



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Carbetocin

Proprietary Product Name: Duratocin

Sponsor: Ferring Pharmaceuticals Pty Ltd

August 2018

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.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright

© Commonwealth of Australia 2018

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

Common abbreviations	4
I. Introduction to product submission	6
Submission details	6
Product background	6
Regulatory status	10
Product Information	11
II. Registration time line	12
III. Quality findings	12
IV. Nonclinical findings	12
V. Clinical findings	12
Introduction	13
Pharmacokinetics	14
Pharmacodynamics	14
Dosage selection for the pivotal studies	14
Efficacy	15
Safety	24
First round benefit-risk assessment	26
First round recommendation regarding authorisation	28
Second round evaluation	28
Second round benefit-risk assessment	28
VI. Pharmacovigilance findings	29
Risk management plan	29
VII. Overall conclusion and risk/benefit assessment	30
Quality	31
Nonclinical	31
Clinical	31
Risk management plan	37
Risk-benefit analysis	37
Outcome	48
Attachment 1. Product Information	49
Attachment 2. Extract from the Clinical Evaluation Report	49

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
SAE	Serious adverse events
SD	Standard deviation

Abbreviation	Meaning
WHO	World Health Organisation

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	16 March 2018
<i>Date of entry onto ARTG:</i>	26 March 2018
<i>ARTG number:</i>	233671
<i>Active ingredient:</i>	Carbetocin
<i>Product name:</i>	Duratocin
<i>Sponsor's name and address:</i>	Ferring Pharmaceuticals Pty Ltd 20 Bridge Street, Pymble NSW 2073
<i>Dose form:</i>	Solution for injection
<i>Strength:</i>	100 microgram/mL
<i>Container:</i>	Clear glass vial
<i>Pack size:</i>	5 vials
<i>Approved therapeutic use:</i>	<i>Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by emergency caesarean section or vaginal delivery.</i> <i>Duratocin must be administered after delivery of the infant.</i>
<i>Routes of administration:</i>	Intravenous (IV); Intramuscular (IM)
<i>Dosage:</i>	Caesarean Section: A single dose of 100 µg (1 mL) of Duratocin (carbetocin injection) should be administered intravenously as a bolus injection, slowly over 1 minute after delivery of the infant. Duratocin can be administered either before or after delivery of the placenta. Vaginal Delivery: A single dose of 100 µg (1 mL) of Duratocin (carbetocin injection) should be administered after delivery of the infant for the active management of the third stage of labour as an intramuscular injection or intravenously as a bolus injection slowly over 1 minute.

Product background

This AusPAR describes the application by the sponsor, Ferring Pharmaceuticals Pty Ltd, to extend the indications for Duratocin (Carbetocin). This was a literature based submission by the sponsor which also proposed to make changes to the Dosing and administration section for the Product Information (PI) for Duratocin.

The currently in Australia approved indication for Duratocin 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 extension of indications for Duratocin in this application 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.

At present, the approved carbetocin dosage is:

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 new 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.

Postpartum haemorrhage (PPH) remains a major cause of both maternal mortality and morbidity within Australia and internationally. PPH is defined by the World Health Organization (WHO) as blood loss from the genital tract exceeding 500 mL after vaginal delivery and 1000 mL after caesarean section (CS) within 24 h of delivery. The incidence reported in Australia is 5 to 15%. 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.¹ PPH usually occurs immediately preceding or after delivery of the placenta.

Approximately 70% of PPH occur due to uterine atony. Risk factors include uterine over distension (such as from macrosomia, polyhydramnios and multiple gestations), previous PPH, previous retained placenta, high parity, antepartum haemorrhage, precipitous or prolonged labour, chorioamnionitis, retained placenta, uterine abnormalities, requiring high dose or prolonged oxytocin during delivery, caesarean section or general anaesthesia (GA).

Caesarean section (CS) 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%).¹

The guidelines for the prevention of PPH in Australia and internationally provide somewhat discrepant advice regarding the use of oxytocics. This may be due to the difference in obstetric care between and within countries which has an important influence of the relative risk benefit balance on any intervention.

¹ RANZCOG; NSW Health Procedures [PD2010_064]

In Australia, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommend use of Oxytocin or Syntometrine for the prevention of PPH. Carbetocin is mentioned but not recommended. It is unclear if this is due to the lack of evidence of the use of carbetocin at the time the guidelines were written (2009) or other reasons. In clinical practice, most hospitals use oxytocin. Some hospitals, particularly private hospitals, use carbetocin. The main concern with carbetocin is its long half-life and if accidentally given before delivery of the infant it may cause foetal distress due to placental insufficiency.

Current treatment options

Chemically, carbetocin is a synthetic octapeptide of oxytocin. It has lower potency (thus given at a higher dose) but a more prolonged duration of action.

Available medicines as uterotonic agents in Australia are summarised in Table 1 below.

Table 1: Uterotonic agents available in Australia

Name	Active components	Indications on ARTG	Advice by RANZCOG	Adverse events (AE)
Oxytocin	Oxytocin 5IU and 10IU per ml. Given IM or IV	Induction of labour Inadequate uterine effort Management of third stage PPH	First line. Only therapy approved for repeat use.	Main AEs are warmth, flushing, and transient increase in heart rate. Potential for water intoxication due to vasopressin like effects
Syntometrine	5 IU oxytocin and 0.5 mg ergometrine. Given IM	Active management of the third stage of labour Prevention and treatment of postpartum haemorrhage associated with uterine atony	Alternative to oxytocin	-hypertension, nausea and vomiting Advice to avoid breast feeding due to potential effect of ergot
Duratocin	Carbetocin, a synthetic octapeptide of oxytocin	See above		Would expect similar AE to oxytocin- but this is a longer acting agent Seems to have greater effect of heart rate

The sponsor's Clinical Overview 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 to 10 IU) by intramuscular injection (IM), slow bolus intravenous (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.

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.

Australian guidelines

The 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 to 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 that by RANZCOG.² 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.² 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.¹ 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.

² RWH (2012): The Royal Women's Hospital (Melbourne, Victoria, Australia). Third Stage of Labour—Guideline. December 2012.

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 than 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 & 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;³ NSW Health Procedures Document;⁴ and the RHW guideline (2012);² do not refer to the use of carbetocin for the prevention of PPH.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 30 April 2004.

The international birth date for carbetocin is 24 June 1997 corresponding to the first approval in Canada. The first approval of carbetocin in the European Union (EU) was 6 October 1997 in the United Kingdom (UK). As of September 2015, carbetocin had been approved in 80 countries under 4 different brand names for the prevention of uterine atony and excessive bleeding following delivery of the infant by CS under epidural or spinal anaesthesia, and/or for prevention of uterine atony in women at risk of PPH following vaginal delivery of the infant. The approved indication in each of the countries in which carbetocin is registered are summarised below in Table 2.

Table 2: Overseas regulatory status of carbetocin under 4 different brand names

Indication	Countries
Caesarean section	Duratocin: Argentina, Bahamas, Plurinational State of Bolivia, Brazil, Canada, Cayman Islands, Chile, China, Czech Republic, Hong Kong, Italy, Jamaica, Korean Republic, Macao, Malaysia, Paraguay, Peru, Philippines, Singapore, Taiwan, Thailand, Trinidad and Tobago, Uruguay, Vietnam. Pabal: Austria, Azerbaijan, Bahrain, Belgium, Denmark, Egypt, Estonia, Finland, France, Germany, Georgia, Greece, Hungary, Iceland, Ireland, Jordan, Kuwait, Lebanon, Lithuania, Luxembourg, Malta, Namibia, Netherlands, Norway, Oman, Poland, Portugal, Qatar, Russian Federation, Saudi Arabia, Slovakia, South Africa, Sudan, Sweden, Switzerland, Syrian Arab Republic, Turkey, Ukraine, United Arab Emirates, United Kingdom, Yemen. Lonactene: Costa Rica, Dominican Republic, Guatemala, Panama, Venezuela. Duratobal: Spain.
Elective caesarean section	Duratocin: Australia, New Zealand
Caesarean section and vaginal delivery	Duratocin: Colombia, Ecuador. PABAL – Kazakhstan, Russian Federation. Lonactene: Cuba, El Salvador, Honduras, Mexico

³ RANZCOG Guideline: Management of Postpartum Postpartum Haemorrhage (PPH)

[https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Management-of-Postpartum-Haemorrhage-\(C-Obs-43\)-Review-July-2017.pdf?ext=.pdf](https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Management-of-Postpartum-Haemorrhage-(C-Obs-43)-Review-July-2017.pdf?ext=.pdf)

⁴ NSW Health Procedures Document PD2010-064. Maternity - Prevention, Early Recognition & Management of Postpartum Haemorrhage (PPH). 2010.

Of note is that in the European Union (EU), Switzerland, Singapore, Canada and NZ there is no approval for use after vaginal delivery or general anaesthesia. It is approved for all caesarean section in EU and Switzerland but not Canada or NZ (see Table 3 below).

Table 3: International regulatory status

Country/ Region	Trade name	Status	Indication
EU Mutual Recognition procedure (MRP)	Pabal	Approved: United Kingdom 6 October 1997 MRP: 8 March 2006 and 17 January 2007	Prevention of uterine atony following delivery of the infant by Caesarean section under epidural or spinal anaesthesia.
Switzerland	Pabal	Approved: 21 October 2008	Prevention of uterine atony following delivery of the infant by caesarean section under epidural or spinal anesthesia.
Canada	Duratocin	Approved: 24 June 1997	Prevention of uterine atony and postpartum haemorrhage following cesarean section under epidural or spinal anaesthesia.
		Approved: 5 December 2016	
New Zealand	Duratocin	Approved: 23 December 2004	Prevention of uterine atony & excessive bleeding following delivery of the infant by elective caesarean section under epidural or spinal anaesthesia.
Singapore	Duratocin	25 August 2003	Prevention of uterine atony & postpartum hemorrhage following elective cesarean section under epidural or spinal anaesthesia

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration time line

The following table captures the key steps and dates for this Standard pathway application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	28 February 2017
First round evaluation completed	31 July 2017
Sponsor provides responses on questions raised in first round evaluation	28 September 2017
Second round evaluation completed	15 November 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	19 December 2017
Sponsor's pre-Advisory Committee response	16 January 2018
Advisory Committee meeting	1-2 February 2018
Registration decision (Outcome)	16 March 2018
Completion of administrative activities and registration on ARTG	26 March 2018
Number of working days from submission dossier acceptance to registration decision*	183

*Statutory timeframe for standard applications in Australia is 255 working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Note: Many published references were submitted in support of this application. These are discussed below and detailed in Tables 2-4 below. Details of cited references are also given under *References* in Attachment 2.

Introduction

Clinical rationale

The sponsor's 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*'.

The evaluator commented that the sponsor's clinical rationale is acceptable.

Guidance

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

Contents of the clinical dossier

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.

- 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.

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 to 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 Pediatric 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.

The evaluator commented that the sponsor's rationale for not submitting paediatric data is acceptable.

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

The dossier included no new PK studies. The sponsor's 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.

Pharmacodynamics

Studies providing pharmacodynamic data

The dossier included no new PD studies. The sponsor's 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.

Dosage selection for the pivotal studies

The sponsor's Clinical Overview stated that the primary efficacy parameter for the dose response studies (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 to 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 to 70 µg experienced sustained uterine contractions at 14 to 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 µµg (n = 1), 30 µg (n = 1), 50 µg (n = 1) and 100 µg (n = 1). The sponsor's 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 sponsor's 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, and 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 to 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). 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 blood pressure (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 beats per minute (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 to 125 µg range and no drug related adverse events (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 to 125 µg range and the potential for fewer adverse effects with 70 µg IM compared to 100 µg IM (see *Clinical questions* in Attachment 2 of this AusPAR).

Efficacy

Studies providing efficacy data

Vaginal delivery

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 4 and evaluated in Attachment 2.

Table 4: 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	Objective	Design	Carbetocin Control	Subjects	Efficacy Outcomes
Boucher et al., 2004. Two centres in Canada.	Reduce the incidence and severity of PPH in women at risk for PPH.	R, db, ac. Injectio n after DP.	Carbetocin, 100 µg IM n = 83. Oxytocin 10 IU, single IVI / 2 h; n = 87.	Vaginal delivery, women with at least 1 risk-factor for PPH.	<u>Primary:</u> Additional uterotonic agents during the first 24h after delivery. <u>Secondary:</u> Uterine massage; reduction in Hb and Hct; mean blood loss; PPH (> 500 mL).
Leung et al., 2006. One centre in HK.	Preventio n of PPH.	R, db, ac. Injectio n 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.	<u>Primary:</u> Reduction in Hb at 48h after delivery. <u>Secondary:</u> 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.	Preventio n of PPH in high-risk women.	R, db, ac. Injectio n 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 (\geq 500 mL); Hb change. No defined primary or secondary outcome measures.
Su et al., 2009. One centre in Singapore.	Preventio n of PPH.	R, db, ac. Injectio n 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.	<u>Primary:</u> PPH requiring additional uterotonicics. <u>Secondary:</u> PPH (\geq 500 mL); severe PPH (\geq 1000 mL); blood transfusion; blood loss; length of hospital stay.
Askar et al., 2011. One centre in Kuwait.	Efficacy and safety in managing third stage of	R, db, ac. Injectio n after AS.	Carbetocin 100 µg IM; n = 120. Syntometrine (5/0.5)* 1 mL	Vaginal delivery, excluded women with high risk-factors for	<u>Primary:</u> PPH requiring additional uterotonicics. <u>Secondary:</u> PPH (\geq 500 mL); severe PPH (\geq 1000 mL); blood transfusion; blood loss;

Study	Objective	Design	Carbetocin Control	Subjects	Efficacy Outcomes
	labour in women with low risk-factors for PPH.		IM; n = 120.	PPH.	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.	<u>Primary:</u> Hb change at 24h after delivery. <u>Secondary:</u> Additional uterotronics. <u>Other:</u> 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 uterotronics; 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.

Askar AA, Ismail MT, El-Ezz AA, Rabie NH. Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. *Arch Gynecol Obstet.* 2011; 284(6): 1359-65

Boucher M, Nimrod CA, Tawagi GF, Meeker TA, Rennicks White RE. Comparison of carbetocin and oxytocin for the prevention of postpartum haemorrhage following vaginal delivery: a double-blind randomized trial. *J Obstet Gynecol Can* 2004; 26:481-8

Leung SW, Ng PS, Wong TH. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *BJOG* 2006; 113:1459-1464

Maged et al. Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women. *J Matern Fetal Neonatal Med*, Early Online: 1-5. First published Online on 3 March 2015

Nirmala K, Zainuddin AA, Ghani NA, Zulkifli S, Jamil MA (2009) Carbetocin versus syntometrine in prevention of postpartum haemorrhage following vaginal delivery. *J Obstet Gynaecol Res* 35(1):48-54

Samimi M, Imani-Harsini A, Abedzadeh-Kalaroudi M. Carbetocin vs. Syntometrine in Prevention of Postpartum Hemorrhage: a Double Blind Randomized Control Trial. *Iranian Red Crescent Medical Journal*. 2013 August; 15(9): 817-22

Su LL, Rauff M, Chan YH, Mohamad Suphan N, Lau TP, Biswas A, Chong YS (2009) Carbetocin versus syntometrine for the third stage of labour following vaginal delivery- a double-blind randomised controlled trial. *BJOG* 116(11):1461-1466

Evaluator's conclusions on efficacy vaginal delivery and 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 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 this paper 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 Intent-to-Treat (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 μ g 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 μ g 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 μ g IM was more efficacious than a lower than approved dose of Syntometrine (5 IU oxytocin/0.2 mg ergometrine) 1 mL IM.

Emergency caesarean section (CS)

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 μ g IV and 424 women treated with single dose oxytocin 5-20 IU IV (El Behery et al., 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 5 and are evaluated in Attachment 2, Extract from the clinical evaluation report.

Table 5: 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.	<u>Primary</u> : Major PPH (\geq 1000 mL) within 24 h of delivery. <u>Secondary</u> : 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.	<u>Primary</u> : Need for additional uterotonic agents on the 24 h after CS. <u>Secondary</u> : type and timing of additional uterotonic agents; estimated blood loss (mean, \geq 500 mL, \geq 1000 mL); total operating time; Hb and 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.	<u>Primary</u> : Need for additional uterotonic agents. <u>Secondary</u> : 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.

El-Behery MM, El Sayed GA, El Hameed AA, et al. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. J Matern Fetal Neonatal Med 2016; 29: 1257-60.

Razali N, Latar IL, Chan YK, Omar SZ, Tan PC 2016. Carbetocin compared to oxytocin in emergency Caesarean section: a randomized trial. European Journal of Obstetrics & Gynecology and Reproductive Biology 198 (2016) 35-39

Whigham CA, Gorelik A, Loughnan TE, Trivedi A. Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial. *J Matern Fetal Neonatal Med.* Early Online: 1-4. Published online 1 March 2016

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 to 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 to 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.

High-risk of postpartum haemorrhage

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 6 and are evaluated in Attachment 2.

Table 6: 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.	<u>Primary</u> : Need for additional uterotonic agent (methergine) due to poor uterine contractions. <u>Secondary</u> : Need for decrease in isoflurane concentration from 1% to 0.5%; need 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.	<u>Primary</u> : PPH requiring use of additional uterotonic agents. <u>Secondary</u> : 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)	<u>Primary</u> : therapeutic failure (defined as use of additional uterotonic agents); manual exploration of the uterine cavity; blood transfusion <u>Secondary</u> : 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 = caesarean section; GA = general anaesthetic; RA = regional anaesthesia; CSD = caesarean section delivery; Hb = haemoglobin IV = intravenous; [DP] = after delivery of the placenta; [DI] = after

Fahmy NG, Hend MY, Hany VZ (2016) Comparative study between effect of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients undergoing cesarean section Egyptian J Anaesthesia 32 (1):117-121

Reyes *et al.* Carbetocin Versus Oxytocin for Prevention of Postpartum Hemorrhage in Patients with Severe Preeclampsia: A Double-Blind Randomized Controlled Trial. J Obstet Gynaecol Can 2011; 33(11):1099–1104.

Reyes. Carbetocin vs oxytocin for the prevention of postpartum hemorrhage in grand multiparous patients: a randomized controlled trial. Clin Invest Gin Obst. 2011; 38(1):2—7

Evaluator's conclusion on clinical efficacy in women at high-risk of postpartum haemorrhage delivering vaginally or via caesarean section under general anaesthesia

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 μ g IV in a total of 101 women to oxytocin 20 IU IV in a total of 149 women. The dose of carbetocin (100 μ g 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 (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 μ g 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.

Analyses performed across trials: pooled and meta-analyses

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. For discussion of these two meta-analyses please see Attachment 2. The two papers are also discussed in the Delegate's *Overall conclusion and risk/benefit assessment, Clinical* below.

Safety

Studies providing safety data and patient exposure

Vaginal delivery

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 in Attachment 2.
- 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.

High-risk of PPH in vaginal and CS delivery

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).

Postmarketing data

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 fourteenth 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 the sponsor's carbetocin was approximately 1.7 million patients, and the estimated cumulative post-marketing exposure to the sponsor's carbetocin from the inflammatory bowel disease (IBD) was approximately 8.5 million patients. The exposure data were based on a single 100 µg IV dose of the sponsor's 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 erythaematosus, pulmonary hypertension and heart failure (NYHA class III).⁵ The sponsor comments that serious cardiovascular disorders are a contraindication for the use of the sponsor's carbetocin and therefore the drug had been administered off-label in this patient. However, a causal relationship between cardiac arrest and the sponsor's 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 adverse drug reactions (ADRs) associated with the sponsor's carbetocin reported cumulatively from the IBD to 30 June 2016 in the clinical trials in 440 patients. Cumulative serious ADRs associated with the sponsor's 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).

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

⁵New York Heart Association (NYHA) Functional Classification are as follows:

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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 Clinical questions in Attachment 2).

First round benefit-risk assessment

First round assessment of benefit-risk balance

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.

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.

Carbetocin versus oxytocin in emergency CS under regional anaesthesia

- The submission included 3 studies comparing the efficacy of carbetocin 100 µg IV to oxytocin 5 to 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 \geq 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 μ g 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.

Carbetocin versus oxytocin in women at high-risk of PPH

- The submission included 3 studies comparing carbetocin 100 μ g 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 (\geq 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 μ g 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.

Carbetocin versus oxytocin CS under general anaesthesia

- 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 μ g 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.

First round recommendation regarding authorisation

- 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
- 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.
- 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.
- 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.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

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 the first round evaluation.

Second round recommendation regarding authorisation

- 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.

VI. Pharmacovigilance findings

Risk management plan

Summary of risk management plan (RMP) evaluation⁶

The clinical evaluator requested an RMP for this product in the first round clinical evaluation report. The sponsor has submitted Core-RMP version 1.0 (31 May 2017; Data Lock Point (DLP) 31 December 2016) and Australian Specific Annex (ASA) version 1.0 (8 September 2017) in support of the extended indications.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (Table 7).

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	None	–	–	–	–
Important potential risks	Hypersensitivity including anaphylactic	Ü	–	Ü	Ü

⁶ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	reaction/ shock				
	Cardiac arrhythmias	Ü	-	Ü	Ü
Missing information	None	-	-	-	-

R = routine; A = additional

There are no additional pharmacovigilance activities proposed for the extension of indication. Routine pharmacovigilance only is considered acceptable as the product has been on the market in Australia since 2004.

There were additional risk minimisation activities proposed by the sponsor in the ASA. The sponsor is proposing a Dear Health care Provider (DHCP) letter be sent to inform healthcare professionals to inform them of the extension of indication and availability of the IM dosing route. The PI will be distributed with this letter.

New and outstanding recommendations from second round evaluation

The RMP and ASA were submitted as part of the sponsor's response to questions following the first round evaluation and have not been evaluated previously by the TGA.

The sponsor should address the following recommendations in a revised RMP to be submitted to the TGA:

The proposed Dear Health Care Professional letter to inform of the new indication and provide the PI to health professionals should be removed from the risk minimisation plan as it is not directed at any of the important safety concerns and is therefore not considered a risk minimisation activity.

Post second round evaluation update

The sponsor has agreed to remove the DHCP letter as requested and will update the RMP to reflect this in the future. There are no outstanding RMP issues for this submission.

Proposed wording for conditions of registration

No RMP condition of registration is recommended.

Other advice to the Delegate

It was noted that the Australian PI and corresponding CMI do not include any precautions or contraindications for use in those with renal or hepatic disease. This is listed as a contraindication in the United Kingdom (UK) Summary of Product Characteristics (SmPC). This inconsistency is raised for the Delegate's consideration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

This was a literature based submission (LBS). The search strategy had been approved by the TGA.

Many published references were submitted in support of this application. These are discussed below and detailed in Tables 2 to 4 above as well under section *References* in Attachment 2.

There were 13 publications: 7 relating to vaginal delivery, 3 related to emergency CS, 3 related to women at high risk of PPH. There were 2 published meta-analysis and systematic reviews. There were 2 PSUR covering the periods 1 July 2015 to 30 June 2016.

Pharmacology

There was very little data available regarding the PK and PD profile. The elimination half-life is around 40 minutes. Renal clearance is low.

The sponsor referred to a previously submitted Study 6.3.1 and literature reference of the PK characteristics of IV boluses of 20-800 µg and IM doses of 400 and 800 µg.

The PD effects of IM carbetocin have previously been described in Studies 6.3.4 and 6.3.3. In these studies, IV carbetocin had a time of onset 1.2 minutes, total duration of action 60 minutes; IM carbetocin had a time of onset of 1.9 minutes and a total duration of 119 minutes. However, the mean doses given were different; 49 µg IM and 15 µg IV. Thus it is unknown if these difference in PK are due to dose or route of administration.

No formal bioavailability studies were performed. Studies submitted suggest around 80% relative bioavailability for area under the concentration versus time curve (AUC) IM versus IV but less for peak plasma concentration (C_{max}).

Vaginal delivery

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, and Malaysia), 2 were conducted in the middle-east (Kuwait and Iran) and 1 was conducted in North Africa (Egypt).

The 7 studies included 798 women treated with Carbetocin and 792 women treated with an active control (177, Oxytocin; 615, Syntometrine). In 4 studies women with significant risk-factors for PPH were excluded (Leung et al., 2006; Su et al., 2009; Askar et al., 2011, Samimi et al., 2013), and 3 studies 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, a dose of 5 IU IM was used in Maged et al (2015) and a 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.

The primary efficacy outcome measure differed across the 7 studies. The primary outcome measure was additional uterotonic agents in 3 studies (Leung et al., 2006; Su et al., 2009; Boucher et al., 2004), 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 evaluator considered that the submitted data have satisfactorily established the efficacy of carbetocin 100 μ g 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 μ g 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 a dose of 5 IU IM and 10 IU IV. In addition, 1 study showed that carbetocin 100 μ g IM was more efficacious than a lower than approved dose of Syntometrine (5 IU oxytocin/0.2 mg ergometrine) 1 mL IM.

Delegate comment regarding NHMRC Grade Criteria⁷:

1. Seven RCT, Level II evidence. Risk of bias high due to subjective efficacy outcomes, variable comparators, no information about anaesthesia. 798 women received carbetocin.
2. Consistent results showing efficacy to prevent PPH.
3. Accepting the evidence to support registration and allow use with vaginal delivery is a relatively large change, as the patient group has more variable risk factors for PPH than those generally low risk women with elective CS.
4. The patient population and setting for many of the studies was different to Australia.

Delivery by caesarean section

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 to 20 IU IV (El Behery et al., 2016; Razali et al., 2016; Whigham et al., 2016). 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).

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 to 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

⁷ NHMRC Evidence hierarchy designations of 'levels of evidence' according to type of research question

Level	Intervention ⁸	Diagnostic accuracy ⁹	Prognosis	Aetiology ¹⁰	Screening Intervention
I ¹¹	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard, ¹² among consecutive persons with a defined clinical presentation ¹³	A prospective cohort study ¹⁴	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard, ¹² among non-consecutive persons with a defined clinical presentation ¹³	All or none ¹⁵	All or none ¹⁵	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> • Non-randomised, experimental trial¹⁶ • Cohort study • Case-control study • Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> • Historical control study • Two or more single arm study¹⁷ • Interrupted time series without a parallel control group 	Diagnostic case-control study ¹⁸	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹⁹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

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.

The evaluator considered that the results of the three studies have adequately demonstrated that carbetocin 100 μ g 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.

Delegate comment regarding NHMRC Grade Criteria:

1. Grade II evidence; 3 RCT with one in Australia. 425 women received carbetocin. High risk of bias due to subjection efficacy outcomes.
2. Study results are consistent.
3. Accepting the evidence would be small shift in the approved indication and practice.
4. Uncertain how well the patient population matches Australia and the external applicability.

High risk PPH

The submission included 3 published studies 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 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 μ g IV in a total of 101 women to oxytocin 20 IU IV in a total of 149 women. The dose of carbetocin (100 μ g 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.

The evaluator 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.

Delegate comment regarding NHMRC Grade Criteria:

1. Level II evidence from 3 clinical studies. High risk of bias as not all risk factors for PPH were examined, the main efficacy parameters were not those of clinical importance.
2. Consistent results.
3. Accepting the results would be a change in practice.
4. Poor generalisability of results as not all risk factors for PPH were examined and studies were performed in a different clinical setting.

Meta-analysis

Two meta-analyses were included. Not all of the clinical studies of the meta-analysis were included in the dossier; there is reasonable justification for this.

Both meta-analysis included studies with vaginal delivery and caesarean section and included women with no and some risk factors for PPH.

Jin et al. Carbetocin for the prevention of postpartum haemorrhage: a systematic review and meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med, Early Online: 1-8

The relative risk and the 95% confidence intervals are summarised in Table 8 below.

Table 8: Relative risks and 95% CI

	Caesarean section		Vaginal delivery	
	Carbetocin versus oxytocin	Carbetocin versus Syntometrine	Carbetocin versus oxytocin	Carbetocin versus Syntometrine
PPH	0.66 (0.42-10.6)		0.95(0.43-2.09)	0.93 (0.46-1.91)

Caesarean section		Vaginal delivery		
Severe PPH	0.91 (0.91-2.15)			0.71 (0.14-3.61)
Need for uterotronics	0.68 (0.55-0.84)		0.95(0.43-2.09)	0.83(0.60-1.15)

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.

Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012;4

The pooled data of four studies comparing the use of carbetocin and oxytocin in women who delivered by CS showed that the risk of any PPH was similar and low in both the group receiving carbetocin (incidence = 23/597) and the group receiving oxytocin (incidence = 35/598, RR 0.66; 95% (CI) 0.42 to 1.06; four trials; 1195 women). For women who underwent vaginal delivery, again the risk of having PPH was similar in both the oxytocin and carbetocin groups (RR 0.95, 95% CI 0.43 to 2.09; one trial (Boucher et al 2004), 131 women).

The pooled data of four studies comparing the use of carbetocin and Syntometrine showed no statistically significant difference between the two interventions (RR 1.00; 95% CI 0.48 to 2.07; four trials, 1030 women) in prevention of PPH after vaginal deliveries, with low incidence of PPH >500 mL being reported in both groups.

The authors conclude that for women, who undergo CS, carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotronics 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.

Safety

Vaginal delivery

Most common AEs are headache and leucocytosis with oxytocin and Syntometrine. Tachycardia is more common with carbetocin compared with 5IU oxytocin. Carbetocin has less nausea, vomiting, sweating than Syntometrine but more tachycardia. There was more hypertension with Syntometrine.

Caesarean section

The safety of carbetocin versus oxytocin is difficult to assess from the submitted studies due to a number of different factors including different dose of oxytocin used than is used in clinical practice in Australia, confounding effects of uterotronics, small number of serious AEs and limited reporting of data in papers.

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 sponsor sent in two PSURs covering the period from 1 July 2013 to 30 June 2015. The international birth data for carbetocin was June 1997. During the reporting period, the estimated post marketing exposure was 1.7 million patients. Overall, the cumulative clinical trial exposure sponsored by this sponsor was 440 patients, and cumulative post market exposure 8.5 million. 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 (rate 0.5 per 1 million). 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 erythaematosus, pulmonary hypertension and heart failure (NYHA class III). 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 (rate 2 per 100 000 exposed) 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 ($n = 6$).

There was no safety data relating to the effect on breast feeding.

Uterine tone and GA

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, the use of carbetocin with general anaesthesia is not expected to differ from oxytocin.

Risk management plan

See Section *Pharmacovigilance findings* above.

Risk-benefit analysis

Delegate's considerations

Literature Based Submissions (LBS)

This approval pathway was developed by the TGA to enable sponsors of products that had been grandfathered onto the TGA to update their product information to be in line with current local or international clinical practice.⁸

Carbetocin was first approved by the TGA in 2003, it was not grandfathered. It is approved for use in caesarean section (elective and emergency) under spinal or epidural aesthetic (not general) in the EU and Switzerland. There are no clinical guidelines or consensus statements from Australia or internationally that support its use with vaginal delivery or caesarean section.

The sponsor has followed the guidelines for LBS but the study quality is poor. There are no large RCTs with appropriate endpoints in a population comparable to that in Australia.

The sponsor's clinical expert for this submission had a pharmacy background and there are no supportive statements from obstetricians or anaesthetists.

⁸Harris, G. Literature-based marketing applications for pharmaceuticals in Australia. International Journal of Pharmaceutical Medicine. 2000, 14: 207-212

Quality of data

The available studies demonstrate that carbetocin has similar efficacy as oxytocin and Syntometrine for the prevention of PPH in vaginal delivery and caesarean section. However, the quality for data is considered to be of a very poor for a number of reasons:

1. The studies were designed as superiority studies. However, the most appropriate study design would have been an equivalence or non-inferiority study.
2. Very few studies had a discussion about the power of the study. It is likely that some of the studies were underpowered for superiority. A positive result for the efficacy endpoints was reached regardless of this. However the studies were not of the appropriate design (should have been non inferiority).
3. The primary endpoints chosen were prone to error and bias. An estimation of blood loss is prone to error and need for additional oxytocin in subjective. A fall in haemoglobin (Hb) may be also affected by haemodilution or concentration. The most important endpoint would be major PPH and need for blood transfusion. The use of this as a primary efficacy endpoint would have meant that the studies would need to be much larger.
4. There was one study in Canada and one in Australia. All other studies were performed in developing countries where the level of obstetric care may be less than seen in Australia. This has a major impact on external extrapolation.
5. Potential for publication bias with literature reviews
6. Limited ability to review safety from published studies. It is unknown how closely adverse events were monitored and reported. And of particular note, it is unknown how long after delivery the women for studied for.
7. The results of the meta-analysis need to be interpreted with caution due to the large heterogeneity.

The evidence for high risk PPH is very limited; many risk factors have not been adequately addressed with the data submitted. The Delegate would not support its use for high risk PPH.

There was only one submitted study under GA. It appears that agents used for general anaesthesia cause uterine relaxation but do not affect binding to the oxytocin receptor. Oxytocin is used under GA and carbetocin has similar structure and pharmacodynamic effects.

What standard of evidence do the TGA accept?

The main question of this application relates to the level of evidence the TGA is willing to accept to extend an indication for medicine which has been available for use for 20 years internationally.

The evidence submitted is poor quality but supports efficacy for use after vaginal delivery and caesarean section.

But it is also important to note that there is no unmet need for these indications. A shortage of oxytocin is unlikely as there are many different manufacturers of oxytocin. Oxytocin will continue to be an essential medicine in an obstetric setting as it is used also for induction of labour and for treatment of PPH.

The risks of carbetocin are known; they are similar to oxytocin but with a greater risk of tachycardia and an additional concern about safety to the foetus if accidentally given before delivery of the infant. Carbetocin was better tolerated than Syntocinon. The deaths and arrhythmias in the PSURs are noted but very rare. Increased availability of carbetocin in

an obstetric setting may increase the risk of adverse events from medication errors if it is confused for oxytocin.

The decision to be made by the Delegate under section 25 of the Act is '*whether the quality, safety and efficacy of the goods for the purpose for which they are to be used have been satisfactorily established*'.

If the Delegate was to consider the evidence alone for emergency caesarean section, the Delegate does not consider the data to be robust nor sufficiently relevant for an Australian setting. However, if the Delegate was to consider the evidence in the context of its current approval for elective caesarean sections its approval by similar regulators internationally and availability of safety data, then the overall benefit/risk balance would be positive.

In relation to the use of carbetocin with vaginal delivery, the Delegate does not consider the evidence alone to be robust enough. However if the Delegate was to take a more pragmatic stance about whether carbetocin *could* be used in clinical practice and extrapolate from the current use and the potential differences between risk of PPH with caesarean and vaginal delivery and the evidence from the RCT then the benefit/risk balance is positive. The potential risks could be mitigated by labelling.

In relation to use under general anaesthetic, there is insufficient evidence to support its use. Patients who require a caesarean section under general anaesthetic are generally more high risk patients and therefore the risk/benefit is less favourable.

The Delegate does not consider that there is sufficient evidence to support use in patients at high risk of PPH. Oxytocin should be readily available in these patients.

Questions for the sponsor

1. Please comment on whether the same formulation of carbetocin as approved in Australia was used in the submitted studies.
2. Please clarify if carbetocin has been studied in patients with placental abnormalities or chorioamnionitis, prolonged labour or where there has been ante-partum haemorrhage.
3. Please provide a comment from the Royal Australian College of Obstetrics and Gynaecology (RANZCOG) regarding the use of carbetocin in vaginal delivery, caesarean section, general anaesthesia and in patients with high risk PPH
4. Please compare the labelling and vials of oxytocin to carbetocin and discuss the potential for medication mix ups.

Summary of delegate's issues

Carbetocin was approved for use for elective caesarean section under spinal anaesthesia in 2003. Its use after emergency CS and high risk PPH was not approved then due to the evidence.

The sponsor has now submitted a literature based submission to support its use. The evidence in relation to its use with vaginal delivery and emergency caesarean section is positive. However the quality of evidence is poor.

Internationally, carbetocin is approved in EU and Switzerland for use after all CS under regional anaesthesia. However the UK, USA and Europe have not approved its use after vaginal delivery. No country has approved its use with GA. The RANZCOG guidelines for PPH were written in 2009 and oxytocin and Syntometrine are the preferred drugs.

There is one trial on its use with GA. Oxytocin (a similar drug) is used in general anaesthetic, and there is no clinical trials for this either.

There is evidence to support use after high risk PPH but includes only some risk factors for high risk PPH.

Proposed action

The Delegate is unsure if the application for carbetocin for use after vaginal delivery or emergency caesarean section should be approved for registration.

The Delegate considers that carbetocin should not be approved for use in women with high risk PPH.

Request for ACPM advice

1. Please comment on the whether the evidence submitted is sufficient to support efficacy of carbetocin for the prevention of PPH in Australia.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Carbetocin is an oxytocin analogue with prolonged action for the prevention of PPH. Duratocin was first registered in 2004 in Australia (AU), and since launch, the sponsor has received frequent enquiries from Australian clinicians querying the relatively confined indication. In particular, clinicians have observed that carbetocin is used overseas following delivery by emergency CS and many have stated that they also find it effective and efficient in this indication (albeit off-label in Australia). They have also questioned/proposed its utility following vaginal delivery (VD).

In response to this clinical need, the sponsor sought advice from the TGA as to whether an expansion of the indications for Duratocin would be possible based on the extensive body of evidence available in the published scientific literature. In a pre-submission meeting with the TGA in December 2015, agreement was obtained from the TGA Delegate to proceed on this basis.

The indication initially proposed with this submission is shown below with changes from the current approved indications marked:

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.

With this pre Advisory Committee on Medicines (ACM) response, the sponsor seeks approval for the indication below, revised from that originally proposed to take into consideration comments from the Delegate and the clinical evaluator:

Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarean section or vaginal delivery. Duratocin must be administered after delivery of the infant.

In line with the proposed changes to the indications above, the Dosage and administration of the draft PI has been modified accordingly.

Delegate's assessment, issues identified and advice sought from ACM

The sponsor notes the Delegate's pre-ACM preliminary assessment as:

- The Delegate is unsure if the application for carbetocin for use after vaginal delivery or emergency caesarean section should be approved for registration.
- The Delegate considers that carbetocin should not be approved for use in women with high risk PPH.

Accordingly, the Delegate is seeking advice from the ACM to:

1. *Please comment on whether the evidence submitted is sufficient to support efficacy of carbetocin for prevention of PPH in Australia and to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

With this response, the sponsor focuses on the circumstances that prompted the preparation of the submission, then the quality of the evidence and then the specific issues raised for each of the patient populations, that is, a) emergency CS, b) VD, and c) high risk of PPH, including those who undergo general anaesthesia (GA). Although this application is seeking expansion of the use of carbetocin to multiple new populations, the sponsor respectfully requests the committee to consider the individual patient populations independently whilst keeping in mind the overall safety profile of the product and the consistency of the results across the various patient groups.

Submission background

As stated above, the sponsor has received a large number of enquiries from Australian clinicians for information on the use of carbetocin following emergency CS delivery (as approved in other major markets), and its use following VD. Uterotonics represent the first-line approach to the prevention of uterine atony and PPH following delivery by CS or VD, and oxytocin is commonly used. The sponsor considers that the need for a safe and well tolerated prophylactic oxytocic agent that reduces the need for additional uterotonics following CS is met by carbetocin as supported by the published literature.

In addition, the expert statement supports the proposed indications and the expert considers carbetocin to provide a superior alternative to ongoing oxytocin infusion for women delivering via CS in reducing the risk of PPH and the need for secondary treatments of PPH. In addition, the expert expresses confidence that carbetocin has a place following VD and the view that the room temperature stable formulation of carbetocin could provide an additional clinical advantage over oxytocin (see section *Evidence to Support Efficacy of Carbetocin*). Since 2009, the expert has been utilising carbetocin for all CS deliveries both under regional and GA and cites the results of the expert's retrospective cohort study, which align with the findings of the submitted literature in that carbetocin is associated with a significant reduction in the need for additional uterotonics versus oxytocin. No differences were reported between patients delivering under regional or GA.

With regards to the international regulatory status of carbetocin, the sponsor wishes to clarify that, in contrast to the Delegate's comment, use in all CS under regional anaesthesia (that is, including emergency CS) was approved in Canada in December 2016, consistent with the long-standing indication in the EU and Switzerland. Furthermore, although carbetocin is not indicated for vaginal use in Canada, the Canadian clinical guidelines recommend:⁹

For women delivering vaginally with 1 risk factor for PPH, carbetocin 100 micrograms IM decreases the need for uterine massage to prevent PPH when compared with continuous infusion of oxytocin

⁹SOGC 2009 Active Management of the Third Stage of Labour: Prevention & Treatment of PPH

The South Australian and Queensland guidelines;¹⁰ also present evidence for the use of carbetocin following both vaginal and caesarean birth. Consideration should also be given to the practice of obstetrics which often follows local guidelines (informed by the literature).

By contrast, broader recommendations such as those approved by RANZCOG take longer to update and would generally reflect approved indications only.

Quality of evidence and LBS

In the absence of additional completed company sponsored clinical studies for the product and with the observation of expanding clinical practice and a body of published evidence supporting use beyond the currently approved indications in Australia, the sponsor, following consultation with TGA, submitted this LBS. The Delegate has questioned whether the level of evidence submitted in support of the extended indications is acceptable.

Current TGA guidance relating to LBS supports the use of such submissions for products that have been marketed for > 10 years in Australia to extend clinical use. In accordance with TGA guidelines and in consultation with the TGA Delegate and TGA librarian, a systematic search of literature was conducted to identify high quality publications that were relevant to the proposed indications, focussing specifically on randomised, double blind, controlled trials, analysed on an intention-to-treat basis, or a systematic review involving a number of trials. Due to the large number of publications relating to the use of carbetocin in prevention of PPH, it was agreed that the search strategy be limited to only publications presenting the highest quality evidence according to National Health and Medical Research Council (NHMRC) criteria (that is, publications of randomised controlled trials and meta-analyses of such trials).

While it is acknowledged that literature publications do not report the same level of detail as company conducted clinical trial reports included in traditional regulatory submissions, all the studies submitted with the application are ranked according to the TGA adopted NHMRC evidence hierarchy as either Level I (meta-analyses) or Level II (individual, appropriately designed randomized controlled trials).

As these represent the highest levels of evidence in the TGA's hierarchy, the submitted data when viewed in the context of an LBS, should not be considered 'poor'.

The sponsor acknowledges that the LBS registration pathway does create challenges for applicants and the TGA in that the sponsor is not able to control the design of submitted studies. Consequently, the Delegate's criticisms regarding the choice of statistical study design, the endpoints chosen or the level of safety data reported in the publications cannot be addressed. However, while there is limited safety data available from published studies, none of the studies reported any safety concerns that differed to the established safety profile of carbetocin since its first international approval in 1997.

It is also acknowledged that there is potential for bias with literature publications and this is partly addressed by the two meta-analyses submitted where included studies were critically assessed using the recommended approach in the Cochrane handbook for systematic reviews of interventions.¹¹ Although it is acknowledged that the submitted meta-analyses included a heterogeneous mix of studies and pre-date many of the individual studies included in the application, the analyses provide overall supportive evidence for the use of carbetocin following CS and VD.

¹⁰SA Health 2016 Oxytocin: Prophylaxis for Third Stage Management & PPH; Queensland Health 2017 Primary PPH

¹¹ Higgins 2011 Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0

Evidence to support efficacy of carbetocin

The Delegate seeks the committee's advice on 'whether the evidence submitted is sufficient to support efficacy of carbetocin for the prevention of PPH in Australia'.

PPH is common in Australia, with an incidence of between 5 to 15% and remains a major, and in fact, an increasing and underreported cause of both maternal mortality and morbidity within Australia and New Zealand.^{12,13,14} Clinical guidelines recommend the active management of the third stage of labour for all pregnant women to reduce the risk of PPH and the need for blood transfusion, with the use of oxytocics recommended following both VD and CS.¹⁵ With the timely application of recommended clinical practices, in particular the use of uterotronics during the management of the third stage of labour, PPH may be the most preventable cause of maternal mortality.

The approval of carbetocin for use following emergency CS and VD in Australia would provide a safe and effective therapeutic option for reducing the risk of PPH and the need for additional uterotronics. Carbetocin has a rapid onset and longer duration of action in comparison to oxytocin. As such, it preserves uterine tone for an extended time so that the need for repeated uterotronics is reduced without an increase in blood loss. It also limits the need for an IV infusion. Furthermore, as described in the expert statement, carbetocin provides practical advantages in the clinical setting over oxytocin in that it does not require refrigeration and as such decreases the risk associated with temperature excursions (with its recommended storage below 30°C) and the impact on product efficacy. This room temperature formulation facilitates transportation and access to an effective uterotonic across a range of clinical and geographic settings.

The safety profile of carbetocin is comparable to that of oxytocin and superior to that of Syntometrine.¹⁶ Effects on the cardiovascular system, hypotension, tachycardia, are addressed in the proposed PI and cardiac arrhythmias is listed as an important potential risk in the risk management plan.

The sponsor supports the Delegate's pragmatic stance to consider the application in the context of the currently approved carbetocin indication for elective CS and that the overall benefit-risk balance remains positive for use following emergency CS and VD. The sponsor agrees with the Delegate that any potential risks can be mitigated by labelling. However, in contrast to the Delegate's view, the sponsor considers that there is also sufficient evidence to support the use of carbetocin in patients undergoing GA or at high risk of PPH. It is important to note that with regards to use in these patient populations, the sponsor is not seeking specific indications for these patients. Instead, it is proposed that the precautionary statements in the PI be strengthened to better reflect the data that is now available and in recognition of the Delegate's concerns:

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

¹²Ford et al, 2012. Hospital data reporting on PPH: under-estimates recurrence and over-estimates the contribution of uterine atony. *Maternal and child health journal*, 16(7), pp.1542-1548.

¹³Roberts et al, 2009. Population rates of haemorrhage and transfusions among obstetric patients in NSW: a short communication. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 49(3), pp.296-298.

¹⁴Knight et al, Trends in PPH in high resource countries: a review and recommendations from the International PPH Collaborative Group.' *BMC pregnancy and childbirth* 9.1 (2009): 55.

¹⁵RANZCOG 2017 Management of PPH, RCOG 2011 Prevention & Management of PPH, SOGC 2009 Active Management of the Third Stage of Labour: Prevention & Treatment of PPH, SA Health 2016 Oxytocin: Prophylaxis for Third Stage Management & PPH

¹⁶Oxytocin 5 I.U. + ergometrine 500 µg / mL

The sponsor notes that the clinical evaluator recommends approval of carbetocin (second round evaluation report) to prevent uterine atony and excessive bleeding following delivery of the infant following emergency CS, VD and in women at high-risk of PPH and including those undergoing GA.

Emergency caesarean section

As indicated by the Delegate carbetocin is approved in the EU and Switzerland for use after all CS under regional anaesthesia. It should be noted that Canada received approval in December 2016 for the same indication. The sponsor considers that the benefit-risk profile for the use of carbetocin following emergency CS is favourable. Furthermore, the expansion of the use of carbetocin to this patient group within Australia represents only a small shift in clinical practice and, as indicated in the expert statement, carbetocin is already routinely used in some clinical settings, both under regional/spinal and GA.

Three recently published studies;¹⁷ as discussed by the Delegate, provided efficacy data in 849 women delivering via emergency CS under regional anaesthesia (425 carbetocin and 424 oxytocin) and showed comparable or better efficacy of carbetocin 100 µg IV versus oxytocin. Fewer subjects receiving carbetocin required additional oxytocic intervention or uterine massage (where assessed), compared to subjects receiving oxytocin, while blood loss was similar across treatment groups. The reduced need for additional oxytocics was thus not associated with an increase in blood loss. The adverse event profile in patients receiving carbetocin in these studies was similar to the established safety profile of patients undergoing elective CS. Supportive evidence on the use of carbetocin in CS can be found in the 2 meta-analyses provided with the application.^{18,19} Although the CS population included patients undergoing elective and emergency procedures, use of carbetocin was associated with a statistically significant reduction in the need for additional uterotronics compared to oxytocin.

The Delegate is uncertain how well the patient population matches Australia and the external applicability. The Whigham study was conducted in Australia and thus the results can be clearly related to the anticipated outcomes in the Australian population. When the findings from the 3 studies are combined with the fact that carbetocin is approved for use following emergency CS in major markets (EU, Canada and Switzerland), the sponsor considers that the use of carbetocin following emergency CS in Australia would align Australia with international practice.

The sponsor also notes, as highlighted by the Delegate that the clinical evaluator considered that the results from the submitted studies '*have adequately demonstrated that carbetocin 100 µg IV and oxytocin 5-20 IU IV are comparable as regards prevention of uterine atony and excessive bleeding following emergency CS under regional anaesthesia in women with risk factors for PPH.*'

Vaginal delivery

Seven randomised controlled studies were included in the submission to support the safety and efficacy of carbetocin IM in women following vaginal delivery. While it is acknowledged that some of the study locations are not directly comparable to the Australia setting, it is important to observe that the outcomes across these jurisdictions were consistent. Consequently, there is no reason to consider that the results obtained in this diverse setting would not be representative of the performance of the product in the Australia patient population.

¹⁷El Behery et al 2016, Whigham et al 2016 and Razali et al 2016. See Table 3 above for details of these references.

¹⁸Jin et al. Carbetocin for the prevention of postpartum haemorrhage: a systematic review and meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med, Early Online: 1-8

¹⁹Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012;4. CD005457.

As noted by the Delegate, whilst the primary efficacy outcome measure differed across the studies, information relating to the volume of blood lost and the incidence of women with blood loss ≥ 500 mL were reported in 6 of the 7 studies. Other primary outcomes included the use of additional uterotonic agents and the reduction in haemoglobin level at 24 or 48 h after delivery. Results were consistent across the 7 studies to establish the efficacy of carbetocin and demonstrate that carbetocin provides a safe and effective option following VD. This is consistent with the evaluator's comment '*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*'.

High risk PPH and general anaesthesia

As summarised in the by the Delegate, three studies;²⁰ in women at high risk of PPH delivering either vaginally or via CS demonstrated that the effects of carbetocin 100 µg IV are comparable to those of oxytocin 20 IU IV for the prevention of uterine atony and excessive blood loss.

Women with severe preeclampsia and grand multiparous deliveries are considered to be at high risk of PPH and the results obtained indicate that carbetocin is an appropriate treatment option in these patients. Whilst it is acknowledged that not all risk factors for PPH were examined, these data provide reassurance that the performance of carbetocin in patients at high risk of PPH is broadly consistent with the data collected in low-to-moderate risk subjects delivering vaginally or via emergency CS. Similarly, the results investigating the performance of carbetocin in patients undergoing CS under GA are also consistent with those in CS patients delivering under spinal anaesthesia. The sponsor notes that the clinical evaluator considered that the '*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*'.

As described in the sponsor's response to the TGA's questions, the use of GAs during CS may alter the uterine tone of women. However, oxytocin (despite the absence of formal studies) is successfully used in this setting and since the GA is not known to alter the binding characteristics of oxytocin receptors, the use of carbetocin with GA is not expected to differ from oxytocin and therefore carbetocin is considered to be a safe and effective alternative to oxytocin in this setting.

To mitigate against any potential risks associated with this patient group and in recognition of the Delegate's concerns, the sponsor proposes to include appropriate precautions in the PI related to patients at high risk and those undergoing GA. In addition, the ASA to the RMP is to be revised to include, as missing information, CS under GA and use in conditions of the placenta, for example abruptions and placenta praevia.

Response to questions for the sponsor

1. *Please comment on whether the same formulation of carbetocin as approved in Australia was used in the submitted studies.*

As discussed in the sponsor's response to questions, the majority of the studies used a formulation of carbetocin obtained from various sponsor affiliates. It has been confirmed that when each of these studies were conducted, only one formulation of the sponsor's carbetocin was available internationally, that is, the original formulation of Duratocin that required refrigeration. This formulation was replaced very recently in Australia (approved April 2015) and internationally, with an adjusted room temperature stable formulation. Both formulations are simple aqueous injections administered parenterally and the available data confirms that the formulations have similar pharmacokinetic profiles.

²⁰ Reyes 2011, Reyes et al 2011, Fahmy et al 2016 (see Table 4 above for details).

2. *Please clarify if carbetocin has been studied in patients with placental abnormalities or chorioamnionitis, prolonged labour or where there has been ante-partum haemorrhage.*

There are limited data available on the use of carbetocin in patients with placental abnormalities or chorioamnionitis, prolonged labour or where there has been ante-partum haemorrhage. Support for the use of carbetocin in such patients is evident within the South Australian health setting, as discussed by the sponsor's expert.

3. *Please provide a comment from the RANZCOG regarding the use of carbetocin in vaginal delivery, caesarean section, general anaesthesia and in patients with high risk PPH.*

Given the time constraints involved with the preparation of a pre-ACM response, especially during early January, it was not possible to provide a comment from RANZCOG. However, the sponsor has been in communication with a number of experts in the field of Obstetrics and Gynaecology and the sponsor has provided an Expert Statement.

4. *Please compare the labelling and vials of oxytocin to carbetocin and discuss the potential for medication mix ups.*

Carbetocin injection is available as vials with the product details clearly labelled in line with TGA requirements. The potential for confusion between carbetocin and oxytocin is limited as the labelling and presentation are quite distinct with little risk of look-a-like/sound-a-like issues. Firstly, carbetocin is presented in clear vials with green caps stored at below 30°C (room temperature), whereas oxytocin is available as ampoules requiring storage at 2 to 8°C (refrigeration). Secondly, the strengths are clearly labelled, carbetocin 100 µg/mL and oxytocin 5 IU/mL respectively. In addition, the colour scheme, font type and general look of the labels differ to minimise confusion.

Comments on RMP

Should include missing information around the use with caesarean section under GA; the data submitted to support this included only one literature reference; use in conditions of the placenta for example, abruptions, placenta praevia; should include potential risk of foetal distress if accidentally used before delivery of the infant.

The sponsor proposes to revise the RMP ASA to include, as missing information, CS section under GA and use in conditions of the placenta such as abruptions and placenta praevia. The sponsor does not consider '*foetal distress if accidentally used before delivery of the infant*' to be a potential risk as the PI clearly states in several sections that the product is to be administered following delivery of the infant and there is no change proposed to the current approved timing of administration of carbetocin.

Conclusions

The sponsor seeks approval to extend the use of carbetocin to include the prevention of uterine atony and excessive bleeding following delivery of the infant by emergency CS and VD, including women with high risk PPH and those undergoing GA. Precautionary statements in the proposed PI have been strengthened to address the Delegate's concerns and to better reflect the data available.

Extensive clinical data supports the use of oxytocic agents in the active management of the third stage of labour. However, the current standard, oxytocin, has a short half-life which often necessitates the use of additional administration of oxytocic or other interventions. The need for a safe and well tolerated prophylactic oxytocic agent that reduces the need for additional uterotronics following CS is met by carbetocin, as it preserves uterine tone for an extended time so that repeated administration is no longer necessary. As evident by the number of enquiries received by the sponsor from clinicians, and support by the expert, there is local clinician support for the extended use of carbetocin as it provides a clinical and practical advantage over oxytocin formulations (see *Evidence to Support Efficacy of Carbetocin* above).

The submitted data, while acknowledging the limitations inherent in the LBS pathway, provide consistent and robust (Level I and Level II) evidence that carbetocin is safe and effective in prevention of PPH in patients delivering via emergency CS and vaginally. The studies were conducted in a diverse patient population and whilst the standard of care may differ, the medications were administered in the same manner at the same time point following delivery of the infant. Given the consistency of the results, there is no reason to anticipate that the data are not applicable to the Australian population. The results are also consistent with the data obtained in the current indication, providing further reassurance of the overall risk/benefit profile.

The sponsor supports the clinical evaluator's recommendation for approval of carbetocin to prevent uterine atony and excessive bleeding after delivery of the infant via emergency CS or VD, and in women at high-risk of PPH, including those undergoing GA.

Advisory Committee Considerations²¹

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM, taking into account the submitted evidence of efficacy and safety, provided advice to the Delegate that considered Duratocin solution for injection in a rubber top vial containing 100 µg/mL of carbetocin to have an overall positive benefit-risk profile for the extension of indication.

The approved indication for Duratocin 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 for Duratocin is:

Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarian section or vaginal delivery. Duratocin must be administered after delivery of the infant.

In providing this advice the ACM noted that:

- This was a literature based application.
- No international regulator had approved this extension of indication.
- There was limited available for its use under general anaesthesia, or for use in high risk of post-partum haemorrhage (PPH), Duratocin appeared to have lower potency but longer duration of action than oxytocin. The adverse reactions appear to be similar to oxytocin.

²¹ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.

The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Please comment on the whether the evidence submitted is sufficient to support efficacy of carbetocin for the prevention of PPH in Australia.*

The ACM was of the view that the evidence submitted was sufficient to support the efficacy of carbetocin for the prevention of PPH in Australia.

The ACM did not express concern over the use of carbetocin after vaginal delivery.

2. *The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACM considered the lack of data for its use in high risk PPH, however, it was noted that this may be an area for Pharmacovigilance activities.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Duratocin carbetocin 100 microgram/mL solution for injection vial AUST R 233671, indicated for:

*Duratocin is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by emergency caesarean section or vaginal delivery.
Duratocin must be administered after delivery of the infant.*

Specific conditions of registration applying to these goods

Periodic Safety Update Reports (PSURs) that include the issues identified in the Australian Specific Annex (ASA) are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. The PSUR should include information about use in Australia, with the following table:

	Major PPH (> 500ml)	Blood transfusion	Maternal death
Elective Caesarean			
Emergency caesarean			
General anaesthesia			
Placental abnormalities			
Prolonged labour			

Attachment 1. Product Information

The PI for Duratocin approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au>