South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Obstetrics

MEDICINE REVIEW:

1. Executive Summary

Date: 22 January 2019
Medicine (INN): Carbetocin room temperature stable (rts) formulation
Medicine (ATC): H01BB03
Indication (ICD10 code): Postpartum haemorrhage (O72.0-3)
Patient population: Pregnant women with postpartum haemorrhage (PPH)
Prevalence of condition: Prophylaxis required for all pregnant women – approximately 1.2 million births per year.
Level of Care: Primary Health Care; Secondary level
Prescriber Level: Nurse prescriber, doctor
Current standard of Care: Oxytocin, oxytocin/ergometrine
Efficacy estimates: (preferably NNT)

1. PPH ≥500 ml

Vaginal delivery – Compared to oxytocin	*Caeserean section – Compared to oxytocin*
• **Ergometrine + oxytocin: NNT 31 (27 to 39)**	• **Ergometrine + oxytocin: NNT 4.3 (4.31 to 4.35) = 5**
• Carbetocin: not statistically significant	• Carbetocin: not statistically significant
• **Misoprostol + oxytocin: NNT 36 (32 to 67)**	• **Misoprostol + oxytocin: NNT 5 (4.8 to 5.6)**

2. PPH ≥1000 ml

Vaginal delivery – Compared to oxytocin	*Caeserean section – Compared to oxytocin*
• **Ergometrine + oxytocin: NNT 125 (84 to 200)**	• **Ergometrine + oxytocin: NNT 31.3 (29.4 to 31.3) = 32**
• Carbetocin: not statistically significant	• Carbetocin: not statistically significant
• Misoprostol + oxytocin: not statistically significant	• Misoprostol + oxytocin: not statistically significant

(Gallos et al, 2018)

Carbetocin shown to be comparable to oxytocin in reducing PPH (either ≥500 ml or ≥1000 ml) and for the need of additional uterotonics for reducing blood loss. Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias.

Combination therapy ergometrine with oxytocin shown to be superior to oxytocin in reducing PPH (either ≥500 ml or ≥1000 ml) that substantiates the current treatment regimen in the Standard Treatment Guidelines that recommends oxytocin, and if no response, add ergometrine.

No data showing a meaningful difference in maternal and neonatal mortality and severe morbidity; or the need for blood transfusions.

Carbetocin may be considered as an alternative to oxytocin for PPH, pending price parity and availability for consistent access in South Africa.

Motivator/reviewer name(s): TD Leong, E Bera, GS Gebhardt
PTC affiliation: E Bera – Gauteng Provincial PTC

2. Name of author(s)/motivator(s)

Primary reviewer:

- TD Leong

Secondary reviewers:

- E Bera, GS Gebhardt

3. Author affiliation and conflict of interest details

Primary reviewers:

- *TD Leong:* National Department of Health, Essential Drugs Programme; Secreteriat to the Adult Hospital Level Committee (2017-2020); No conflict of interests declared.

Secondary reviewers:

- *E Bera:* Department of Obstetrics & Gynaecology, University of the Witwatersrand; Adult Hospital Level Committee (2017-2020); No conflict of interests declared.
- *GS Gebhardt:* Department of Obstetrics & Gynaecology, University of Stellenbosch; Adult Hospital Level Committee (2017-2020); No conflict of interests declared.

4. Introduction/ Background

Postpartum haemorrhage (PPH), blood loss greater than 500 mL following delivery is the leading cause of maternal mortality worldwide (WHO, 2012). The STGs and EML recommends oxytocin for the prevention of postpartum haemorrhage (PPH). Compared with the combination of ergometrine/oxytocin, it is associated with less frequent nausea, vomiting & hypertension. However, where PPH is not controlled it is recommended that ergometrine be added. There are concerns regarding the erratic supply of oxytocin; and ergometrine is only available as combination product oxytocin/ergometrine. An external comment was received from a specialist anaesthesiologist from Limpopo, motivating for the consideration of long-acting carbetocin. The rationale provided was that combination product oxytocin/ergometrine is administered intramuscularly, and the dose may not be appropriate for the required indication; carbetocin is long-acting and use thereof may improve post-operative care. Additionally, it was motivated that including carbetocin to the EML would "improve post-operative care" that is "currently lacking".

Thus, this evidence review was undertaken to explore the possibility of considering carbetocin for inclusion to the EML; noting the erratic supply of oxytocin and that medication, alone, would not be able to correct the service delivery challenges. And, that carbetocin room temperature stable (rts) formulation is heat stable and has a longer duration of action.

5. Purpose/Objective i.e. PICO question

-P: Pregnant women at delivery
-I: Carbetocin
-C: Oxytocin
-O: Prevention of postpartum haemorrhage

6. Methods:

a. Data sources

i. *Cochrane Library*
- Search strategy:

‘ "post-partum haemorrhage" in Title Abstract Keyword AND oxytocin in Title Abstract Keyword AND carbetocin in Title Abstract Keyword OR uterotonic in Title Abstract Keyword - in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)'

25 Cochrane reviews and 1 Cochrane protocol were retrieved; of which 1 Cochrane review (Gallos et al, 2018) was reviewed as other literature was not relevant to the PICO question.

ii. *EMBASE*

- Search strategy:

'pregnant women' AND ('carbetocin'/exp OR '1 butyric acid 2 [3 (4 methoxyphenyl) alanine]oxytocin' OR 'carbetocin' OR 'carbetocina' OR 'crinesal' OR 'duratobal' OR 'duratocin' OR ' oxytocin [1 butyric acid 2 [3 (4 methoxyphenyl) alanine]]' OR 'pabal') AND 'oxytocin'/exp AND ('postpartum hemorrhage'/exp OR 'fluxus postpartum' OR 'haemorrhage, postpartum' OR 'hemorrhage, postpartum' OR 'lochia' OR 'post partum haemorrhage' OR 'post partum hemorrhage' OR 'postpartal haemorrhage' OR 'postpartal hemorrhage' OR 'postpartum bleeding' OR 'postpartum haemorrhage' OR 'postpartum hemorrhage' OR 'puerperal haemorrhage' OR 'puerperal hemorrhage' OR 'secondary postpartum haemorrhage' OR 'secondary postpartum hemorrhage') AND ('randomized controlled trial'/exp OR 'systematic review'/exp OR 'review, systematic' OR 'systematic review')

13 studies were retrieved, but none were relevant to the PICO question.

iii. *Additional studies*

The Cochrane review by Gallos et al, 2019, reported two key studies that were ongoing and not completed, at the time the systematic review was done. The UK study results was completed in October 2018, and is yet to be published; but the WHO-led multi-centre non-inferiority RCT comparing oxytocin, IM to carbetocin (room temperature stable), IM for prevention of PPH in women having vaginal birth was completed and published in June 2018 (Widmer et al, 2018).

The Cochrane review (Gallos et al, 2019) and RCT (Widmer et al, 2018) are synthesised in the table below.

b. Evidence synthesis and quality

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Gallos et al, 2018  Gallos_Uteronics_Preventing PPH_Cochr	Network meta-analysis	88,947 (140 RCTs)	Women having a vaginal birth (predominantly > 37 wks gestation)	*1.PPH ≥ 500 mL* • Ergometrine + oxytocin (n=13138); or • Carbetocin (n=917); or • Misoprostol + oxytocin (n=9651) ***vs*** • Oxytocin *2.PPH ≥ 1000 mL* • Ergometrine + oxytocin (n=13038); or • Carbetocin (n=1026); or • Misoprostol + oxytocin (n=9897) ***vs*** Oxytocin	**Two primary outcomes** *1.PPH ≥ 500 mL* *2. PPH ≥ 1000 mL*	**Primary outcome** (vs oxytocin) **<u>1.PPH ≥ 500 ML</u>** ***Vaginal delivery*** • Ergometrine + oxytocin: 7.2% (6 to 8.7) vs 10.5% (9.8 to 11.3); RR 0.72 (0.56 to 0.92) (Pairwise) ; I2=57.4% • Carbetocin:7.6% (5.5 to 10.5) vs 10.5% (9.8 to 11.3); RR 0.69 (0.45 to 1.07) (Pairwise) ; I2=49.9% • Misoprostol + oxytocin:7.7%(6.3 to 9.5) vs 10.5% (9.8 to 11.3); RR 0.74 (0.62 to 0.88) (Pairwise) ; I2=60.5% ***Caesarean section:*** • Ergometrine + oxytocin: 51.7%(42.7 to 62.2) vs 74.9%(65.7 to 85.4); RR 0.72 (0.56 to 0.92) (Pairwise) ; I2=57.4% • Carbetocin: 53.9%(38.9 to 74.9) 74.9%(65.7 to 85.4); RR 0.69 (0.45 to 1.07) (Pairwise) ; I2=49.9% • Misoprostol + oxytocin: 54.7%(44.9 to 67.4) vs 74.9%(65.7 to 85.4); RR 0.74 (0.62 to 0.88) (Pairwise) ; I2=60.5% *Ergometrine + oxytocin, and misoprostol + oxytocin shown to be marginally superior to oxytocin.*	Well-conducted network meta-analysis: '*a priori*' design and addressed clear questions; analytical framework described the search strategy of a number of databases, across languages; statistical analysis was appropriate; quality assessment of included RCTs by 3 reviewers with disputes resolved through consensus, minimising the potential for error and/or bias; RCTs included in analysis reported. But, RCTs very heterogenous.Sixty nine (49%) did not provide sufficient information to assess allocation concealment, and the risk of bias unclear (moreso with RCTs comparing carbetocin). Over third of the RCTs did not have sufficient information on blinding of participants. Eight RCTs (6%) had high risk of bias as they were funded directly by pharmaceutical industry. Overall, only 30% of RCTs at low risk of bias. For primary outcome PPH≥500 ml, there was evidence of global inconsistency (dosing, route of administration, treatment protocol, setting of delivery, etc).. No meaningful differences between all comparators for maternal mortality or severe morbidity; these outcomes were rare. There was a trend towards a reduction in the need for blood transfusion with ergometrine/ oxytocin and carbetocin vs oxytocin, but background data was not provided. RCTS done mostly in hospital settings may not be generalizable to local setting.

						Carbetocin showed a trend towards reducing PPH ≥ 500 ml. **<u>2. PPH ≥ 1000 mL</u>** ***Vaginal delivery*** • Ergometrine + oxytocin: 2.8%(2.2 to 3.4) vs 3.6% (3.4 to 3.9); RR 0.73 (0.57 to 0.93) (Pairwise) , I2=0% • Carbetocin: 2.5%(1.4 to 4.6) vs 3.6% (3.4 to 3.9); RR 0.71 (0.38 to 1.35) (Pairwise) , I2=0% • Misoprostol + oxytocin:3.2% (2.6 to 4.1) vs 3.6% (3.4 to 3.9), RR 0.89 (0.71 to 1.12) (Pairwise) , I2=0% ***Caesarean section*** • Ergometrine + oxytocin: 10.7%(8.5 to 13.2) vs 13.9%(11.7 to 16.6); RR 0.73 (0.57 to 0.93) (Pairwise) , I2=0% • Carbetocin: 9.7% (5.3 to 17.8) vs 13.9%(11.7 to 16.6); RR 0.71 (0.38 to 1.35) (Pairwise) , I2=0% • Misoprostol + oxytocin: 12.5% (10 to 15.8) vs 13.9%(11.7 to 16.6); RR 0.89 (0.71 to 1.12) (Pairwise) , I2=0% *Ergometrine/oxytocin was the only medicine found to be more effective than oxytocin for reducing PPH ≥1000ml.* *There was a trend towards a reduction in the need for blood transfusion with*	Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias.

						ergometrine/oxytocin and carbetocin vs oxytocin. Manual removal of the placenta not significantly reduced. Of note is that maternal death or severe maternal morbidity were rare outcomes in the included studies.	
Widmer et al, 2018  Widmer_Carbetocin VsOxytocin_PPH_NE.	Non-inferiority RCT	29,645	Women giving birth vaginally	Carbetocin (RTS) 100 mcg, IM; n=14,771; *vs* Oxytocin 10 IU, IM; n=14,768	**Two primary composite outcomes:** 1. Proportion of women with blood loss **≥500 ml** or use of additional uterotonic agents at 1 hr and up to 2 hrs where bleeding continued after 1 hr. 2. Proportion of women with blood loss **≥1000 ml** at 1 hr and up to 2 hrs where bleeding continued after 1 hr.	**Primary outcome** (carbetocin vs oxytocin): 1. Blood loss**≥500ml**/uterotonic agent: 14.5% vs 14.4%; *Risk diff*: 0.09 (-0.68 to 0.87); carbetocin was shown to be non-inferior to oxytocin. 2. Blood loss**≥1000ml**: 1.51 vs 1.41; *Risk diff*: 1.04 (0.87 to 1.25); carbetocin not shown to be non-inferioir to oxytocin, probably as underpowered. There were no significant differences between the two groups in other measures of bleeding or in adverse effects (chest pain, flushing, abdominal pain, and vomiting).	Multicenter, double-blind, RCT; ITT analysis, adequately powered to determine noninferiority of carbetocin vs oxytocin to prevent PPH with loss **≥500ml** or use of uterotonic agent(s). There was no meaningful differences in maternal and neonatal mortality and severe morbidity; or the need for blood transfusions. Setting was in hospitals; women who were distressed or at an advanced stage of labor were excluded. This may not be generalisable to the South African setting (where most vaginal deliveries occurs at primary level of care) – though South Africa was included as a study site, (sites included developed and developing countries). Support provided by pharmaceutical industry and study was submitted for regulatory approval, that may contribute to bias.

7. Alternative agents: n/a

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [X] Not confident [ ] Uncertain [ ]</td><td>Meta-analysis data</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [X] No [ ]

List the members of the group.
Oxytocin
Oxytocin + misoprostol
Oxytocin + ergometrine

List specific exclusion from the group:
n/a</td><td>Rationale for therapeutic alternatives included:
Evidence of efficacy shown in network meta-analysis.

References:
Gallos et al, Cochrane, 2018</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?

Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [ ]</td><td>Cost of treatment::
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Oxytocin 10 IU, IM</td><td>5.34*</td></tr><tr><td>Carbetocin 100 mcg, IM</td><td>192.05**</td></tr><tr><td>Ergometrine/oxytocin 0.5 mg/5 IU, IM</td><td>17.49*</td></tr><tr><td>Misoprostol 600 mcg*** / oxytocin 10 IU</td><td>19.58</td></tr></table>*Contract circular HP06-2017SVP
** Quotation from Ferring Pharmaceuticals, 2018
***Contract circular RT287-2017: misoprostol 200 mcg = R4.746
Additional resources: n/a</td></tr>
</table>

EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Carbetocin is available as a room temperature stable formulation; and is an alternative option where other uteronics are in short supply.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	[ ]	[ ]	[ ]	[ ]

Recommendation: Based on this evidence review the Adult Hospital Level Expert Review Committee (ERC) acknowledges that the evidence of efficacy shows that carbetocin is not inferior to oxytocin for the prevention of PPH. However, the ERC reccomends that carbetocin not be included on the EML for PPH prophylaxis, until there is a substantial price reduction comparable to oxytocin which is the current standard of care.

Where oxytocin is unavailable, oxytocin and ergometrine combination can be considered, provided there are no complications of heart disease and hypertension.

Level of Evidence: II Network meta-analysis, disease oriented RCT

Review indicator: Price reduction

Evidence of efficacy	Evidence of harm	Price reduction
		X

VEN status:

Vital	Essential	Necessary
X		

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC accepted the Adult Hospital Level Committee's proposal not to include carbetocin, room temperature stable formulation on the Adult Hospital Level EML as it is currently cost-prohibitive.

Rationale: Health systems strengthening was required through an adequate service delivery platform to ensure adequate cold chain distribution and appropriate storage of the currently recommended medicine, oxytocin, IV. It was considered unreasonable to pay for a more expensive medicine, because the health system was insufficient and fridges were not available at all healthcare facilities. *(Note: The Ideal Clinic/Hospital Framework lists fridges as essential furniture).*

It was further recommended that the National Department of Health engage with relevant parties to access carbetocin rts at the agreed upon price that was available to low middle income countries.

Monitoring and evaluation considerations

Research priorities

References:

- National Department of Health, Essential Drugs Programme: Adult Hospital level STG, 2015. http://www.health.gov.za/
- Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018 Apr 25;4:CD011689. https://www.ncbi.nlm.nih.gov/pubmed/29693726
- Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, Coomarasamy A, Abdel-Aleem H, Mallapur AA, Qureshi Z, Lumbiganon P, Patel AB, Carroli G, Fawole B, Goudar SS, Pujar YV, Neilson J, Hofmeyr GJ, Su LL, Ferreira de Carvalho J, Pandey U, Mugerwa K, Shiragur SS, Byamugisha J, Giordano D, Gülmezoglu AM; WHO CHAMPION Trial Group. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018 Aug 23;379(8):743-752.