summarised below in Table 37.

Table 37: Reyes et al, 2011 Adverse effects in the carbetocin and oxytocin arms

	Carbetocin n = 26 n (%)	Oxytocin n = 29 n (%)	*P*
Headaches	3 (11.5)	0 (0)	0.09
Palpitations	0 (0.0)	1 (3.4)	0.53
Fever	0 (0.0)	1 (3.4)	0.53
Nausea and vomiting	1 (3.8)	0 (0)	0.47
Others	1 (3.8)	0 (0)	0.47
Hot sensation	1 (3.8)	0 (0)	0.47
Facial flushing	1 (3.8)	0 (0)	0.47
Malaise	1 (3.8)	0 (0)	0.47

Source: Reyes et al., 2011, Table 6.

Haemodynamic status before and after admission of the study drugs is summarised below in Table 38.

Table 38: Reyes et al. 2011 Haemodynamic status before and after administration of the study drug in the carbetocin and oxytocin arms

	Carbetocin n = 26 mean (SD)	Oxytocin n = 29 mean (SD)	*P*
Mean arterial pressure, mmHg			
(a) 1 hour before administration	109.50 (9.93)	106.73 (10.37)	0.45
(b) 1 hour after administration	111.75 (7.84)	105.90 (9.17)	0.39
(c) 2 hours after administration	111.17 (4.44)	107.06 (8.65)	0.33
Heart rate, bpm			
(a) 1 hour before administration	73.66 (5.68)	79.57 (15.21)	0.64
(b) 1 hour after administration	81.25 (8.99)	78.50 (19.40)	0.66
(c) 2 hours after administration	84.75 (9.63)	87.83 (17.75)	0.74

Source: Reyes et al., 2011, Table 1.

Comment: There were only a small number of women in both treatment arms who experienced adverse effects. There was a numerical imbalance in the number of women experiencing adverse effects towards the carbetocin arm for most events. However, it is difficult to draw meaningful conclusions about this observation due to the small number of adverse effects reported in this study. The authors stated that '*many of the adverse effects observed in both groups..... can be attributed to the underlying pathology (preeclampsia)*'.

There were numerical differences between the two treatment arms in the change in mean arterial blood pressure and heart rate from before to after administration of the study drugs but the differences were not statistically significant and are of doubtful clinical significance. At 1 h after administration, the mean arterial blood pressure was 2.25 mmHg higher compared to 1 h before administration in the carbetocin arm and 0.83 mmHg lower 1 h after administration compared to 1 h before administration in the oxytocin arm. At 2 h after administration, the mean arterial blood pressure was 1.67 mmHg higher compared to 1 h before administration in the carbetocin arm and 0.33 mmHg higher 2 h after administration compared to 1 h before administration in the oxytocin arm.

8.3.3. Fahmy et al., 2016

In Fahmy et al., 2016, the effects of carbetocin 100 µg IV (n = 30) and oxytocin 20 IU IV (n = 30) were compared with respect to haemodynamics, uterine contraction and postpartum blood loss in women with twin births undergoing elective CS under general anaesthesia. The study drugs were administered immediately after the birth of the infants. In this study, 13.3% of women in the carbetocin arm and 50% of women in the oxytocin arm needed 1 additional dose of an uterotonic agent (methergine), $p < 0.001$, and 33.3% of women in the oxytocin arm needed 2 additional doses of methergine. Adverse effects were not assessed in this study. However, the study did assess the effects of the study drugs on mean arterial blood pressure (MABP) and mean heart rate (MHR) over the first 60 minutes following administration (see Table 39 and 40 below, respectively).

Table 39: Fahmy et al., 2016 Mean (SD) change in arterial blood pressure in the carbetocin and oxytocin arms over the first 60 minutes following administration of the study drugs

Time	Group C (n = 30)	Group O (n = 30)	p value
Baseline MABP	71 ± 6.3	72.1 ± 4.8	0.44
MABP 5 min	69.6 ± 3.6	70 ± 3.4	0.8
MABP 10 min	75.8 ± 2.7	74.3 ± 4	0.08
MABP 15 min	75.2 ± 2.8	71 ± 2.3	0.068
MABP 20 min	75 ± 2.6	70 ± 3.8*	0.003
MABP 25 min	74 ± 2.4	68.7 ± 3*	0.005
MABP 30 min	73.6 ± 2.4	68.8 ± 2.3*	0.004
MABP 35 min	73 ± 2.4	69.4 ± 5*	0.004
MABP 40 min	74 ± 1.8	69.3 ± 4.8*	< 0.001
MABP 50 min	75 ± 4.7	70.5 ± 3.7*	0.03
MABP 60 min	74.4 ± 5	70.6 ± 2.2	0.068

Group C: Those patients who received carbetocin.
Group O: Those patients who received oxytocin.
Data are presented as mean ± SD.
* $p < 0.05$ was considered statistically significant.

Source: Fahmy et al., 2016, Table 3.

Table 40: Fahmy et al., 2016 Mean (SD) change in heart rate in the carbetocin and oxytocin arms over the first 60 minutes following administration of the study drugs

Time (min)	Group C (n = 30)	Group O (n = 30)	p value
0 (baseline)	76.2 ± 5.16	75.9 ± 4.9	0.83
HR 5 min	84.3 ± 3.1	83.1 ± 2.4	0.07
HR 10 min	83.3 ± 3.09	82.8 ± 2.7	0.058
HR 15 min	84.5 ± 2.74	84.1 ± 3	0.6
HR 20 min	81 ± 3.5	84.5 ± 3	0.08
HR 25 min	78.9 ± 3.1	84.8 ± 3*	< 0.001
HR 30 min	76.3 ± 1.8	82.5 ± 3.4*	0.023
HR 35 min	75.6 ± 2.8	80 ± 3.4*	< 0.001
HR 40 min	74.2 ± 3.1	80 ± 2*	< 0.001
HR 50 min	76.8 ± 3.6	79 ± 3*	0.03
HR 60 min	78.7 ± 2.8	79.4 ± 2.4	0.29

Group C: Those patients who received carbetocin.
Group O: Those patients who received oxytocin.
Values are expressed as mean ± SD.
* $p < 0.05$ was considered statistically significant between the 2 groups.

Source: Fahmy et al., 2016, Table 2.

Comment: The differences between the two treatment arms in MHR after administration were not statistically significant through to 20 minutes, while the differences in MHR from 25 to 50 minutes were statistically significant at each time-point with the MHR being higher in the oxytocin arm than in the carbetocin arm. At 60 minutes after administration of the study drugs the MHR was not statistically significantly different between the two treatment arms. Over the first 60 minutes following administration of the study drugs there was an increase from baseline in MHR ranging from 0.1 to 8.3 bpm in the carbetocin arm with the maximum increase

occurring at 15 minutes, and an increase from baseline in MHR of 3.5 to 8.9 bpm in the oxytocin arm with the maximum increase occurring at 25 minutes. In neither treatment arm was the MHR greater than 85 bpm at any time-point through to 60 minutes after administration.

The differences between the two arms in MABP after administration were not statistically significant through to 15 minutes, while the differences in MABP from 20 to 50 minutes were statistically significant at each time-point with the MABP being lower in the oxytocin arm than in the carbetocin arm. At 60 minutes after administration of the study drugs the MABP was not statistically significantly different between the two treatment arms. Over the first 60 minutes following administration there was a change from baseline in MABP ranging from -1.4 mmHg to +4.8 mmHg in the carbetocin arm with the maximum increase occurring at 10 minutes, and a change from baseline in MABP ranging from -2.8 mmHg to +2.2 mmHg with the maximum decrease being at 25 minutes. There was no increase or decrease in MABP from baseline of ≥ 5 mmHg in either of the two treatment arms.

Overall, the differences in MHR and MABP between the two treatment arms are considered to be not clinically significant, given that the study population included healthy young women and excluded participants with a history of preeclampsia, hypertension, or cardiac disease.

8.3.4. Reyes, 2011

In Reyes, 2011 a total of 135 grand multiparous women (≥ 5 births) were treated with carbetocin 100 µg IVI (n = 45) or oxytocin (20 IU) IVI (n = 90) after expulsion of the placenta following vaginal delivery. The number of women needing additional uterotonic agents was small in both the carbetocin and oxytocin treatment arms (n = 0, 0% versus n = 3, 3.3%, respectively). The frequency of adverse events in the two treatment arms within the first 24 h postpartum were determined following review of the clinical notes and patient questioning. The results are summarised below in Table 41.

Table 41: Reye 2011 Adverse events (secondary outcomes) in the two treatment arms

Evaluated variable	Oxytocin (n=90)[a]	Carbetocin (n=45)	p*
Nausea	0 (0)	1 (2.2)	0.33
Vomiting	0 (0)	0 (0)	
Headache	1 (1.1)	2 (4.4)	0.25
Abdominal pain	1 (1.1)	0 (0)	0.66
Tremor	0 (0)	0 (0)	
Itching	0 (0)	0 (0)	
Dizziness	0 (0)	1 (2.2)	0.33
Chills	0 (0)	0 (0)	
Facial flushing	0 (0)	0 (0)	

[a] Values presented as numbers (%).
* p <0.05 (statistically significant).

Source: Reye 2011 Table 4.

Comment: Adverse events were reported infrequently in both treatment arms and there were no significant differences between the two arms in the incidence of women experiencing events. There were no data on changes in blood pressure or heart rate following administration of the study drugs.

8.3.5. Evaluator's comment on clinical safety in women with high-risk of PPH delivered vaginally or by CS

In the 3 studies comparing carbetocin 100 µg IV (n = 101) to oxytocin 20 IU IV (n = 149) in women at high risk of PPH the limited safety data showed no clinically significant differences between the two treatment arms with respect to adverse events and changes in blood pressure

or heart rate following administration of the study drugs (Reyes et al, 2011; Fahmy et al., 2016; Reyes, 2011). The 3 studies are considered to be of good quality.

Safety was assessed in 60 women (30, carbetocin; 30, oxytocin) with twins delivered by CS under general anaesthesia (Fahmy et al., 2016). No other data relating to women delivered by CS under general anaesthesia could be identified in the submitted dossier. In Reyes et al (2011), safety was assessed in 55 women (26, carbetocin; 29 oxytocin) with severe preeclampsia delivering vaginally (n = 30) or by CS (n = 25). In this study, the anaesthetic method used for CS was not stated. The authors commented that many of the adverse effects observed in this study were attributable to the underlying condition of preeclampsia. In Reyes 2011, safety was assessed in 135 grand multiparous (≥ 5 births) women delivering vaginally (45, carbetocin; 90, oxytocin).

8.4. Meta-analyses and systematic reviews

8.4.1. Jin et al., 2015

In Jin et al. 2015, pooled analyses of the safety data comparing carbetocin with either oxytocin or Syntometrine were provided from 12 randomised controlled clinical trials, published from 1998 to 2013, involving 2975 participants,.

8.4.1.1. Carbetocin versus oxytocin cesarean section (CS)

The pooled safety data from the studies comparing carbetocin to oxytocin in women undergoing CS are summarised below in Table 42.

Table 42: Jin et al., 2015 Adverse effects in the carbetocin and oxytocin arms following caesarean section

Outcome measures	Studies (no. of subjects)	Carbetocin *n/N*	Oxytocin *n/N*	Relative risk (95% CI)	Heterogeneity (*p*)
Adverse effects					
Abdominal pain/back pain	4 (1197)	167/598	166/599	1.01 (0.86–1.19)	0.94
Nausea	4 (1149)	107/574	115/575	0.93 (0.74–1.17)	0.91
Flushing	3 (1068)	93/533	81/535	1.15 (0.89–1.49)	0.93
Headache	5 (1253)	58/626	62/627	0.94 (0.67–1.31)	0.43
Feeling of warmth	2 (715)	66/357	56/358	1.18 (0.86–1.13)	0.56
Tremors	2 (1036)	39/517	53/519	0.74 (0.50–1.09)	0.64
Vomiting	3 (1093)	36/546	41/547	0.88 (0.57–1.35	0.37
Metallic taste	2 (936)	22/517	22/419	0.95 (0.54–1.70)	0.99
Sweating	2 (1036)	11/517	11/519	1.00 (0.44–2.29)	1.00
Dizziness	2 (538)	5/269	16/269	0.31 (0.12,0.83)	0.35
Short of breath/dyspnea	3 (537)	7/268	9/269	0.79 (0.31–2.01)	0.58
Tachycardia	2 (433)	2/216	1/217	1.50 (0.25–8.89)	0.22
Hypotension	1 (377)	4/188	2/189	2.01 (0.37–10.85)	NE
Pruritus	1 (57)	3/28	3/28	0.97 (0.21–4.39)	NE
Chills	1 (57)	1/28	2/28	0.48 (0.05–5.03)	NE
Blurred vision	1 (377)	0/188	1/189	0.34 (0.01–8.17)	NE

NE, not estimable.

Source: Jin et al., 2015, adapted from Table 2.

Comment: The only statistically significant difference between the two treatment groups was the lower risk of dizziness in the carbetocin group relative to the oxytocin group (RR = 0.31 (95% CI: 0.12, 0.83)); pooled data from 2 studies in 538 women).

8.4.1.2. Carbetocin versus oxytocin –vaginal delivery

The adverse effects in women following vaginal delivery were reported for 1 study (Boucher et al., 2004), which included a total of 160 women (83, carbetocin arm; 77, oxytocin arm). There were no significant differences between the two treatment arms in the risks of nausea (RR = 0.66), chills (RR = 1.06), headache (RR = 0.51), vomiting (RR = 0.07), abdominal pain (RR =10.21), dizziness (RR = 1.08), pruritus (RR = 0.10), or tremors (RR = 1.16).

8.4.1.3. Carbetocin versus Syntometrine vaginal delivery

The pooled safety data from the studies comparing carbetocin to oxytocin in women following vaginal delivery are summarised below in Table 43.

Table 43: Jin et al., 2015 Adverse effects in the carbetocin and Syntometrine arms following vaginal delivery

Outcome measures	Studies (no. of subjects)	Carbetocin *n/N*	Syntometrine *n/N*	Relative risk (95% CI)	Heterogeneity (*p*)
Adverse effects					
Nausea	4 (1030)	17/515	71/515	0.15 (0.24–0.40)	0.95
Vomiting	4 (1030)	11/515	54/515	0.21 (0.11–0.39)	0.89
Headache	4 (1030)	19/515	23/515	0.83 (0.46–1.48)	0.83
Flushing	4 (1030)	8/515	17/515	0.49 (0.22–1.09)	0.45
Short of breath/dyspnea	1 (370)	5/185	6/185	0.83 (0.26–2.68)	NE
Feeling of warmth	2 (490)	11/245	14/245	0.79 (0.37–1.69)	NE
Sweating	2 (490)	5/245	15/245	0.33 (0.12–0.90)	NE
Abdominal pain/back pain	3 (730)	8/365	9/365	0.89 (0.35–2.28)	0.24
Tremors	3 (790)	13/395	32/395	0.41 (0.22–0.76)	0.79
Dizziness	1 (370)	21/185	28/185	0.75 (0.44–1.27)	NE
Tachycardia	1 (300)	32/150	19/150	1.87 (1.01–3.47)	NE
Pruritus	1 (370)	16/185	12/185	1.33 (0.65–2.74)	NE
Retching	1 (370)	2/185	14/185	0.14 (0.03–0.62)	NE
Hypertension (immediately after delivery)	2 (540)	4/270	8/270	0.50 (0.15–1.64)	1.00
Hypertension (30 min after delivery)	2 (540)	0/270	16/270	0.06 (0.01,0.44)	1.00
Hypertension (60 min after delivery)	2 (540)	0/270	13/270	0.07 (0.01–0.54)	0.94

NE, not estimable.

Source: Jin et al., 2015, adapted from Table 3.

Three studies investigated changes in blood pressure and/or the incidence of hypertension at 30 and 60 minutes after administration of the study drugs in women who received carbetocin compared to women who received Syntometrine. Pooled data from the 2 studies showed that hypertension (defined as blood pressure 140/90 mmHg) occurred significantly less frequently in the carbetocin group relative to the Syntometrine group in women who delivered vaginally: at 30 minutes, RR = 0.06 (95% CI: 0.01, 0.44); I^2 = 0%; at 60 minutes, RR = 0.07 (95% CI: 0.01, 0.54); I^2 = 0%. No significant difference between the two groups as regards the increase in pulse rate at 30 minutes and 60 minutes after vaginal delivery was reported in 2 out of the 3 studies.

Comment: Following vaginal delivery, women in the carbetocin group were notably less likely to experience nausea, vomiting, retching, sweating, tremors and hypertension (30 and 60 minutes after delivery) than women in the Syntometrine group, and the difference between the two treatment groups was statistically significant for each of these adverse events. The incidence of tachycardia was statistically significantly greater in the carbetocin group than in the Syntometrine group. Overall, the adverse effect profile following vaginal delivery was notably superior in the carbetocin group compared to the Syntometrine group.

8.4.2. Su et al., 2012

In Su et al (2012), a meta-analysis was undertaken including 11 randomised, controlled trials (2635) comparing carbetocin to oxytocin, Syntometrine or placebo in women following CS or vaginal delivery. The safety results for this study were consistent with the safety results reported for Jin et al (2015).

8.5. Post marketing experience

The international birth data (IBD) of carbetocin is 24 June 1997 (Canada). The dossier included two Periodic Safety Update Reports (PSURs), one for the period 1 July 2013 to 30 June 2015

(13th PSUR) and one for the period 1 July 2015 to 30 June 2016 (14th PSUR). The post marketing information in the latest of the two PSURs has been reviewed below.

The 14th PSUR indicates that at 30 June 2016, Ferring carbetocin was approved in 80 countries. The estimated cumulative exposure to carbetocin in clinical trials sponsored by Ferring was 440 patients. The estimated post-marketing exposure in the reporting period to Ferring carbetocin was approximately 1.7 million patients, and the estimated cumulative post-marketing exposure to Ferring carbetocin from the IBD was approximately 8.5 million patients. The exposure data were based on a single 100 μg IV dose of Ferring carbetocin.

In the reporting period, 17 cases with 21 serious and 18 non-serious adverse drug reactions (ADRs) had been received, including one report with a fatal outcome. The fatal outcome was due to a cardiac arrest in a woman following administration of carbetocin to prevent atony and PPH after CS. The patient had a medical history of systemic lupus erythaematosis, pulmonary hypertension and heart failure (NYHA class III). The sponsor comments that serious cardiovascular disorders are a contraindication for the use of Ferring carbetocin and, therefore, the drug had been administered off-label in this patient. However, a causal relationship between cardiac arrest and Ferring carbetocin could not be ruled out because of the temporal relationship between the event and the administration of carbetocin.

There had been a total of 23 serious ADRs associated with Ferring carbetocin reported cumulatively from the IBD to 30 June 2016 in the clinical trials in 440 patients. Cumulative serious ADRs associated with Ferring carbetocin reported in ≥ 2 patients were postpartum haemorrhage (n = 7), and retained placenta or membrane (n = 4). No cardiac disorders had been reported and 1 vascular disorder had been reported (hot flush). Three psychiatric disorders had been reported (1 each for confusional state, disorientation, and psychotic disorder) and 1 nervous system disorder had been reported (dizziness). No maternal or neonatal deaths had been reported.

There had been a total of 340 spontaneous serious ADRs reported cumulatively from the IBD to 30 June 2016 in the post-marketing data, comprising 155 serious and 185 non-serious ADR reports. Spontaneous ADRs by preferred term with ≥ 5 reports were drug ineffective (n = 24), postpartum haemorrhage (n = 11), cardiac arrest (n = 6), tachycardia (n = 5), hypertension (n = 5), hypotension (n = 5), post-procedural haematoma (n = 5), and headache (n = 6). Spontaneous non-serious cumulative adverse drug reactions by preferred term with ≥ 5 reports were no adverse effect (n = 44), off-label use (n = 43), drug ineffective (n = 23), headache (n = 7), and nausea (n = 5).

Comment: No significant safety signals associated with carbetocin for the prevention of uterine atony and excessive blood loss have been identified in the post marketing data. The post marketing experience appears to be consistent with the safety data in the published clinical studies included in the dossier. However, reporting of safety data from published studies is not as comprehensive as reporting of safety data from full study reports. Therefore, comparison of post-marketing safety data and safety data from published studies should be undertaken with caution. There are no post-marketing data specifically addressing the safety of carbetocin in patients delivered by CS under general anaesthesia, which is a limitation of the post-marketing safety data. The sponsor is requested to comment on the 6 spontaneous reports of cardiac arrest reported in the cumulative data reported from the IBD of carbetocin to 30 June 2016 (see Questions, Section 12 of this CER).

9. First round benefit-risk assessment

9.1. First round assessment of benefits

9.1.1. General comments

9.1.1.1. Estimation of blood loss

The methods used to estimate blood loss differed across the studies. Therefore, cross-study comparisons of estimated blood loss should be interpreted with caution. The RANZCOG guidelines on the Management of Postpartum Haemorrhage (PPH) state that '(*a)ssessment of ongoing blood loss is an essential aspect of post-partum care. Visual estimation of blood loss is notoriously unreliable and often underestimates true blood loss. More accurate measures such as weighing drapes, pads and swabs can also be used. Clinical signs of shock or tachycardia should prompt a thorough assessment of the mother including an accurate appraisal of blood loss, both concealed and revealed*'.

Vaginal delivery

In Nirmala et al (2009) and Askar et al (2011) blood loss was estimated by the gravimetric method which started immediately after drug administration and continued for 1 or 2 h after delivery, respectively, in Maged et al (2016) blood loss was estimated the gravimetric method and pictorial charts, in Su et al (2009) blood loss in the third stage of labour was estimated by visual inspection by both the midwife and the obstetrician, in Boucher et al (2004) blood loss was estimated clinically from the time of drug administration to delivery, in Leung et al (2006) blood loss was estimated by visual inspection but no further information was provided, and in Samimi et al (2013) no information was provided on the method used to assess blood loss.

Emergency Caesarean Section

In El Behery et al (2016) blood loss was estimated by the surgeon in the usual was (visual estimation, number of used swabs, and amount of aspirated blood), in Razali et al (2016) blood loss was estimated by summation of aspirated losses, surgical field spillage, and uptake into surgical gauzes, in Whigham et al (2016) blood loss was estimated by the surgeon but no further information was provided.

Women at high-risk of postpartum haemorrhage

In Fahmy et al (2016), the amount of blood loss following CS under general anaesthesia was estimated by the number of blood stained swabs and the amount of aspirated blood and in Reyes et al (2011) and Reyes (2011) no information on the estimated volume of blood lost following delivery was collected.

9.1.1.2. Estimation of postpartum haemoglobin concentration

In those studies assessing changes in haemoglobin concentration following delivery, most assessed the postpartum haemoglobin concentration at 24 h after delivery. Cross-study comparisons of change in haemoglobin concentration should be interpreted cautiously due to differences in the study populations relating to estimated postpartum blood loss and other known risk factors (for example, maternal characteristics, antenatal history, pregnancy risks, new born characteristics, and method and duration of delivery).

9.1.2. Vaginal delivery

9.1.2.1. Carbetocin versus oxytocin

Individual studies

The submission included 2 studies in 360 women comparing carbetocin (n = 183) to oxytocin (n = 177) for the active management of the third stage of labour to prevent uterine atony and

excessive bleeding following vaginal delivery (Boucher et al., 2004; Maged et al., 2016). In Boucher et al (2004), women were required to have at least 1 risk-factor for PPH and in Maged et al (2016), women were required to have at least 2 risk-factors for PPH.

In Boucher et al (2004), carbetocin 100 µg IM (n = 83) was compared to oxytocin 10 IU IV administered over 2 h (n = 77) and in Maged et al (2016), carbetocin 100 µg IM (n = 100) was compared to oxytocin 5 IU IM (n = 100). The dose of carbetocin 100 µg IM in both studies is the proposed dose following vaginal delivery, while the oxytocin dose of 5 IU IM in Maged et al (2016) is an approved IM dose (5 or 10 IU) for the third stage of labour and the oxytocin dose of 10 IU IV in Boucher et al (2004) is greater than the approved IV dose (5 IU) for the third stage of labour.

The 2 studies are considered to show that the benefits of carbetocin for the prevention of uterine atony and excessive bleeding are comparable to those of oxytocin in women with risk-factors for PPH following vaginal delivery. The benefits of carbetocin compared to oxytocin for the efficacy outcome measures are summarised below.

Need for additional uterotonic agents

The need for additional uterotonic agents was assessed in both studies. The need for additional uterotonic agents was higher in women in the oxytocin arm compared to the carbetocin arm in both studies, with the difference being statistically significant 1 of the studies. The results are summarised below in Table 44.

Table 44: Need for additional uterotonic agents in the carbetocin vs oxytocin studies, vaginal delivery.

Study	Carbetocin *	Oxytocin **	Statistics
Boucher et al., 2004	14.5% (12/83)	15.6% (12/77)	p > 0.05
Maged et al., 2016	23% (23/100)	37% (37/100)	p = 0.031

*Carbetocin 100 µg IM in Boucher et al., 2004 and Maged et al., 2016. **Oxytocin 10 IU IV in Boucher et al., 2004; oxytocin 5 IU IM in Maged et al., 2016.

The need for additional uterotonic agents was notably higher in both treatment arms in Maged et al (2016) than in Boucher et al (2004). This might relate to women in Maged et al (2016) being at a greater risk of PPH compared to women in Boucher et al (2004). The carbetocin dose was the same in both studies (100 µg IM), while the oxytocin dose was lower in Maged et al (2016) (5 IU IM) than in Boucher et al (2004) (10 IU IV infusion over 2 h). The majority of women in both treatment arms in both studies did not require additional uterotonic agents.

Incidence of blood loss ≥ 500 mL and ≥ 1000 mL

The incidence of blood loss > 500 mL was assessed in both studies. In Maged et al (2016), the incidence of blood loss > 500 mL was 4-fold higher in the oxytocin arm than in the carbetocin arm, and the difference between the two arms was statistically significant. In Boucher et al 2004), the incidence of blood loss > 500 mL was similar in the two treatment arms, and the difference between the arms was not statistically significant. The incidence of blood loss > 1000 mL was assessed in Maged et al (2016) and blood loss > 1000 mL was reported in 1 woman in the oxytocin arm. The results are summarised below in Table 45.

Table 45: Blood loss > 500 mL and > 1000 mL in the carbetocin versus oxytocin studies vaginal delivery

Study	Carbetocin *	Oxytocin **	Statistics
> 500 mL (Boucher et al., 2004)	15.6% (10/64)	16.4% (11/67)	p > 0.05
> 500 mL (Maged et al., 2016)	4% (4/100)	16% (16/100)	p = 0.037
> 1000 mL (Maged et al., 2016)	0% (0/100)	1% (1/100)	p = 0.316

*Carbetocin 100 µg IM in Boucher et al., 2004 and Maged et al., 2016. ** Oxytocin 10 IU IV in Boucher et al., 2004; oxytocin 5 IU IM in Maged et al., 2016.

Mean blood loss

The mean blood loss was assessed both studies. In *Boucher et al (2004)*, there was no statistically significant difference between the two treatment arms in the mean amount of blood lost, while in *Maged et al (2016)* blood loss was statistically significantly higher in the oxytocin arm compared to the carbetocin arm by an estimated 41 mL. The results are summarised below in Table 46.

Table 46: Mean (SD) blood loss (mL) in the carbetocin versus oxytocin studies vaginal delivery

Study	Carbetocin *	Oxytocin **	Statistics
Boucher et al., 2004	413.3 (197.5) mL; n = 83	410.4 (194.1) mL; n = 77	p > 0.05
Maged et al., 2016	337.73 (118.77) mL; n = 100	378 (143.2) mL; n = 100	p = 0.03

*Carbetocin 100 µg IM in Boucher et al., 2004 and Maged et al., 2016. **Oxytocin 10 IU IV in Boucher et al., 2004; oxytocin 5 IU IM in Maged et al., 2016.

Reduction in haemoglobin

The reduction in haemoglobin concentration from pre- to post-delivery was assessed in both studies. In *Boucher et al (2004)*, the reduction in the haemoglobin concentration was not statistically significantly different between the two treatment arms, while in *Maged et al (2016)* the reduction in the haemoglobin concentration was statistically significantly greater in the oxytocin arm than in the carbetocin arm. The results are summarised below in Table 47.

Table 47: Mean (SD) reduction in haemoglobin concentration (g/dL) in the carbetocin versus oxytocin studies vaginal delivery

Study	Carbetocin *	Oxytocin **	Statistics
Boucher et al., 2004	n = 83	n = 77	

Study	Carbetocin *	Oxytocin **	Statistics
Hb Δ 24 h after delivery	-1.28 (1.08) g/dL	-1.59 (1.16) g/dL	p > 0.05
Hb ≥ 10% drop	53.7% (n = 44)	63.0% (n = 47)	p > 0.05
Hb ≥ 25% drop	7.3% (n = 6)	12.3% (n = 9)	p > 0.05
Maged et al., 2016	n = 100	n = 100	
Hb Δ 24 h after delivery	-0.55 (0.35) g/dL	-0.96 (0.62) g/dL	p < 0.001

*Carbetocin 100 µg IM in *Boucher et al., 2004* and *Maged et al., 2016*; carbetocin 100 µg IV in *Reyes, 2010*.
**Oxytocin 10 IU IV in *Boucher et al., 2004*; oxytocin 5 IU IM in *Maged et al., 2016*; oxytocin 20 IU IV in *Reyes, 2011*.Δ = Mean (SD) difference between pre- and post-delivery haemoglobin concentration.

Need for blood transfusion

The need for blood transfusion was assessed in Maged et al (2016). In this study, the need for blood transfusion was infrequent in both treatment arms. The results are summarised below in Table 48.

Table 48: Need for blood transfusion following carbetocin vs oxytocin, vaginal delivery

Study	Carbetocin *	Oxytocin **	Statistics
Maged et al., 2016	1% (1/100)	2% (2/100)	p = 1

*Carbetocin 100 µg IM in *Boucher et al., 2004* and *Maged et al., 2016*; carbetocin 100 µg IV in *Reyes, 2010*.
**Oxytocin 10 IU IV in *Boucher et al., 2004*; oxytocin 5 IU IM in *Maged et al., 2016*; oxytocin 20 IU IV in *Reyes, 2011*.

Uterine atony

In Boucher et al (2004), if uterine tone or the amount of bleeding was unsatisfactory after the administration of the study drug then additional uterotonic medication was given, uterine massage was performed, or both were undertaken. In this study, the incidence of women needing at least 1 uterine massage was statistically significantly lower in the carbetocin 100 µg IM arm than in the oxytocin 10 IU IV arm (43.8% (36/83) versus 62.3% (48/77); p < 0.2).

In Maged et al (2016), it was stated that the need for uterine massage and additional uterotonic agents was significantly lower in women in the carbetocin 100 µg IM arm compared to the oxytocin 5 IU IM arm, but the data supporting this statement was not provided in the report. No criteria for the use of additional uterotonic agents could be identified in Maged et al (2016).

9.1.3. Meta-analyses and systematic reviews

In both Su et al (2012) and Jin et al (2015), there were no pooled data assessing the efficacy outcome measures in women following vaginal delivery. Both studies evaluated the data from 1 study only (Boucher et al., 2004). The results for the efficacy outcomes relating to Boucher et al., 2004 reported in the two meta-analyses did not notably differ from those presented in the published report for this study.

9.1.3.1. Carbetocin versus Syntometrine

Individual studies

The submission included 5 studies comparing carbetocin (100 µg) IM to Syntometrine 1 mL IM for the active management of the third stage of labour in women delivering vaginally. In 4 of the 5 studies, Syntometrine 1 mL was the approved dose (5 IU oxytocin/0.5 ergometrine) (Leung et al., 2006; Nirmala et al., 2009; Su et al., 2009; Askar et al., 2011), while in 1 of the 5 studies Syntometrine 1 mL was lower than the approved dose (5IU oxytocin/0.2 mg ergometrine) (Samimi et al., 2013). The 5 studies included a total of 1230 women treated with either carbetocin (n = 615) or Syntometrine (n = 615).

The benefits of carbetocin 100 µg IM administered in the third stage of labour to women following vaginal delivery were comparable to the benefits of the approved dose of Syntometrine 1 mL IM with respect to the prevention of uterine atony and excessive bleeding (Leung et al., 2006; Nirmala et al., 2009; Su et al., 2009; Askar et al., 2011). The benefits of carbetocin 100 µg IM were significantly greater than the benefits of the lower than approved dose of Syntometrine 1 mL IM (Samimi et al., 2013). The results for the 4 studies comparing the benefits of carbetocin to the approved dose of Syntometrine are summarised below.

9.1.3.2. Need for additional uterotonic agents

There were no statistically significant or clinically meaningful differences between the two treatment arms in the 4 studies comparing carbetocin with the approved dose of Syntometrine. The results are summarised below in Table 49.

Table 49: Need for additional uterotonic agents in the carbetocin versus Syntometrine (approved dose) studies, vaginal delivery

Study	Carbetocin 100 µg IM	Syntometrine 1 mL IM *	Statistics
Su et al., 2009 (a)	13.5% (25/185)	16.8% (31/85)	p = 0.38
Askar et al., 2011 (b)	15.0% (18/120)	17.5% (21/120)	p > 0.05
Leung et al., 2006	8.7% (13/150)	6.7% (10/150)	RR = 1.3 (95% CI: 0.5, 3.1)
Nirmala et al, 2009	5% (3/60)	15% (9/60)	p > 0.05

*Syntometrine (5 IU oxytocin/0.5 mg ergometrine).

9.1.3.3. Incidence of blood loss ≥ 500 mL and ≥ 1000 mL

In the comparisons between carbetocin and the approved dose of Syntometrine, the incidence of women with blood loss ≥ 500 mL was small in both treatment arms in each of the 4 studies and the difference between the two arms was not statistically significant. In the comparisons between carbetocin and the approved dose of Syntometrine, the incidence of women with blood loss ≥ 1000 mL was negligible in both treatment arms in each of the 3 studies with data. The results are summarised below in Table 50.

Table 50: Incidence of blood loss ≥ 500 mL and ≥ 1000 mL in the carbetocin versus Syntometrine (approved dose) studies vaginal delivery

Study	Carbetocin 100 µg IM	Syntometrine 1 mL IM *	Statistics
Su et al., 2009	n = 185	n = 185	
PPH ≥ 500 mL	1.6% (3/185)	1.6% (3/185)	p = 1.0
Severe PPH ≥ 1000 mL	0.5% (1/185)	0% (0/185)	p = 1.0
Askar et al., 2011	n = 120	n = 120	
Primary PPH ≥ 500 mL	1.7% (2/120)	2.5% (3/120)	p = 0.99
Severe PPH ≥ 1000 mL	0% (0/120)	0.8% (1/120)	p = 0.85
Leung et al., 2006	n = 150	n = 150	
Primary PPH	4% (6/150)	2% (3/150)	RR = 2.0 (95% CI: 0.5, 8.3)
Blood loss ≥ 500 mL	4% (6/150)	1.3% (2/150)	RR = 3.0 (95% CI: 0.6, 15.5)
Blood loss ≥ 1000 mL	0% (0/150)	0.7% (1/150)	-
Nirmala et al., 2009	n = 60	n = 60	
≥ 500 mL	5% (3/60)	10% (6/60)	p > 0.05

*Syntometrine (5 IU oxytocin/0.5 mg ergometrine). .

In studies with relevant data, the incidence of the need for uterotonic agents was greater than the incidence of blood loss ≥ 500 mL (Su et al., 2009; Askar et al., 2011; Leung et al., 2009). In Su et al (2006) and Askar et al (2011) the standard criteria for the use of additional uterotonic agents were (a) suboptimal uterine tone and (b) brisk estimated blood loss exceeding 300 mL with or without hypotension (blood pressure <90/60) or tachycardia (pulse rate > 100 bpm). In Leung et al (2006) additional doses of Syntometrine IM or oxytocin IV were administered if uterine atomy was suspected or diagnosed. The available data suggest that additional uterotonic agents in both treatment arms in these 3 studies were likely to have been administered prior to blood loss reaching 500 mL.

9.1.3.4. Mean blood loss

In the comparisons between carbetocin and the approved dose of Syntometrine, the mean blood loss was lower in the carbetocin arm than in the Syntometrine arm in all 4 studies, and the difference between the two treatment arms was statistically significant in 2 of the 4 studies. The results are summarised below in Table 51.

Table 51: Mean (SD) blood loss (mL) in the carbetocin versus Syntometrine (approved dose) studies vaginal delivery

Study	Carbetocin 100 µg IM	Syntometrine 1 mL IM *	Statistics
Su et al., 2009	217.4 (99.2) mL; n = 185	223.1 (76.3) mL; n = 185	p = 0.29
Askar et al., 2011	224.6 (110.6) mL; n = 120	306.1 (95.65) mL; n = 120	p < 0.0001
Leung et al., 2006	232 (122) mL; n = 150	249 (175) mL; n = 150	Δ = -17 mL (95% CI: -51, 18)
Nirmala et al., 2009	244 (114); n = 60	343 (143); n = 60	p < 0.001

* Syntometrine (5 IU oxytocin/0.5 mg ergometrine); Δ = mean difference between the two treatment arms.

9.1.3.5. Reduction in haemoglobin from pre- to post-delivery

In the comparisons between carbetocin and the approved dose of Syntometrine, the reduction in haemoglobin concentration (pre- to post-delivery) was lower in the carbetocin arm than in the Syntometrine in 3 of the studies with data, with the difference between the two arms being statistically significant in 2 of the studies. However, the differences between the two treatment arms are considered to be clinically insignificant in each of the 3 studies. The results are summarised below in Table 52.

Table 52: Mean (SD) reduction in haemoglobin concentration (g/dL) in the carbetocin versus Syntometrine (approved dose) studies vaginal delivery

Study	Carbetocin 100 µg IM	Syntometrine 1 mL IM *	Statistics
Askar et al., 2011	n = 120	n = 120	
Hb Δ 24 h after delivery	-0.8 (0.2) g/dL	-1.1 (0.3) g/dL	p < 0.0001
Leung et al., 2006	n = 150	n = 150	
Hb Δ 48 h after delivery	-1.4 (1.1) g/dL	-1.5 (1.3) g/dL	Δ*: -0.1 g/dL (95% CI: -0.4, 0.2)
Hb > 10% drop	50.0% (75/150)	54.7% (82/150)	RR = 0.9 (95% CI: 0.8, 1.9)
Hb > 20% drop	16.0% (24/150)	22.0% (33/150)	RR = 0.7 (95% CI: 0.3, 1.2)
Nirmala et al., 2009	n = 60	n = 60	

Study	Carbetocin 100 µg IM	Syntometrine 1 mL IM *	Statistics
Hb Δ 24 h after delivery	-0.3 (0.2) g/dL	-0.4 (0.2) g/dL	p < 0.001

Syntometrine (5 IU oxytocin/0.5 mg ergometrine); Δ = Mean (SD) difference between pre- and post-delivery Hb levels; Δ = Mean difference between pre- and post-delivery Hb levels between the two treatment arms; RR = Relative risk

9.1.3.6. Need for blood transfusion

The incidence of women needing blood transfusions was negligible in both treatment arms in each of the 4 studies comparing carbetocin to the approved dose of Syntometrine. The results are summarised below in Table 53.

Table 53: Need for blood transfusion in women in the carbetocin vs Syntometrine (approved dose) studie, vaginal delivery

Study	Carbetocin 100 µg IM	Syntometrine 1 mL IM *	Statistics
Su et al., 2009	0.5% (1/185)	0% (0/185)	p = 1
Askar et al., 2011	0% (0/120)	0.8% (1/120)	p = 0.85
Leung et al., 2006	3.3% (5/150)	1.3% (2/150)	RR = 2.5 (95% CI: 0.5, 13.4)
Nirmala et al., 2009	0% (0/60)	1.7% (1/60)	-

* Syntometrine (5 IU oxytocin/0.5 mg ergometrine); RR = Relative risk.

9.1.3.7. Uterine atony

In Leung et al (2006) it was stated that an additional dose of Syntometrine was administered by IM injection or oxytocin administered by IV infusion if the attending midwife or physician suspected or diagnosed uterine atony. Similarly, in Su et al (2009) it was stated that additional uterotonic agents were started on making the diagnosis of uterine atony and in Askar et al (2011) it was stated that additional doses of uterotonic agents were administered if uterine atony was suspected or diagnosed. Therefore, in Leung e al (2006), Su et al (2006) and Askar et al (2011) the need for additional uterotonic agents can be considered to be a surrogate measure of the incidence of uterine atony following administration of the study drugs. In Nirmala et al (2009) an additional uterotonic agent was administered if uterine tone was not firm or the amount of bleeding was unsatisfactory after the administration of the study drug. There were no data in the 4 studies on the need for uterine massage following administration of the study drugs.

9.1.3.8. Meta-analyses and systematic reviews

In both Su et al (2012) and Jin et al (2015) there were no statistically significant differences between the carbetocin and Syntometrine (approved dose) groups in pooled data in the need for additional uterotonic agents, the incidence of PPH > 500 mL, the incidence of severe PPH > 1000 mL, and the need for blood transfusion. Pooled data provided in Su et al (2012) showed that the mean estimated blood loss was statistically significantly lower in the carbetocin group compared to the Syntometrine group (Δ = 48.4 mL (95% CI: -94.8, -2.9 mL)).

9.1.4. Emergency caesarean section (CS)

The submission included 3 studies comparing the efficacy of carbetocin 100 µg IV (n = 425) to oxytocin 5-20 IU IV (n = 424) for the prevention of uterine atony and excessive bleeding in women delivering via emergency CS under regional anaesthesia. In each of the 3 studies carbetocin was administered at a dose of 100 µg IV, which is proposed dose for emergency CS performed under regional anaesthesia. In 1 of the 3 studies, oxytocin was administered at a dose of 5 IU IV (Whigham et al., 2016), which is the approved dose for CS. In 2 of the 3 studies, oxytocin was administered at a higher dose than approved for CS (10 IU IV in Razali et al., 2016 and 20 IU IV in El Behery et al., 2016).

The results of these 3 studies adequately demonstrated that the benefits of carbetocin 100 µg IV in women undergoing emergency CS under regional anaesthesia are comparable to the benefits of oxytocin 5-20 IU IV for the prevention of uterine atony and excessive bleeding. The benefits of carbetocin and oxytocin with respect to the efficacy outcome measures observed in the 3 studies are summarised below.

9.1.4.1. Need for additional uterotonic agents

The incidence of women needing additional uterotonic agents was assessed in each of the 3 studies. In Razali et al (2016) and Whigham et al (2016) the need for additional uterotonic agents was the primary efficacy outcome measure and in El Behery et al (2016) it was a secondary efficacy outcome measure. The results are summarised below in Table 54.

Table 54: Need for additional uterotonic agents in the studies comparing carbetocin to oxytocin, emergency CS under regional anaesthesia

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
El Behery et al., 2016	2.2% (2/90)	71.1% (64/90)	p = 0.002
Razali et al., 2016	38.8% (107/276)	57.2% (155/271)	p < 0.001; RR = 0.68 (95%CI: 0.57, 0.81)
Whigham et al., 2016	22.0% (13/59)	13.2% (7/53)	p = 0.323

*Carbetocin 100 µg IV in each of the 3 treatment arms. **Oxytocin 5 IU in *Whigham et al., 2016*; oxytocin 20 IU IV in *El Behery et al., 2016*; and oxytocin 10 IU IV in *Razali et al., 2016.*

The benefit of carbetocin compared to oxytocin in reducing the need for additional uterotonic agents differed markedly across the 3 studies. In El Behery et al (2016), carbetocin demonstrated a markedly significantly greater benefit than oxytocin and in Razali et al (2016) carbetocin demonstrated a significantly greater benefit than oxytocin. In contrast, Whigham et al (2016) showed that the benefit was numerically better in women in the oxytocin arm compared to the carbetocin arm, but the difference between the two treatment arms was not statistically significant.

9.1.4.2. Incidence of blood loss ≥ 500 mL and ≥ 1000 mL

The incidence of blood loss ≥ 1000 mL was assessed in each of the 3 studies and the incidence of blood loss ≥ 500 mL was assessed in 1 of the 3 studies. In Behery et al (2016), the incidence of postpartum blood loss ≥ 1000 mL was significantly lower in women in the carbetocin arm than in the oxytocin arm, while in both Razali et al (2016) and Whigham et al (2016) the incidence was similar in the two treatment arms. No statistical analyses of the results reported in

Whigham et al (2016) were undertaken. In the 1 study assessing blood loss ≥ 500 mL there was no significant difference in the incidence between the two treatment arms (Razali et al., 2016). The results are summarised below in Table 55.

Table 55: Blood loss ≥ 500 mL and ≥ 1000 mL in the studies comparing carbetocin to oxytocin, emergency CS under regional anaesthesia

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
El Behery et al., 2016	n = 90	n = 90	
≥ 500 mL	-	-	-
≥ 1000 mL in 24 h	2.2% (n = 2)	13.3% (n = 12)	p = 0.03
Razali et al., 2016	n = 276	n = 271	
≥ 500 mL	39% (n = 107)	36% (n = 97)	p = 0.47; RR =1.1 (95% CI: 0.9, 1.3)
> 1000 mL	5.4% (n = 15)	3.7% (n = 10)	p = 0.33; RR = 1.5 (95% CI: 0.7, 3.2)
Whigham et al., 2016	n = 59	n = 53	
≥ 500 mL	-	-	-
≥ 1000 mL, in theatre	6 (10.2%)	5 (9.4%)	-
≥ 1000 mL in 24 h	7 (11.9%)	8 (15.1%)	

*Carbetocin 100 µg IV in each of the 3 treatment arms. **Oxytocin 5 IU in *Whigham et al., 2016;* oxytocin 20 IU IV in *El Behery et al., 2016*; and oxytocin 10 IU IV in *Razali et al., 2016*.

9.1.4.3. Mean blood loss

The estimated mean blood loss was assessed in each of the 3 studies. In Behery et al (2016), the estimated mean blood loss was significantly lower in women in the carbetocin arm than in the oxytocin arm, while in both Razali et al (2016) and Whigham et al (2016) the estimated mean blood loss was similar in the two treatment arms. The mean estimated blood loss in Whigham et al (2016) was 25 mL greater in women in the carbetocin arm compared to the oxytocin arm and no statistical analysis of the difference between the two arms was undertaken. However, in this study the blood loss difference between the two treatment arms is small and not clinically meaningful. The results are summarised below in Table 56.

Table 56: Estimated mean (SD) blood loss (mL) in the studies comparing carbetocin to oxytocin, emergency CS under regional anaesthesia

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
El Behery et al., 2016	689 (580) mL; n = 90	1027 (659) mL; n = 90	p = 0.002

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
Razali et al., 2016	458 (258) mL; n = 276	446 (281) mL; n = 271	p = 0.6
Whigham et al., 2016	586 mL (SD not provided); n = 59	561 mL (SD not provided); n = 53	-

*Carbetocin 100 µg IV in each of the 3 treatment arms. **Oxytocin 5 IU in *Whigham et al., 2016*; oxytocin 20 IU IV in *El Behery et al., 2016*; and oxytocin 10 IU IV in *Razali et al., 2016.*

9.1.4.4. Change in haemoglobin concentration

The mean change in haemoglobin concentration was assessed in each of the 3 studies. In both *Razali et al (2016*) and *Whigham et al (2016),* the haemoglobin concentration fell in both treatment arms and there were no significant differences between the two arms in either study. The results in *El Behery et al (2016)* were uninterpretable. The results are summarised below in Table 57.

Table 57: Mean haemoglobin change in the studies comparing carbetocin to oxytocin, emergency CS under regional anaesthesia

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
El Behery et al., 2016	Uninterpretable; n = 90	Uninterpretable; n = 90	-
Razali et al., 2016	- 1.2 g/dL; n = 276	- 1.3 g/dL; n = 271	p = 0.18
Whigham et al., 2016	- 1.76 g/dL n = 59	- 1.82 g/dL; n = 53	p = 0.784

*Carbetocin 100 µg IV in each of the 3 treatment arms. **Oxytocin 5 IU in *Whigham et al., 2016*; oxytocin 20 IU IV in *El Behery et al., 2016*; and oxytocin 10 IU IV in *Razali et al., 2016.*

9.1.4.5. Need for blood transfusion

The need for blood transfusion was assessed in each of the 3 studies. In *Behery et al (2016),* the incidence of women needing blood transfusion was significantly lower in the carbetocin arm than in the oxytocin arm, while in both *Razali et al (2016)* and *Whigham et al (2016)* the need for blood transfusion was low in both treatment arms and there was no clinically meaningful difference between the two arms in either study. The results are summarised below in Table 58.

Table 58: Need for blood transfusion in the studies comparing carbetocin to oxytocin, emergency CS under regional anaesthesia

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
El Behery et al., 2016	0% (0/90)	15.6 % (14/90)	p = 0.04
Razali et al.,	2.2% (6/276)	3.7% (10/271)	p = 0.30; RR = 0.6 (95% CI:

Study	Carbetocin 100 µg IV *	Oxytocin 5-20 IU IV **	Statistics
2016			0.22, 1.6)
Whigham et al., 2016	1.7% (1/59)	1.9% (1/53)	-

*Carbetocin 100 µg IV in each of the 3 treatment arms. **Oxytocin 5 IU in *Whigham et al., 2016*; oxytocin 20 IU IV in *El Behery et al., 2016*; and oxytocin 10 IU IV in *Razali et al., 2016.*

9.1.4.6. Uterine tone

There was no information in Whigham et al (2016) on the criteria used to trigger the use of additional uterotonic agents. However, in this study it was stated that there was no difference between the two treatment arms in the need for intra-operative uterine massage, but the data supporting this statement were not included in the study report. In Razali et al (2016) it was stated that the decision to use additional uterotonic agents was a subjective assessment made by the surgeon based on uterine tone and blood loss. In this study it was stated that there was a significant reduction in the need for additional uterotonic agents to maintain uterine tone in women the carbetocin arm compared to the oxytocin arm. No data on the need for uterine massage was identified in Razali et al (2016).

In El Behery et al (2016), uterine tone was evaluated by palpation and was described as soft or well contracted. Administration of additional uterotonic agents was at the discretion of the investigator if blood loss exceeded 500 mL, with or without hypotension, poor uterine tonicity was present or tachycardia occurred. There was a significant difference in uterine tone between the two treatment arms, with contractility being better in the carbetocin arm at 2 h, and 12 h after CS ($p < 0.05$). Uterine tone was soft in 2.2% (n = 2) of women in the carbetocin arm compared to 15.6% (n = 15) of women in the oxytocin arm, and firm in 97.8% (n = 22) of women in the carbetocin arm compared to 86.5% (n = 75) of women in the oxytocin arm. No data on the need for uterine massage was identified El Behery et al (2016).

9.1.5. Women at high-risk of postpartum haemorrhage delivering vaginally or via cesarean section (including under general anaesthesia)

The dossier included 3 studies stated by the sponsor to support the extension of indication of carbetocin to include women at high risk of PPH following vaginal delivery or CS (including under general anaesthesia). The 3 studies compared carbetocin 100 µg IV (proposed dose) to oxytocin 20 IU IV (that is, higher than the approved dose of 5 IU IV). The high risk-factors and methods of delivery in the 3 studies were twins delivered via CS under general anaesthesia (Fahmy et al, 2016), grand multiparity (≥ 5 births) following vaginal delivery (Reyes, 2011), and severe preeclampsia following vaginal delivery or CS (method of anaesthesia not stated) (Reyes et al., 2016).

The studies included a total of 101 women treated with carbetocin 100 µg IV and a total of 149 treated with oxytocin 20 IU IV. Overall, the data are considered to support the benefits of carbetocin for the prevention of uterine atony and excessive blood loss in women at high risk of PPH delivered either vaginally or via CS (including under general anaesthesia). The benefits of carbetocin 100 µg IV were at least comparable to those of oxytocin 20 IU IV with respect to reduction in need for additional uterotonic agents, mean blood loss, reduction in haemoglobin concentration and need for blood transfusion. The need for additional uterotonic agents and the need for blood transfusion were assessed in each of the 3 studies. However, there were no data in the 3 studies assessing postpartum haemorrhage ≥ 500 mL or ≥ 1000 mL, and only 1 of the 3 studies assessed mean estimated blood loss (Fahmy et al., 2016) and reduction in mean haemoglobin concentration (Reyes et al., 2016).

9.1.5.1. Need for additional uterotonic agents

The need for additional uterotonic agents was assessed in each of the 3 studies. The incidence was significantly greater in women in the oxytocin arm than in the carbetocin arm in Fahmy et al (2016), but did not significantly differ between the two treatment arms in Reyes (2011) and Reyes et al (2011). The results are summarised below in Table 59.

Table 59: Need for additional uterotonic agents in studies comparing carbetocin to oxytocin, women at high risk of PPH delivering either vaginally or by CS (including under general anaesthesia)

Study	Carbetocin 100 µg IV	Oxytocin 20 IU IV	Statistics
Fahmy et al., 2016	13.3% (4/30)	50.0% (15/30), one dose	p < 0.001
	-	33.3% (10/30), two doses	-
Reyes et al., 2011	0% (0/26)	3.4% (1/29)	p = 0.50
Reyes, 2011	0% (0/45)	3.3% (3/90)	p = 0.29

The trigger for the use of additional uterotonic agents was different across the 3 studies, which might account for the notable difference in the incidence of the need for additional uterotonic agents in Fahmy et al (2016) compared to both Reyes (2011) and Reyes et al (2011). In Fahmy et al (2016), if the uterine contraction score was less than 3 (that is, score 2 (sufficient), score 1 (poor) or score 0 (atony)) at 5 minutes after administration of the study drug then the isoflurane concentration was reduced from 1% to 0.5%, and if uterine contraction was still unsatisfactory then additional uterotonic agents were administered (that is, methergine 0.4 mg route not stated). In Reyes et al (2011), the primary outcome was the development of postpartum haemorrhage requiring the use of additional uterotonic agents (oxytocin or prostaglandins), but the volume of blood loss needed to trigger treatment was not specified. In Reyes (2011), additional uterotonic agents (misoprostol PR) were administered in the event of suspected or clinically 'evidenced' uterine atony.

9.1.5.2. Mean blood loss

Mean blood lost after delivery was estimated in only 1 of the 3 studies (Fahmy et al, 2016). In this study, mean blood loss in the carbetocin arm was significantly lower than in the oxytocin arm (see Table 60, below).

Table60: Mean (SD) blood loss (mL) in the carbetocin versus oxytocin studies

Study	Carbetocin 100 µg IV	Oxytocin 20 IU IV	Statistics
Fahmy et al., 2016	437 (45) mL, n = 30	721 (50) mL, n = 30	p < 0.001

9.1.5.3. Reduction in haemoglobin concentration

The change in mean haemoglobin concentration from admission to postpartum was assessed in only 1 of the 3 studies (Reyes et al., 2011). In this study, the reduction was numerically greater in the oxytocin arm than in the carbetocin, but the difference between the two arms was not statistically significant and is considered to be not clinically meaningful. The results are summarised below in Table 61.

Table 61: Mean (SD) reduction in haemoglobin concentration (g/dL) in the carbetocin versus oxytocin studies

Study	Carbetocin 100 µg IV	Oxytocin 20 IU IV	Statistics
Reyes et al., 2011	1.24 (0.87) g/dL, n = 26	1.41 (1.12) g/dL, n = 29	0.81

9.1.5.4. Need for blood transfusion

The need for blood transfusion was assessed in each of the 3 studies. In Fahmy et al (2016), the need for blood transfusion was higher in women in the oxytocin arm compared to the carbetocin arm, and although the difference was statistically significant only a small number of women in the two treatment arms required a blood transfusion. There were no statistically significant differences between the two treatment arms in Reyes et al (2011) and Reyes (2011). Overall, the total number of women needing blood transfusions in the 3 studies was small. The results are summarised below in Table 62.

Table 62: Need for additional uterotonic agents in the carbetocin versus oxytocin studies

Study	Carbetocin 100 µg IV	Oxytocin 20 IU IV	Statistics
Fahmy et al., 2016	3.3% (1/30)	13.3% (4/30)	p < 0.001
Reyes et al., 2011	0% (0/26)	10.3% (3/29)	p = 0.13
Reyes, 2011	2.2% (1/45)	0% (0/90)	p = 0.33

Uterine atony

In Fahmy et al (2016), additional uterotonic agents were administered if poor uterine tone did not respond to a reduction in the concentration of isoflurane. In this study, uterine tone at 2 minutes and 2 h after injection of the study drug was statistically significantly better in the carbetocin arm than in the oxytocin arm. In Reyes et al (2011), cases of uterine atony (determined by physical examination and continuous postpartum bleeding) were considered a therapeutic failure, and additional uterotonic agents were used at the discretion of the attending physician. In this study, uterine massage was used significantly less frequently in the carbetocin arm than in the oxytocin arm. In Reyes (2011), the use of additional uterotonic agents were permitted in the event of suspected or clinically evident uterine atony

9.1.6. Meta-analyses and systematic reviews in women undergoing caesarean section carbetocin versus oxytocin

In Su et al (2012), pooled data from 4 studies in women undergoing CS demonstrated a statistically significant reduction in the need for additional uterotonic agents of 36% in the carbetocin group relative to the oxytocin group (RR = 0.64 (95% CI: 0.51, 0.81)), and in pooled data from 2 studies there was a statistically significant reduction in the need for uterine massage of 46% in the carbetocin group relative to the oxytocin group (RR = 0.54 (95% CI: 0.31, 0.96)). However, pooled data from 4 studies showed that the risk of PPH (> 500 mL or as defined by the investigators) was not statistically significantly different between the two treatment groups (RR = 0.66 (95% CI: 0.42, 1.06)), and pooled data from 2 studies showed that the risk of severe PPH was not statistically significantly different between the two treatment groups (RR = 0.91 (95% CI: 0.39. 2.15)).

The results for the need for additional uterotonic agents from 5 pooled studies in Jin et al (2016) (RR = 0.68 (95% CI: 0.55, 0.84)) was consistent with the result from 4 pooled studies in

Su et al (2012). In Jin et al 2015, the analysis of the need for additional uterotonic agents included the same 4 studies as included in the analysis in Su et al (2012) (that is, Attilakos et al., 2010; Borruto et al., 2009; Boucher et al., 1998; Dansereau et al., 1999), and 1 additional study (Elgafor El Sharkwy; 2013) which compared carbetocin to sublingual misoprostol plus oxytocin in women undergoing CS.

In the 4 studies included in both meta-analyses, CS was performed under regional anaesthesia in 3 of the studies (Attilakos et al., 2010; Boucher et al., 1998; Dansereau et al., 1999), and the method of anaesthesia was not stated in 1 study (Borruto et al., 2009). No information on the method of anaesthesia used for CS in the additional study included in Jin et al (2016) could be identified in the dossier (Elgafor El Sharkwy; 2013).

9.2. First round assessment of risks

9.2.1. Vaginal delivery

9.2.1.1. Carbetocin versus oxytocin

The submission included 2 studies comparing the safety of carbetocin 100 µg IM to oxytocin 5 IU IM or 10 IU IV following vaginal delivery in women with risk-factors for PPH (Boucher et al., 2004; Maged et al., 2016). The studies included a total of 360 women, including 183 randomised to carbetocin and 177 randomised to oxytocin.

The frequency of additional uterotonic agents administered to women in the 2 studies was similar in the two treatment arms. Therefore, it is reasonable to assume that the differences in the adverse event profiles observed between the two treatment arms primarily reflect differences between carbetocin and oxytocin administered in the third stage of labour following vaginal delivery.

Overall, the risk profile of carbetocin is considered to be comparable to that of oxytocin following vaginal delivery in women with risk-factors for PPH (that is, at least 1 risk-factor in Boucher et al., 2004 and at least 2-risk factors in Maged et al., 2016).

Adverse events

In Boucher et al (2004), carbetocin 100 µg was administered IM (n = 83) and oxytocin 10 IU (n = 77) was administered IV as an infusion over 2 h to women with at least 1 risk-factor for PPH. The incidence of women reporting at least one adverse event was similar in the two treatment arms (51.8%, carbetocin versus 54.5%, oxytocin). In general, there were no marked differences between the two treatment arms in the incidence of adverse events reported in ≥ 5% of women in either arm (that is, headache, chills, abdominal pain, dizziness, tremor, vasodilatation, leukocytosis, nausea, vomiting, and pruritus). Adverse events reported in ≥ 5% of women in either treatment arm and in ≥ 5% more women in the oxytocin arm than in the carbetocin arm were headache (14.3% versus 7.2%) and pruritus (5.2% versus 0%). Adverse events reported in ≥ 5% of women in either treatment arm and in ≥ 5% more women in the carbetocin arm than in the oxytocin arm were vomiting (7.8% versus 0%) and abdominal pain (6.0% versus 0%). The frequency of administration site reactions in the carbetocin IM arm and the oxytocin IV infusion arm was comparable (1.2% versus 2.6%, respectively).

In Maged et al (2016), carbetocin 100 µg was administered IM (n = 100) and oxytocin 5 IU (n = 100) was administered IM to women with at least 2 risk-factors for PPH. Adverse events reported in ≥ 5% of women in either of the two treatment arms (carbetocin versus oxytocin) were anaemia (29% versus 27%), tachycardia > 100 bpm (10% versus 2%), and headache (5% versus 2%). Adverse events reported in < 5% of women in both treatment arms and with no significant difference between the two arms were nausea, vomiting, flushing, dizziness, shivering, metallic taste, dyspnoea, palpitations and itching.

Vital signs

In Boucher et al (2004), vital signs were monitored at regular intervals over the first 24 h after delivery. The were no notable differences between the two treatment arms following injection of the study drugs in changes in mean systolic or diastolic blood pressure, mean heart rate or mean respiratory rate.

In Maged et al (2016), both systolic and diastolic blood pressure measured immediately after delivery and at 30 and 60 minutes after delivery were significantly higher in the oxytocin arm than in the carbetocin arm, with the mean difference in systolic blood pressure between the two arms ranging from 6 to 7 mmHg and the mean difference in diastolic blood pressure ranging from 2 to 6 mmHg. Tachycardia (> 100 bpm) was reported significantly more frequently in the carbetocin arm than in the oxytocin arm (10% versus 2%, respectively; p = 0.017).

9.2.1.2. Carbetocin versus Syntometrine

The submission included 5 studies comparing the safety of carbetocin (100 μg) IM to Syntometrine (5 IU oxytocin/0.5 ergometrine (4 studies) or 5 IU of oxytocin/0.2 mg ergometrine (1 study)) following vaginal delivery. The studies included a total of 1230 women treated with either carbetocin (n = 615) or Syntometrine (n = 615).

The frequency of additional uterotonic agents administered to women in 4 of the 5 studies was similar in the two treatment arms. Therefore, it is reasonable to assume that the differences in the adverse event profiles observed between the two treatment arms in these studies primarily reflect differences between carbetocin and Syntometrine administered in the third stage of labour following vaginal delivery.

Adverse Events

Based on the totality of the available safety data from the 5 studies the adverse event profile of carbetocin is considered to be superior to that of Syntometrine, with the most notable difference between the two drugs being the higher incidence of nausea and vomiting in women treated with Syntometrine compared to women treated with carbetocin.

In Leung et al (2006), adverse events reported in ≥ 5% of women in either of the two treatment arms (carbetocin (n = 150) versus Syntometrine (n = 150), respectively) were nausea (1.3% versus 7.3%), vomiting (0.7% versus 6.7%), and tachycardia > 100 bpm (21.3% versus 12.7%). The duration of the tachycardia observed in both treatment arms was not reported. Adverse events reported in < 5% of women in both of the two treatment arms were facial flushing, headache, shivering, and pain over the injection site.

In Nirmala et al (2009), the only adverse event reported in ≥ 5% of women in either treatment arm was abdominal pain (2% (1/60) carbetocin versus 5% (3/60) Syntometrine). Adverse events reported in at least 1 woman in either of the two treatment arms and with an incidence of < 5% of women in both arms were nausea, vomiting, back pain, and headache.

In Su et al (2009), adverse events reported in ≥ 5% of women in either of the two treatment arms (carbetocin (n = 185) versus Syntometrine (n = 185), respectively) were nausea (5.9% versus 24.9%), vomiting (3.8% versus 16.2%), headache (8.1% versus 9.7%), retching (1.1% versus 7.6%), flushing (3.8% versus 5.4%), tremor (5.9% versus 14.1%), pruritus (8.6% versus 6.5%), sweating (2.7% versus 8.1), anxiety (4.9% versus 5.4%), dizzy (11.4% versus 15.1%), warmth (5.9% versus 7.6%) and uterine pain (11.4% versus 20.0%). Women in the Syntometrine arm relative to the carbetocin arm had a 4-fold increased risk of nausea (RR=4.2 (95% CI: 2.2, 7.8)), a 4-fold increased risk of vomiting (RR = 4.3 (95% CI: 1.9, 9.5)), and a 7-fold increased risk of retching (RR = 7.0 (95% CI: 1.6, 30.3)).

In Askar et al (2011), adverse events reported in ≥ 5% of women in either of the two treatment arms (carbetocin (n = 120) versus Syntometrine (n = 120), respectively) were nausea (3.3% versus 10.4%) and vomiting (2.5% versus 10.0%). The results showed notably that both nausea

and vomiting occurred more frequently in women in the Syntometrine arm than in the carbetocin arm. Adverse events reported in at least 1 woman in either treatment arm and in < 5% of women in both arms were headache, flushing, and abdominal pain.

In Samimi et al (2013) adverse events reported in at least 1 woman in either treatment arm and in < 5% of women in both arms were nausea, vomiting, chill and abdominal pain. There were no significant adverse events in this study in either of the two treatment arms.

Vital signs

In 3 of the 5 studies, blood pressure (systolic and diastolic) was measured immediately following delivery and then at 30 and 60 minutes after delivery (Leung et al., 2006; Nirmala et al., 2009; Samimi et al, 2013), in 1 of the 5 studies blood pressure was measured every 30 minutes after delivery but reporting was limited (Askar et al., 2013), and in 1 of the 5 studies changes in blood pressure were not reported (Su et al., 2009).

In 3 of the 5 studies, the incidence of hypertension (BP > 140/90) was reported (Leung et al., 2006; Samimi et al, 2013; Askar et al., 2013), in 1 of the 5 studies hypertension was reported but the cut-off level was not stated (Nirmala et al, 2009), and in 1 of the 5 studies the incidence of hypertension was not reported (Su et al., 2009).

The totality of the submitted data indicate that the changes in systolic and diastolic blood pressure immediately after delivery and at 30 and 60 minutes after delivery are greater in the Syntometrine arm than in the carbetocin arm, and the incidence of hypertension is higher following Syntometrine compared to carbetocin. There were data from 2 studies showing that the incidence of tachycardia (> 100 bpm) in the first 60 minutes following delivery was greater in women treated with carbetocin than in women treated with Syntometrine (Leung et al., 2006; Samimi et al., 2013). However, data from 2 studies showed no differences in heart rate between the two treatment arms immediately after delivery and at 30 and 60 minutes after delivery (Nirmala et al., 2009; Askar et al., 2011).

In Leung et al (2006), the mean systolic blood pressure immediately after delivery and at 30 and 60 minutes after delivery was higher in the Syntometrine arm than in the carbetocin arm at each time-point, with the mean increases being 3.0, 5.2, and 3.8 mmHg, respectively. The mean diastolic blood pressure immediately after delivery and at 30 and 60 minutes after delivery was also higher in the Syntometrine arm than in the carbetocin arm at each time-point, with the mean increases being 3.8, 3.6, and 3.2 mmHg, respectively. The incidence of hypertension (BP > 140/90) was greater in the Syntometrine arm than in the carbetocin arm immediately after delivery (2.7%, n = 4 versus 1.3%, n = 2; p > 0.5), at 30 minutes after delivery (5.3%, n = 8 versus 0%; p < 0.01), and at 60 minutes after delivery (4.0%, n = 6 versus 0%; p < 0.5). The incidence of tachycardia (> 100 bpm) within 60 minutes post-delivery was notably higher in women in the carbetocin arm than in the Syntometrine arm (21.3% versus 12.7%; RR = 1.7 (95% CI: 1.0, 3.6)).

In Nirmala et al (2009), there were no significant differences between the two treatment arms in mean systolic blood pressure, mean diastolic blood, or mean pulse rate immediately after delivery and at both 30 and 60 minutes after delivery. There were no significant differences in the number of women with hypertension between the two treatment arms (7 (12%), carbetocin versus 9 (15%), Syntometrine), but the cutoff levels for hypertension were not provided.

In Askar et al (2011), the authors stated that there was a highly significant difference between the two groups as regards the increase in systolic and diastolic blood pressure at 30 and 60 minutes after delivery, with the increase being greater in the Syntometrine arm (p < 0.01). However, only the numerical results for increases in diastolic blood pressure at 60 minutes after delivery were presented in the study report (2.6 mmHg, carbetocin versus 3.5 mmHg, Syntometrine; p < 0.01), with the numerical results for increases in diastolic blood pressure at 60 minutes after delivery not being provided. The incidence of hypertension (BP > 140/90) was greater in the Syntometrine arm than in the carbetocin arm immediately after delivery (3.3%, n

= 4 versus 1.7%, n = 2; p > 0.05), at 30 minutes after delivery (6.7%, n = 9 versus 0%; p < 0.01), and at 60 minutes after delivery (5.8%, n = 7 versus 0%; p < 0.5). No significant differences in the pulse rate between the two treatment arms were reported immediately after delivery or at 30 and 60 minutes after delivery.

In Samimi et al (2013), there were clinically significant differences in mean systolic blood pressure, but not in mean diastolic blood pressure, between the two treatment arms immediately after delivery and at 30 and 60 minutes after delivery. At each of the three time-points the mean systolic blood pressure was 2 to 8 mmHg higher in the Syntometrine arm than in the carbetocin arm, with the difference being most marked immediately after delivery. None of the women in this study had hypertension (blood pressure > 140/90) at 0, 30, and 60 minutes after administration of the study drugs. Tachycardia (pulse rate ≥ 100 bpm) immediately after delivery was reported more frequently in the carbetocin arm than in the Syntometrine arm (13% versus 5%, respectively; p = 0.04).

9.2.2. Emergency CS under regional anaesthesia

The assessment of the risks of carbetocin in women undergoing emergency CS under regional anaesthesia is based on limited safety data from 2 studies comparing carbetocin 100 µg IV (n = 366) to oxytocin 10-20 IU IV (n = 361) (El Behery et al., 2016; Razali et al., 2016). There was one other study assessing the efficacy of carbetocin 100 µg IV compared to oxytocin 5 IU IV in women undergoing emergency CS under regional anaesthesia, but this study did not include safety data (Whigham et al., 2016). The limited safety data in the women undergoing CS under regional anaesthesia might reflect the difficult in separating adverse effects of the study drug from adverse effects associated with the surgical procedure.

In El Behery et al (2016), carbetocin 100 µg IV (n = 90) was compared to oxytocin 20 IU IV (n = 90) in obese nulliparous women undergoing emergency CS under regional anaesthesia. In this study, the study drugs were administered after the delivery of the infant and preferably before removal of the placenta. Headache was the most commonly reported adverse effect in both treatment arms, and was reported notably more frequently in the oxytocin arm than in the carbetocin arm (75% versus 57.5%, respectively). Other adverse effects reported notably more frequently in the oxytocin arm than in the carbetocin arm were nausea and vomiting (57.5% versus 7.5%), and sweating (67.5% versus 2.5%). Fever was reported notably more frequently in the carbetocin arm than in the oxytocin arm (20% versus 0%). Of note, palpitations were not reported in either treatment arm. The study report stated that blood pressure after injection was a secondary outcome, but no results for blood pressure changes could be identified in the report. It is possible that the markedly higher use additional uterotonic agents in the oxytocin arm compared to the carbetocin arm (71.7%, n = 64 versus 2.2%, n = 2) might have contributed to the notably higher incidence of some adverse effects in the oxytocin arm compared to the carbetocin arm (that is, headache, nausea and vomiting, and sweating).

In Razali et al (2016), carbetocin 100 mg IV (n = 276) was compared to oxytocin IV (n = 271), with the drugs being administered after delivery of the infant. Three events were referred to as adverse outcomes and each of these events occurred in a small number of women in both treatment arms. The adverse outcomes were (carbetocin versus oxytocin), need for blood transfusion (2.2% versus 3.7%), additional surgical intervention (0% versus 0.4%) and cardiac arrhythmias (0.4% versus 0%). Blood pressure and pulse rate were measured at regular intervals over the first 60 minutes following administration of the study drug. The results showed a small but statistically significant higher increase in systolic blood pressure in the oxytocin arm than in the carbetocin arm, but no significant differences between the two treatment arms in diastolic blood pressure or pulse rate. The incidence of women needing additional uterotonic agents was significantly greater in the oxytocin arm than in the carbetocin arm (57.2% versus 38.8%), but the difference between two treatment arms was not reflected in differences in the adverse outcome results.

Overall, the limited safety data from El Behery et al (2016) and Razali et al (2016) suggest that the risks of carbetocin in women undergoing emergency CS performed under regional anaesthesia are at least comparable to those of oxytocin. However, the risk comparison between the two treatment arms should be interpreted having regard to the higher incidence of additional uterotonic agents needed by women in the oxytocin arm compared to the carbetocin arm in both studies and the higher dose of oxytocin administered in both studies than approved for CS.

9.2.3. High-risk PPH Vaginal or CS (under general ± regional anaesthesia)

In the 3 studies comparing carbetocin 100 µg IV (n = 101) to oxytocin 20 IU IV (n = 149) in women at high risk of PPH delivering either vaginally or by CS, the limited safety data showed no clinically significant differences between the two treatment arms with respect to adverse events and blood pressure or heart rate changes following administration of the study drugs (Reyes et al, 2011; Fahmy et al., 2016; Reyes, 2011)

In Reyes et al., 2011, adverse effects were reported infrequently in both treatment arms, and there were no clinically significant differences between the two treatment arms in the incidence of any of the reported adverse effects (that is, headaches, palpitations, fever, nausea and vomiting, others, hot sensation, facial flushing, malaise). There were numerical differences between the two arms for the changes in mean arterial blood pressure and heart rate from before to after administration of the study drugs, but the differences were not statistically significant and are of doubtful clinical significance. The author's commented that many of the adverse effects observed in this study were attributable to the underlying condition of preeclampsia. Additional uterotonic agents were needed by no women in the carbetocin arm needed and 1 (3.4%) woman in oxytocin arm. Therefore, the adverse effects reported in the two treatment arms are not associated with the additional uterotonic agents administered in the study.

In Fahmy et al., 2016, no data on adverse effects were reported, while differences in the MHR and MAB between the two treatment arms over the 60 minutes following administration of the study dugs were not clinically significant. In neither treatment arm did the MHR increase to ≥ 85 bpm or decrease to ≤ 76 bpm at any of the time-points through to 60 minutes. In neither treatment arm did the MABP increase to ≥ 76 mmHg or decrease to ≤ 68 mmHg at any time-point through to 60 minutes or increase or decrease by ≥ 5 mmHg from baseline. The incidence of women needing additional uterotonic agents was notably greater in the oxytocin arm than in the carbetocin arm (50% (n = 15) versus 13.3% (n = 4), respectively, needing one additional dose of methergine; 33.3% (n = 10) in the oxytocin arm needing two additional doses of methergine).

In Reyes, 2011, adverse events were reported infrequently in the two treatment arms and there were no significant differences between the two arms in the incidence of each of the reported adverse events. The only adverse event reported in 2 women in either of the two treatment arms was headache (n = 2, 4.4%, oxytocin versus n = 1, 1.1%, carbetocin). The only adverse event reported in 1 (1.1%) woman in the carbetocin arm and no women in the oxytocin arm was abdominal pain. The adverse events reported in 1 (2.2%) woman in the oxytocin arm and no women in the carbetocin arm were nausea, and dizziness. Adverse events reported in no women in either treatment arm were vomiting, tremor, itching, chills, and facial flushing. There were no data in this study on blood pressure or heart rate changes following administration of the study drugs. Additional uterotonic agents were needed by no women in the carbetocin arm and 3 (3.3%) women in the oxytocin arm. Therefore, the adverse effects reported in the two treatment arms are not associated with the additional uterotonic agents administered in the study.

Overall, the limited safety data from Reyes et al, 2011, Fahmy et al., 2016, and Reyes, 2011 suggest that the risks of carbetocin in women at high risk of PPH delivering either vaginally or

by CS are comparable to those of oxytocin. However, the risks should be interpreted having regard to the higher dose of oxytocin used in each of the three studies compared to the approved dose (that is, 20 IU IV versus 5 IU IV).

9.2.4. Meta-analyses and systematic reviews

9.2.4.1. Jin et al., 2015

In Jin et al. 2015, pooled analyses of the safety data comparing carbetocin with oxytocin or Syntometrine were provided from 12 randomised controlled trials involving 2975 women following CS or vaginal delivery.

In the adverse effects data comparing carbetocin to oxytocin in women undergoing CS the only statistically significant difference between the two treatment groups was the lower risk of dizziness in the carbetocin group relative to the oxytocin group (RR = 0.31 (95% CI: 0.12, 0.83)); pooled data from 2 studies in 538 women). The other non-statistically significant results (RR) based on pooling from 2 or more studies in the carbetocin arm relative to the oxytocin arm, in decreasing order of RR, were: tachycardia (RR = 1.50, 2 studies in 433 women); flushing (RR = 1.15, 3 studies in 1068 women); feeling of warmth (RR = 1.18, 2 studies in 715 women); abdominal pain/back pain (RR = 1.01, 4 studies in 1197 women); sweating (RR = 1.0, 2 studies in 1036 women); metallic taste (RR = 0.95, 2 studies 936 women); headache (RR = 0.94; 5 studies in 1253 women); nausea (RR = 0.93, 4 studies in 1149 women); vomiting (RR = 0.88, 3 studies in 1093 women); short of breath/dyspnoea (RR = 0.79, 3 studies in 537 women); and tremors (RR = 0.74, 2 studies in 1036 women).

The adverse effects for carbetocin and oxytocin in women following vaginal delivery were derived from 1 study (Boucher et al., 2004), which included a total of 160 women (83 in the carbetocin arm and 77 in the oxytocin arm). There were no statistically significant differences between the carbetocin and oxytocin arms in the risks of nausea (RR = 0.66), chills (RR = 1.06), headache (RR = 0.51), vomiting (RR = 0.07), abdominal pain (RR =10.21), dizziness (RR = 1.08), pruritus (RR = 0.10), or tremors (RR = 1.16).

In women following vaginal delivery, risks in the carbetocin group were statistically significantly less likely than risks in the Syntometrine group for: nausea (RR = 0.15 (95% CI: 0.24, 0.40), 4 studies in 1030 women); vomiting (RR = 0.21 (95% CI: 0.11, 0.39), 4 studies in 1030 women); retching (RR = 0.14 (95% CI: 0.03, 0.6), 1 study in 370 women); sweating (RR = 0.33 (95% CI: 0.12, 0.90), 2 studies in 490 women); tremors (RR = 0.41 (95% CI: 0.22m 0.76), 3 studies in 790 women); hypertension 30 minutes after delivery (RR = 0.06 (95% CI: 0.01, 0.44), 2 studies in 540 women; and hypertension 60 minutes after delivery (RR = 0.07 (95% CI: 0.01, 0.54), 2 studies in 540 women. The only adverse effects reported more frequently in women in the carbetocin group relative to the Syntometrine group were tachycardia (RR = 1.87 (95% CI: 1.01, 3.47), 1 study in 300 women) and pruritus (RR = 1.33 (95% CI: 0.65, 2.74), 1 study in 370 women). The increased frequency of tachycardia in the carbetocin group relative to the Syntometrine group was statistically significant, while the difference between the two treatment groups in the risk of pruritus was not statistically significant.

9.2.5. Su et al., 2012

In Su et al., 2012, pooled analyses of the safety data comparing carbetocin with oxytocin, Syntometrine or placebo were provided from 11 randomised controlled trials involving 2635 women following CS or vaginal delivery.

There were 4 studies comparing carbetocin to oxytocin in women following CS. There were no statistically significant differences between the two treatment groups in the risks of experiencing any of the adverse drug reactions reported in the studies in women following CS.

There was 1 study comparing carbetocin to oxytocin in women following vaginal delivery (Boucher et al., 2004). There were no statistically significant differences in this study between

the two treatment groups in the risks of experiencing any of the adverse drug reactions reported in the studies in women following vaginal delivery.

There were 4 studies comparing carbetocin to Syntometrine in women following vaginal delivery. The pooled adverse drug reactions data in Su et al (2011) were consistent with the corresponding data described above for Jin et al (2015). This is not unexpected as both meta-analyses pooled safety data from the same 4 studies.

9.3. First round assessment of benefit-risk balance

9.3.1. Carbetocin versus oxytocin vaginal delivery

The submission included 2 studies comparing carbetocin 100 µg IM to oxytocin 5 IU IM or 10 IU IV for the active management of the third stage of labour to prevent uterine atony and excessive postpartum bleeding in women with risk-factors for PPH delivering vaginally (Boucher et al., 2004; Maged et al., 2016). The two meta-analyses (Su et al., 2011; Jin et al; 2015) did not include pooled data comparing carbetocin to oxytocin from studies in women following vaginal delivery, with both studies only analysing the data from Boucher et al., 2004.

Based on the results of Boucher et al (2004) and Maged et al (2016) it is considered that the benefits and risks of carbetocin following vaginal delivery are at least comparable to those of oxytocin. Therefore, it is considered that the benefit-risk balance for carbetocin 100 µg IM for the active management of the third stage labour following vaginal delivery is favourable, given that oxytocin 5-10 IU IM or 5 IU IV is approved for this indication.

9.3.2. Carbetocin versus Syntometrine vaginal delivery

The submission included 5 studies comparing carbetocin (100 µg) IM to Syntometrine IM for the active management of the third stage of labour following vaginal delivery. In 4 of the 5 studies, Syntometrine consisted of the approved dose (Leung et al., 2006; Nirmala et al., 2009; Su et al., 2009; Askar et al., 2011), and in 1 of the 5 studies Syntometrine consisted of a lower than approved dose (Samimi et al., 2013). The two meta-analyses (Su et al., 2011; Jin et al; 2015) both included pooled data from the 4 studies comparing carbetocin 100 µg IM to the approved dose of Syntometrine (Leung et al., 2006; Nirmala et al., 2009; Su et al., 2009; Askar et al., 2011).

Based on the results from the two meta-analyses pooling the data from the 4 studies comparing carbetocin 100 µg IM to the approved dose of Syntometrine IM (Leung et al., 2006; Nirmala et al., 2009; Su et al., 2009; Askar et al., 2011), and evaluation of each of the 4 studies individually it is considered that the benefits of carbetocin for the active management of the third stage of labour are comparable to those of Syntometrine, while the risks of adverse effects of carbetocin are lower than the risks of Syntometrine. Therefore, it is considered that the benefit-risk balance for carbetocin 100 µg IM for the active management of the third stage of labour following vaginal delivery is favourable, given that Syntometrine 1 mL IM is approved for this indication.

9.3.3. Carbetocin versus oxytocin emergency CS under regional anaesthesia

The submission included 3 studies comparing the efficacy of carbetocin 100 µg IV to oxytocin 5-20 IU IV to prevent postpartum haemorrhage in women delivering via emergency CS under regional anaesthesia (El Behery et al, 2016; Razali et al., 2016; Whigham et al., 2016).

Based on the results from El Behery et al (2016) and Razali et al (2016) it is considered that benefits of carbetocin are superior to oxytocin with respect to the need for additional uterotonic agents and comparable with respect to postpartum haemorrhage. However, based on the results of Whigham et al (2016), the benefits of carbetocin did not significantly differ from those of oxytocin with respect to the need for additional uterotonic agents, PPH ≥ 1000 mL, estimated mean blood loss and reduction in haemoglobin concentration. Based on the limited safety data

from El Behery et al (2016) and Razali et al (2016), it is considered the risks of carbetocin are least comparable to those of oxytocin. Overall, it is considered that the benefit-risk balance for carbetocin 100 µg IV for the prevention of uterine atony and excessive bleeding in women undergoing emergency CS under regional anaesthesia is favourable, given that oxytocin is approved for at 5 IU by IV infusion or slow bolus IV injection after delivery of the infant.

9.3.4. Carbetocin versus oxytocin women at high-risk of PPH

The submission included 3 studies comparing carbetocin 100 µg IV with oxytocin 20 IU IV in women at high risk of PPH delivering vaginally or via CS (including under general anaesthesia) (Fahmy et al, 2016; Reyes et al., 2011; Reyes, 2011).

Based on the results of Fahmy et al (2016), the benefits of carbetocin were significantly superior to those of oxytocin in women delivering twins via CS under general anaesthesia with respect to the need for additional uterotonic agents, estimated mean blood loss, and the need for blood transfusion. Based on the results of Reyes (2011), there were no significant differences between the carbetocin and oxytocin arms in grand multiparous women (≥ 5 births) following vaginal delivery with respect to the need for additional uterotonic agents and the need for blood transfusion. Based on the results of Reyes et al (2011), there were no significant differences between the carbetocin and oxytocin arms in women with severe preeclampsia following vaginal delivery or CS with respect to the need for additional uterotonic agents, reduction in haemoglobin concentration following delivery, and the need for blood transfusion. The limited safety data from the 3 studies suggests that the risks of carbetocin in women at high risk of PPH are at least comparable to those of oxytocin.

Overall, it is considered that the risk-benefit balance of carbetocin 100 µg IV in women at high risk of PPH following vaginal delivery or CS favourable, given that oxytocin 5 IU by IV infusion or slow bolus IV infusion is approved for CS after delivery of the infant.

9.3.5. Carbetocin versus oxytocin CS under general anaesthesia 1 study only (Fahmy et al., 2016)

The submission included only 1 study assessing the benefits and risks of carbetocin compared to oxytocin in a small number of women undergoing CS under general anaesthesia (Fahmy et al., 2016). In this study, the benefits of carbetocin (100 µg IV; n = 30) in women at high risk of PPH (twin pregnancy) were significantly superior to those of oxytocin (20 IU IV; n = 30) with respect to the need for additional uterotonic agents, estimated mean blood loss, and the need for blood transfusion. In addition, uterine tone was significantly greater at 2 minutes and at 2 h after administration in the carbetocin arm compared to the oxytocin arm, and the need to reduce isoflurane (inhalational anaesthetic) from 1% to 0.5% was significantly lower in the carbetocin arm than in the oxytocin arm (suggesting that uterine tonicity was significantly greater in the carbetocin arm than in the oxytocin arm). There were no adverse effect data reported in the study, while differences in the mean heart rate and mean arterial blood pressure over the 60 minutes after administration of the study drugs are considered to be clinically insignificant. Overall, the limited data from Fahmy et al (2016) suggest that the benefit-risk balance for carbetocin in women at high risk of PPH (twin pregnancy) is at least comparable to that for oxytocin.

Although the submission included only 1 relatively small study in 60 women at high risk of PPH undergoing CS under general anaesthesia (Fahmy et al., 2016), it is considered that the totality of the benefit-risk data of carbetocin relative to oxytocin following vaginal delivery and emergency CS is sufficiently robust to support carbetocin for use in women undergoing CS under general anaesthesia to prevent uterine atony and excessive bleeding.

10. First round recommendation regarding authorisation

1. It is recommended that the extension to the indication being sought by the sponsor be approved with the following wording:

   Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant.

2. It is recommended that carbetocin be approved to prevent uterine atony and excessive bleeding following delivery of the infant for the following populations:
   - women following vaginal delivery;
   - women delivering by emergency caesarean section;
   - women with high risk of PPH; and
   - women delivering by caesarean section under general anaesthesia.
3. It is recommended that single dose carbetocin 100 µg be approved for intramuscular (IM) injection or intravenous (IV) injection for the active management of the third stage of labour following vaginal delivery.
4. It is recommended that if the extension of indication is approved by the TGA then it should be a condition of registration that the sponsor has a Risk Management Plan (RMP) in place for Duratocin specific for Australia. The reasons for this recommendation are provided below in Section 11.3.

11. Clinical questions

11.1. General

1. Please provide an estimate of the current use of carbetocin in Australia.
2. Does the sponsor have any information on the relationship between the carbetocin formulations used in the submitted published studies and the carbetocin formulation currently registered in Australia?
3. Did the sponsor's search strategy aimed at identifying relevant literature for inclusion in the submission?
4. Please provide information on the effect on uterine tone of general anaesthetic agents used in Australia for caesarean section.

11.2. Pharmacokinetics

5. Please provide a formal justification for not undertaking an absolute bioavailability study for the proposed 100 µg dose of carbetocin to be administered by IM injection compared to the 100 µg dose of carbetocin to be administered by IV injection.

11.3. Pharmacodynamics

6. The primary goal of the dose tolerability study (van Dongen et al., 1998) was to determine the MTD of carbetocin administered by the IM route to women undergoing normal vaginal delivery at term without epidural anaesthesia. The authors suggested that the optimal dose of carbetocin was 100 µg, as the lowest blood loss was recorded in the 70-125 µg range and no drug related AEs were demonstrated until the 125 µg dose. The authors commented that

they intended to use the 100 µg dose of carbetocin to prevent PPH in further clinical research. However, it would appear that the 70 µg IM and 100 µg IM doses might be of similar efficacy, while the potential for adverse events might be lower with the 70 µg IM dose. The sponsor is requested to justify why the lower 70 µg dose of carbetocin was not selected for IM administration.

11.4. Safety

7. Please provide information on the 6 spontaneous reports of cardiac arrest listed in the cumulative spontaneous post marketing experience reported from the IBD of carbetocin to 30 June 2016.
8. Please provide an Australian specific Risk Management Plan for evaluation by the TGA for the reasons provided in Section 11.3 of this CER.

11.5. First round evaluation errata

The sponsor provided the following comments on the first round clinical evaluation report. The clinical evaluator has provided an 'action' for each comment.

Table 63: Sponsor's comments on errata and evaluator's action

Section reference	Sponsor's comment.	Evaluator's action
Section 7.2.3 Evaluator's conclusion on clinical efficacy – emergency CS	Of the 3 studies conducted in women delivering by emergency CS, (Razali) et al., 2016) and Whigham et al., 2016, the CS was performed under regional anaesthesia. El Behery et al., 2016 excludes patients delivering under general anaesthesia and therefore it is inferred that regional anaesthesia was used. Reference: m5.3.5.1 Razali et al., 2016, Whigham et al., 2016, El Behery et al., 2016	The sponsor's comment is not inconsistent with the information provided in the evaluator's conclusions. However, for completeness the second sentence in the second paragraph under *Evaluator's conclusion of clinical efficacy* has been deleted and replaced with - *However, in the 3 studies conducted in women delivering by emergency CS the procedure was performed under regional anaesthesia in Razali et al (2016) and Whigham et al (2016), while in El Behery et al (2016) it can be inferred that regional anaesthesia was used as patients delivering under general anaesthesia were excluded from the study.*
Section 7.3.1 Evaluator's comment following Table 16	In the Clinical overview, reference 58 is correctly referred to as Reyes et al., 2011 whereas reference 59 should be Reyes 2011 (single author). Reference: m5.3.5.1 Reyes et al., 2011 (ref#113), Reyes 2011 (ref#130)	The sponsor's comment is not inconsistent with the information provided by the evaluator. However, as the evaluator's comment following Table 16 does not add clinically important information to the CER it has been deleted.

The sponsor commented that apart from the above comments, no errors or omissions of fact have been identified in the clinical evaluation report.

12. Second round evaluation

12.1. Clinical questions sponsor's response to first round questions

12.1.1. General

1. Please provide an estimate of the current use of carbetocin in Australia.

12.1.1.1. Sponsor's response

[information redacted]

12.1.1.2. Evaluator's comment

The response is acceptable.

2. Does the sponsor have any information on the relationship between the carbetocin formulations used in the submitted published studies and the carbetocin formulation currently registered in Australia?

12.1.2. Sponsor's response

The sponsor provided a tabulated summary of the source of carbetocin used in each of the submitted published studies. The sponsor stated that the majority of the studies utilised a formulation of carbetocin obtained from various Ferring affiliates. Furthermore, the sponsor confirmed that when each of these studies was conducted only one formulation of Ferring carbetocin was available internationally. The sponsor commented that the original formulation required refrigeration and was replaced very recently in Australia (approved April 2015) and internationally, with an adjusted formulation that is stable at room temperature. Therefore, the sponsor concludes that, as all the studies included in the dossier were conducted prior to 2015, the Ferring-sourced carbetocin product utilised in these studies was the original formulation of Duratocin that was approved in Australia. The sponsor provided further discussion relating to the relationship between the formulation used in the clinical studies and the presentation currently available in Australia in its response to Question 5 (Pharmacokinetics), see below.

12.1.2.1. Evaluator's comment

The sponsor's response is acceptable.

3. Did the sponsor's search strategy aimed at identifying relevant literature for inclusion in the submission?

12.1.2.2. Sponsor's response

In line with TGA guidance relating to literature based submissions, a search strategy was developed to include the proposed database search strategies, a list of proposed databases, a justification for the approach taken and the criteria for determining which results to include/exclude from the application. The aim of this strategy was to identify high-quality individual studies and meta-analyses that were relevant to the proposed indications. The search strategy for this literature based submission was reviewed and accepted by the TGA Delegate on 10 December 2015.

12.1.2.3. Evaluator's comment

The response is acceptable.

4. Please provide information on the effect on uterine tone of general anaesthetic agents

12.1.2.4. Sponsor's response

In vitro studies show that propofol has a relaxant effect on isolated uterine smooth muscle from pregnant women, but does not interfere with the binding characteristics of oxytocin

receptors.[3] Propofol, pentobarbitone, and ketamine each show concentration-dependent inhibition of uterine muscle contraction, with ketamine being the least potent.[3]

In other in vitro and one in vivo study, ketamine was found to produce a dose related increase in uterine tone[4][5], although reports vary largely due to the studies being conducted at different stages of gestation.[6]

Similar to propofol, volatile anaesthetic agents have been demonstrated to cause dose-dependent myometrial relaxation and therefore, increasing the dose of the volatile agent (to decrease the risk of awareness) may be associated with an increased risk of uterine atony.[7]

In general, the use of general anaesthetics during caesarean section may alter the uterine tone of the women. However, as the binding characteristics of oxytocin receptors do not change[3], the use of carbetocin with general anaesthesia is not expected to differ from oxytocin.

12.1.2.5. Evaluator's comment

The response is acceptable. The sponsor's references are listed below.

12.1.3. Pharmacokinetics

5. *Please provide a formal justification for not undertaking an absolute bioavailability study for the proposed 100 µg dose of carbetocin to be administered by IM injection compared to the 100 µg dose of carbetocin to be administered by IV injection.*

12.1.3.1. Sponsor's response

The sponsor referred to the original registration application for Duratocin which included the results from a number of studies investigating the PK of carbetocin administered by IV and IM routes. The sponsor referred to the results of Study CLN 6.3.1 which studied the PK of carbetocin in 25 healthy non-pregnant women to determine the absolute bioavailability of carbetocin administered by IM injection (Clinical Overview, Current Submission). The tabulated summary of the results of the study are provided immediately below.

[3]Tsujiguchi, N., Yamakage, M. and Namiki, A., 2001. Mechanisms of direct inhibitory action of propofol on uterine smooth muscle contraction in pregnant rats. Anesthesiology: The Journal of the American Society of Anesthesiologists, 95(5), pp.1245-1255.
[4] Galloon, S., 1976. Ketamine for obstetric delivery. The Journal of the American Society of Anesthesiologists, 44(6), pp.522-524.
[5] Forsling, M.L., Kirby, M.J. and Simpson, P.J., 1973. Proceedings: Possible mechanisms of action for the influence of ketamine on uterine tone. British journal of pharmacology, 49(1), p.152P.
[6]Craft, J.B., Coaldrake, L.A., Yonekura, M.L., Dao, S.D., Co, E.G., Roizen, M.F., Mazel, P., Gilman, R., Shokes, L. and Trevor, A.J., 1983. Ketamine, catecholamines, and uterine tone in pregnant ewes. American journal of obstetrics and gynecology, 146(4), pp.429-434.
[7]Wong, C.A., 2010. General anesthesia is unacceptable for elective cesarean section. International Journal of Obstetric Anesthesia, 19(2), pp.209-212

Table 63: Summary of pharmacokinetic parameters of carbetocin (Study CLN 6.3.1)

		Intravenous injection		Intramuscular injection	
		400 µg IV N = 6	800 µg IV N = 6	400 µg IM N = 6	800 µg IM N = 6
AUC (0-∞)	Mean ± SD	749.2 ± 131.0	1,370.4 ± 214.9	553.5 ± 132.9	1,107.4 ± 56.5
(µg*min/L)	Min-max	539.5-916.9	1,148.8-1,733	403.3-733.7	1,028-1,181.4
Cmax	Mean ± SD	-	-	6.35 ± 1.39	12.04 ± 1.88
(µg/L)	Min-max			4.1 - 8.1	9.4 - 14.7
Tmax	Mean ± SD	-	-	20.0 ± 0	28.0 ± 11.0
(min)	Min-max			20 - 20	20 - 40
F	Mean ± SD	-	-	76.0 ± 10.8	83.4 ± 17.6
(%)	Min-max			60.8 - 84.8	59.3 - 102.8

AUC = Area under the curve C_{max} = peak concentration Tmax = time to peak concentration F = percent bioavailability of intramuscular carbetocin.

The sponsor noted that the clinical evaluator and the TGA Delegate for the original submission concluded that the data indicated that the absolute bioavailability of carbetocin administered IM is approximately 80%. The sponsor commented that data indicate that the PK of carbetocin are dose-proportional for both IV and IM administration, with the mean $AUC_{(0-\infty)}$ for the 800 µg dose being approximately twice that of the 400 µg dose. The sponsor noted that '*while these data were generated utilising doses higher than that proposed for IM administration following vaginal delivery, as Duratocin is formulated as a simple aqueous solution and the observed high bioavailability was found to be dose proportional, it is reasonable to conclude that the absolute bioavailability of the 100 µg dose would not be dissimilar to that of the higher doses administered in Study CLN 6.3.1 (that is, approximately 80%)'.* The following paragraphs have been taken verbatim from the sponsor's response.

> *While a formal absolute bioavailability study with the 100 µg IM dose has not been conducted, it is important to note that the safety and efficacy of this dose in preventing uterine atony and excess bleeding following vaginal delivery has been established in the 7 studies (including a total of 798 patients treated with the proposed IM dose) submitted with this application. Consequently, there is no evidence to suggest that even if the absolute bioavailability of the 100 µg IM dose is slightly lower than the 80% figure calculated in Study CLN 6.3.1, there would be an adverse impact on the clinical profile.*
>
> *Additional reassurance of the safety of the 100 µg IM dose can be found in the established safety of carbetocin when an equivalent dose is administered intravenously. While there is no evidence to suggest the bioavailability of the 100 µg IM dose to be significantly higher than that reported in Study CLN 6.3.1 at higher doses, even if the absolute bioavailability was in fact higher, it cannot be higher than 100%, which is equivalent to that currently approved for IV administration for the existing indication.*
>
> *Consequently, a study to determine the absolute bioavailability for the IM administration of the 100 µg injection used in the original clinical studies is not considered necessary as the safety and efficacy of the proposed dose and route has been established in clinical trials, and the bioavailability data generated with higher doses provides a reasonable indication that the absolute bioavailability is approximately 80%. Should the actual bioavailability be slightly higher or lower than this figure, the available clinical data on patients receiving the 100 µg IM dose and receiving the 100 µg IV dose provide reassurance that the clinical impact would not be significant.*

As indicated in Ferring's response to Question 2 above, the presentation of Duratocin currently available in Australia is the room temperature stable formulation whereas the formulation

(where known) used in the studies presented in the literature references was the original formulation that requires refrigeration. No studies comparing the relative bioavailability of the old and new formulations of carbetocin administered via 100 µg intramuscular injection have been conducted. Study FE 992097) has however been conducted measuring the absolute bioavailability of the new formulation administered as a 100 µg intramuscular dose. (Table 64 below) below summarises the key parameters from this study.

Table 64: Summary of the PK parameters of carbetocin

	Carbetocin 100 µg IV	Carbetocin 100 µg IM
Parameter	**n-19**	**N=20**
AUC [h*ng/mL]	2.762 (21.6%)	2.147 (18.7%)
AUCt [h*ng/mL]	2.697 (21.8%)	2.022 (20.3%)
Cmax [ng/mL]	7.232 (17.4%)	1.030 (30.4%)

Source: Study report FE992097 Table 9-1

Results from this study indicated that the absolute bioavailability of a 100 µg intramuscular dose of the room temperature formulation is approximately 77%, which is in accord with the absolute bioavailability of the original formulation as recorded in Study CLN 6.3.1 discussed above. Consequently, while data on the absolute bioavailability of a 100 µg IM dose of the formulation used in the clinical studies is not available, the bioavailability of the currently available formulation has been measured at around 77%, which is consistent with that reported for higher doses of the original formulation in Study CLN 6.3.1. Please note that the full study report for Study FE 992097, investigating the absolute bioavailability of carbetocin room temperature stable formulation, is not available at the moment and results have not been published.

12.1.3.2. Evaluator's comment

The response is acceptable.

12.1.4. Pharmacodynamics

6. *The primary goal of the dose tolerability study (van Dongen et al., 1998) was to determine the MTD of carbetocin administered by the IM route to women undergoing normal vaginal delivery at term without epidural anaesthesia. The authors suggested that the optimal dose of carbetocin was 100 µg, as the lowest blood loss was recorded in the 70-125 µg range and no drug related AEs were demonstrated until the 125 µg dose. The authors commented that they intended to use the 100 µg dose of carbetocin to prevent PPH in further clinical research. However, it would appear that the 70 µg IM and 100 µg IM doses might be of similar efficacy, while the potential for adverse events might be lower with the 70 µg IM dose. The sponsor is requested to justify why the lower 70 µg dose of carbetocin was not selected for IM administration.*

12.1.4.1. Sponsor's response

The rationale for the 100 µg IM dose selection is partly based on the results from the approved IV dose of carbetocin for elective Caesarean section, and partly on the investigator driven ascending IM dose tolerance study by van Dongen et al (1998). The objective of the van Dongen study was to determine the maximum tolerated IM dose (MTD) of carbetocin for use immediately postpartum. The dosages selected for the study were based upon previous clinical data showing that IM dosages between 10–70 µg resulted in prolonged uterine activity

following vaginal delivery. The MTD was defined as the dose expected to produce dose limiting adverse events (DLAEs) in 20% of the population. DLAEs did not appear until the 200 µg group and based on these findings the MTD was estimated to be 200 µg. As maximum blood loss was greatest at the upper and lower dose levels and lowest in the 70-125 µg dose range, and no drug related serious adverse events were demonstrated until the 125 µg dosage, carbetocin 100 µg was selected as the optimal therapeutic dose for IM administration. This was also selected on a pragmatic basis to align with the existing IV dose in elective caesarean section.

As IM administration of carbetocin is recommended for women undergoing vaginal delivery, direct support for the safety and efficacy of the selected dose resides with the clinical data submitted the application. This submission includes 7 published studies with a total of 1590 women or which 798 received carbetocin and 792 received either oxytocin or Syntometrine as active control. In each of the 7 studies, a single dose of 100 µg carbetocin IM was administered and results show that carbetocin is as effective as the comparator. Safety data from these studies indicate that carbetocin has a similar safety profile to oxytocin and superior to that of Syntometrine following vaginal delivery.

Whilst a slightly lower IM dose for carbetocin may be theoretically effective, the supporting data indicates that the proposed 100 µg carbetocin IM dose is safe and effective. In addition, the IM dosage is consistent with the simple dose regimen already approved for IV administration.

12.1.4.2. Evaluator's comment

The response is acceptable. However, the possibility remains that the benefit-risk profile of a 70 µg IM dose might be superior to a 100 µg IM dose. This could only be demonstrated by an appropriately designed comparative study. Nevertheless, the available data indicate that the benefit-risk profile of the 100 µg IM dose for the active management of the third stage of labour in women delivering vaginally is acceptable.

12.1.5. Safety

7. Please provide information on the 6 spontaneous reports of cardiac arrest listed in the cumulative spontaneous post marketing experience reported from the IBD of carbetocin to 30 June 2016.

12.1.5.1. Sponsor's response

In total, 11 cases of cardiac arrest have been reported during the period 24 June 1997 up to 31 August 2017. A short description of the above mentioned six cases are presented in the RMP v1.0 together with one additional case, received after the RMP data lock point in 2016. The 4 remaining cases were reported in the period ending 31 July 2017, where 2 of the cases were from the French authorities and relate to events that occurred in 2009. Of these eleven reports of cardiac arrest, nine patients recovered and two cases were fatal. The sponsor provided a full narrative for each of the 11 cases.

12.1.5.2. Evaluator's comment

The post-marketing data included 11 cases of cardiac arrest reported over approximately 20 years following first world-wide authorisation of carbetocin in Canada in June 1997. Review of the narratives for the 11 cases indicates that each case was temporally associated with carbetocin (presumably all single dose IV) in the context of CS at a dose of 100 µg in 8 cases, 100 mg in 1 case (presumably an error in recording the dose rather than the actual dose), and not stated in 3 cases. The case narratives indicate that carbetocin was administered to prevent uterine atony/PPH in 6 cases and to treat PPH in 3 cases, with the indication not being provided in 2 cases.

Cumulative post-marketing data up to 31 December 2016 provided by the sponsor estimates that 9,507,471 patients have been exposed to carbetocin, based on a single IV dose of 100 µg, since the international birthdate of the drug in 1997. Based on the Council of International

Organizations of Medical Sciences (CIOMS) definitions of adverse drug reactions the incidence of cardiac arrest based on post-marketing data and cumulative post-marketing exposure is 'very rare' (<1/10,000). The RMP (31 May 2017) includes review of important potential risks of 'cardiac arrest' and 'cardiac arrhythmias'. The RMP refers to a publication (Mhyre et al., 2014), which estimates the background frequency of cardiac arrest among women hospitalised for childbirth to be 1 out of 11,749 births.

The amended PI provided with the sponsor's response contraindicates the use of carbetocin '*in patients with cardiovascular disease, especially coronary artery disease, valvular heart disease, cardiomyopathy and heart failure except with extreme caution'.* It is recommended that the *Adverse Effects* section of the PI include a statement noting that there have been post-marketing reports of cardiac arrest associated with the use of carbetocin IV in patients undergoing caesarean section.

12.1.6. References provided by in the sponsor's response

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14. Fabian, M., Forsling, M.L., Jones, J.J. and Pryor, J.S., 1969. The clearance and antidiuretic potency of neurohypophysial hormones in man, and their plasma binding and stability. The Journal of physiology, 204(3), pp.653-668.

15. Wathes, D.C., Borwick, S.C., Timmons, P.M., Leung, S.T. and Thornton, S., 1999. Oxytocin receptor expression in human term and preterm gestational tissues prior to and following the onset of labour. Journal of Endocrinology, 161(1), pp.143-151.

16. Yulia, A. and Johnson, M.R., 2014. Myometrial oxytocin receptor expression and intracellular pathways. Minerva ginecologica, 66(3), pp.267-280.

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13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

Following review of the sponsor's response, the benefits of carbetocin for the proposed usages are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

Following review of the sponsor's response, the benefits of carbetocin for the proposed usages are unchanged from those identified in Section 9.2.

13.3. Second round assessment of benefit-risk benefit balance

Following review of the sponsor's response, the benefit-risk balance of carbetocin for the proposed usages is unchanged from those identified in Section 9.3.

14. Second round recommendation regarding authorisation

1. It is recommended that carbetocin be approved for the following indications:

   Caesarean section

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

   Vaginal delivery

   Duratocin is indicated for the active management of the third stage of labor for the prevention of uterine atony and excessive bleeding following vaginal delivery.

2. It is recommended that carbetocin be approved to prevent uterine atony and excessive bleeding following delivery of the infant for the following populations:

- *women following vaginal delivery;*
- *women delivering by emergency caesarean section;*
- *women with high risk of PPH; and*
- *women delivering by caesarean section under general anaesthesia.*

3. It is recommended that single dose carbetocin 100 µg be approved for intramuscular (IM) injection or intravenous (IV) injection for the active management of the third stage of labour following vaginal delivery.

15. References

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