SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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carbetocin 100 micrograms/mL solution for injection (Pabal®) SMC No 309/06

Ferring Pharmaceuticals Ltd

8 December 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

carbetocin (Pabal®) is not recommended for use within NHS Scotland.

Indication under review: For the prevention of uterine atony following delivery of the infant by Caesarean section under epidural or spinal anaesthesia.

A double-blind, randomised, controlled study in 377 women undergoing Caesarean section demonstrated a significant reduction in additional uterotonic treatment in women receiving carbetocin compared with oxytocin, although this result was not supported by two smaller double-blind, randomised, controlled studies.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the prevention of uterine atony following delivery of the infant by Caesarean section (CS) under epidural or spinal anaesthesia.[1]

Dosing Information

100 micrograms carbetocin by slow intravenous (IV) injection over one minute, only after delivery of the infant by CS. It should be given as soon as possible after delivery, preferably before removal of the placenta. Carbetocin is intended for single use only and no further doses should be administered.[1]

Carbetocin is intended for use only at well-equipped specialist obstetrics units with experienced and qualified staff available at all times.[1]

Carbetocin is contraindicated during pregnancy and must not be used for the induction of labour.[1]

Product availability date

April 2006

Summary of evidence on comparative efficacy

Carbetocin is a long acting oxytocin agonist that selectively binds to oxytocin receptors in the smooth muscle of the uterus and can increase the rate and force of spontaneous uterine contractions in the postpartum uterus.[1] Uterine atony is the most common cause of postpartum haemorrhage (PPH) and CS is a recognised risk factor for PPH.[2, 3] The recommended treatment in Scotland for maintaining uterine tone after delivery of the baby during CS is oxytocin 5 international units by slow IV injection.[4]

The submitting company presented evidence from an in house meta-analysis of nine studies. However, only three of these used the licensed dose of oxytocin as the comparator and were considered to be relevant to this submission. All three studies were double-blind, randomised, controlled, post-marketing authorisation studies in women with singleton pregnancies.[3, 5, 6]

The Attilakos et al. study included 377 women ≥37 weeks gestation undergoing elective or emergency CS with regional anaesthesia.[3] The women were randomised in a 1:1 ratio to receive blinded IV treatment with 100 micrograms carbetocin (n=188) or 5 international units oxytocin (n=189). The primary outcome was the proportion of women in each treatment group that, at the discretion of the operating surgeon, required additional uterotonic agents and it was analysed in the intention to treat population (all randomised patients). There was a reduction in additional uterotonic drugs in women receiving carbetocin compared with oxytocin: 34% (63/188) versus 46% (86/189), respectively; relative risk (RR) 0.74 (95% confidence interval [CI]: 0.57 to 0.95), p=0.023. Most of the additional treatment comprised an infusion of 40 international units oxytocin, typically over four hours in 21% (40/188) and 29% (55/189) of women in the respective groups. Almost all of the remaining additional treatment comprised IV injections of 5 international units or 10 international units oxytocin. The purpose of the additional oxytocic medication was to treat established PPH in 11% (20/188) of carbetocin patients and 18% (35/189) of oxytocin patients, RR 0.57 (95% CI: 0.35 to 0.96) p=0.043. In the remainder of patients the purpose was prophylaxis.[3] There was no significant difference between treatment groups in the secondary outcomes of estimated blood loss, difference in preoperative and post-operative haemoglobin, proportions of patients receiving blood transfusions or uterine tone.[3]

The Whigham et al. study included 114 women ≥37 weeks gestation undergoing emergency CS under regional anaesthesia.[5] The women were randomised in a 1:1 ratio to receive blinded IV treatment with 100 micrograms carbetocin or 5 international units oxytocin. The primary outcome was the requirement for additional uterotonic agents, as determined by the clinician, and it was analysed in all randomised patients who received regional anaesthesia; two patients were excluded as they required a general anaesthetic. There was no significant difference between treatment groups in the proportions of women that needed additional uterotonic agents, although a numerically higher proportion of those receiving carbetocin than oxytocin needed further treatment: 22% (13/59) versus 13% (7/53), p=0.323. There was also no significant difference between treatment groups in the secondary outcomes of incidence of PPH; estimated blood loss; haemoglobin drop pre- and post-operation or need for blood transfusion.[5]

The Rosseland et al. study was primarily a haemodynamic study that included 76 healthy women who were ≥18 years old and ≥36 weeks gestation who were scheduled to undergo a CS under spinal anaesthesia.[6] Patients were randomised in a 1:1:1 ratio to receive double-blind IV treatment with 100 micrograms carbetocin (n=25), 5 international units oxytocin (n=26) or placebo (0.9% sodium chloride) (n=25). The primary outcome measured systolic arterial pressure, continuously using an invasive technique during the first five minutes after treatment intervention and it was analysed in all randomised patients. There was no significant difference between the carbetocin and oxytocin groups in decrease in systolic arterial pressure, time to trough decrease or time to recovery from this adverse effect. The secondary outcome of requirement for additional uterotonic treatment was not significantly different between the carbetocin and oxytocin groups: 24% (6/25) of carbetocin patients; 27% (6/26) of oxytocin patients and 92% of placebo patients. The calculated estimated blood loss was lower in the carbetocin group than the oxytocin group, but the difference was not statistically significant. However the study was underpowered to detect differences in bleeding.[6]

A meta-analysis of nine studies found that for women who underwent CS (n=2,167), carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, RR 0.65 (95% CI: 0.48 to 0.88). In addition to the three studies described above, the meta-analysis included a further six studies that used higher unlicensed doses of oxytocin as the comparator. Five were randomised controlled studies: Borruto et al. (n=104);[7] Boucher et al. (n=57);[8] Dansereau et al. (n=659);[9] Elbohoty et al. (n=263),[10] and Razali et al. (n=600);[11] and one was a case controlled, non-randomised study: De Bonis et al. (n=110).[12] This meta-analysis supported results from an earlier Cochrane review of four of these nine studies.[13]

Summary of evidence on comparative safety

In the Attilakos et al. study the adverse event profile was comparable between the carbetocin and oxytocin groups and similar proportions of women experienced at least one event; 12% (22/188) versus 14% (26/189), respectively. The most common adverse events were nausea and/or vomiting (5.3% [10/188] versus 6.3% [12/189] patients) and dizziness or hypotension (2.6% [5/188] versus 2.6% [5/189] patients).[3]

The Rosseland et al. haemodynamic safety study showed that heart rate elevation after carbetocin was slightly more prolonged than after oxytocin, which may be relevant for pregnant women with increased risk of cardiac events. With this exception, none of the other differences between the two active treatment groups in haemodynamic variables tested would have clinical relevance in healthy pregnant women. Adverse events occurred in 36% (9/25) of carbetocin patients, 35% (9/26) of oxytocin patients and 8.0% (2/25) of placebo patients. Adverse events that occurred in more than one patient in any treatment group (carbetocin, oxytocin and placebo) were: headache (2, 3 and 0); feeling of warmth (2, 2 and 1); chest pain (2, 2 and 0); palpitations (0, 3 and 0) and flushing (0, 2 and 1).[6]

The summary of product characteristics (SPC) notes that the occurrence of interactions known to be associated with oxytocin cannot be excluded. In general, carbetocin should be used cautiously in the presence of migraine, asthma and cardiovascular disease or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. Specific studies have not been undertaken in gestational diabetes mellitus.[1]

Clinical expert advice received by SMC noted a concern that, compared to oxytocin, carbetocin's longer half life could result in less flexibility in adjusting dosage for adverse effects such as hypotension.

Summary of clinical effectiveness issues

Carbetocin is a long acting analogue of oxytocin used to encourage contraction of the postpartum uterus and prophylaxis of uterine atony during CS.[1] Uterine atony is the most common cause of PPH, accounting for approximately 70% of cases.[2] Oxytocin (5 international units by slow IV injection) is recommended to maintain uterine tone after delivery of the baby during CS.[4] Clinical experts advise that this may be followed by a 4-hour infusion if indicated.

Three double-blind, randomised controlled studies compared licensed doses of carbetocin and oxytocin with regard to the need for additional uterotonic treatment, which was the primary outcome in the Attilakos et al. (emergency or elective CS) and Whigham et al. (emergency CS) studies, and was a secondary outcome in the Rosseland et al. (elective CS) study. There was a significant benefit for this outcome for carbetocin compared with oxytocin in the Attilakos et al. study, but not in the other two studies.[3, 5, 6] In the Whigham et al. study a numerically higher proportion of patients in the carbetocin group than the oxytocin group needed uterotonic rescue treatment.[5] Studies did not show statistically significant differences between carbetocin and oxytocin in terms of risk of PPH.

Limitations of the Whigham et al. study include small patient numbers (n=112), possible lack of power for the primary outcome and insufficient information in the published paper about patients who were excluded due to broken treatment ampoules. Limitations of the Rosseland et al. study include small patient numbers (n=51 in active treatment groups), that the need for additional uterotonic drugs was a secondary outcome and a possible lack of power for the comparison of this outcome with oxytocin.[6]

The in house meta-analysis, which underpinned the economic case, had a number of limitations. Only three studies (described above) used a relevant dose of the comparator oxytocin. The other six studies used a range of higher, unlicensed doses.[7-12] The meta-analysis included a non-randomised study,[12] two studies that were conducted in the 1990's when clinical management may have differed from current practice[8, 9] and studies with varied primary outcomes.

While decreased use of additional uterotonic treatment may lead to reduction in time spent in recovery, there is a lack of robust evidence to support this in women receiving carbetocin compared with oxytocin.

Because carbetocin is intended for single administration only, if further uterotonic treatment is required, oxytocin has to be used. In case of persisting uterine hypotonia or atonia and the consequent excessive bleeding, additional therapy with oxytocin and/or ergometrine should be considered.[1] In the Attilakos et al. study, more than a third of carbetocin patients required further uterotonic treatment with oxytocin.[3] Carbetocin could not therefore totally displace oxytocin in CS, consequently both these medicines would need to be available.

Summary of comparative health economic evidence

The submitting company presented a cost-comparison analysis evaluating the value for money of carbetocin for the postpartum prevention of uterine atony in women undergoing a CS which is in line with the licensed indication. The comparator included in the analysis was IV oxytocin.

In the analysis patients received either carbetocin (100 micrograms solution for injection), or IV oxytocin (initial 5 international units slow bolus in all patients, with 17% of patients routinely re-treated with 34.3 international units infusion over four hours). The primary outcome in the economic model was the use of additional uterotonics, assumed to take the form of oxytocin infusion at the same dose as routine infusions; that is, 34.3 international units. The time horizon of the analysis was the duration of a CS, from the point at which carbetocin/oxytocin is administered to when the patient leaves recovery.

Clinical data came from the in house meta-analysis of nine studies described previously comparing the additional use of uterotonics between carbetocin and oxytocin. Across all the studies included in the baseline meta-analysis, 30.15% of women receiving oxytocin required retreatment with uterotonics, compared to a rate of 19.6% for carbetocin and these figures were used in the analysis to impact upon the relative costs of the two treatment options.

Medicine costs were included in the analysis alongside equipment costs, staff costs and hospitalisation costs associated with the extra time spent in recovery during the retreatment with uterotonics, which was assumed to be an additional 2 hours and 25 minutes based on a recent UK single-centre observational study by Luni et al.[14]. This study collected data for 400 women undergoing emergency or elective CS (227 receiving carbetocin and 173 given oxytocin) and found a large reduction in the use of additional oxytocics in the carbetocin group (7% versus 48% in the oxytocin group).[14] The company assumed that during the extra time in recovery women would receive 1:1 monitoring by staff. Although some studies indicate a reduction in PPH and subsequent blood products use associated with carbetocin, the savings resulting from these were not factored in the analysis as the difference was not statistically significant.

The analysis did not include utility gains associated with a reduced time in recovery or reuniting the baby and mother more quickly. Consequently, no quality-adjusted life-years (QALYs) were estimated and the analysis only evaluates the direct costs from the perspective of NHS Scotland, with the results being presented as a cost comparison between the two treatments.

The base case results and key sensitivity analysis are presented in Table 1 and Table 2 respectively.

Table 1: Base case results

	Oxytocin	**Carbetocin**	**Incremental cost***
Initial treatment			
Medicine costs	£1.33	£17.64	£16.31
Equipment costs	£0.65	£0.00	-£0.65
Retreatment with uterotonics			
Medicine costs	£0.94	£0.61	-£0.33
Staff costs	£66.98	£43.54	-£23.44
Hospitalisation costs	£29.08	£18.90	-£10.18
Equipment costs	£1.16	£0.75	-£0.41
TOTAL	**£100.15**	**£81.45**	**-£18.70**

*A minus sign indicates a net cost saving in favour of carbetocin

As shown in Table 1, in the base case analysis, the submitting company estimated that carbetocin is associated with cost savings of £18.70 per patient.

Table 2: Key sensitivity analysis

Parameter varied*	**Lower bound incremental cost**	**Upper bound incremental cost**
Cost oxytocin per 5 unit	-£18.54	-£18.86
Cost oxytocin per 10 unit	-£18.52	-£18.87
Proportion oxytocin patients routinely retreated	-£18.46	-£18.94
Oxytocin infusion dose (international units)	-£18.53	-£18.87
Cost of IV equipment: saline	-£18.66	-£18.75
Cost of IV equipment: giving set	-£18.54	-£18.87
Oxytocin retreatment rate	-£11.83	-£25.57
Relative riskof retreatment with uterotonics for carbetocin patients	-£35.39	£3.88
Duration of retreatment infusion	-£18.40	-£19.00
Cost of staff time per hour for infusion and recovery	-£14.01	-£23.39
Additional recovery time following infusion	-£12.28	-£25.12
Cost of day case	-£16.67	-£20.74

*One-way sensitivity analysis is conducted by varying the carbetocin RR within its 95% CI and all parameters by an arbitrary 20%

The company provided a one-way sensitivity analysis which was conducted by varying the RR associated with the additional use of uterotonics following carbetocin within its 95% CI and all other parameters by an arbitrary 20%, as shown in Table 2. The results indicate that the savings associated with carbetocin are most sensitive to the RR of using additional uterotonics associated with carbetocin. The results are relatively insensitive to all other parameters.

The base case results suggest carbetocin to be cost saving compared to oxytocin, and this result remains fairly consistent when various parameters and costs were varied. However, further investigations indicated there are some weaknesses related to the validity of some of the data used in the analysis which can potentially have a large impact on the cost savings associated with carbetocin. These are detailed below.

The main weaknesses of the analysis relate to:

- The study by Luni et al. used as the source for the additional time spent in recovery was non-randomised and conducted in a single centre. SMC clinical expert opinion was that additional treatment with uterotonics would be unlikely to increase the time spent in recovery by the patients in clinical practice. Hence, a scenario analysis was requested from the company in which the additional use of uterotonics is not associated with an increased time spent in recovery. This is a pivotal assumption since most of the predicted cost savings for carbetocin are built around the extra 2 hours and 25 minutes used in the initial analysis for patients requiring additional treatment with oxytocin. Removing this additional time spent in recovery results in an incremental cost associated with the use of carbetocin of £13.41.
- The dose used for the comparator oxytocin in most of the studies included in the meta-analysis is not consistent with the 5 international units dose used in the economic model and reflected in the Scottish clinical practice. The company submitted additional results based on four studies using a 5 international units dose, although this list was not restricted to RCTs only. These showed the cost saving of carbetocin use drops considerably (to £2.81 in baseline) and is associated with incremental costs in various scenarios explored in the sensitivity analysis. Additional results were requested based only on the three RCTs that use the licensed 5 international units dose of oxytocin

which were identified in the comparative efficacy section. Analysis using the Attilakos, Whigham and Rosseland studies only show an incremental cost associated with carbetocin of £10.81.

- The routine oxytocin use in 17% of patients on top of the additional uterotonics use in the oxytocin arm could potentially represent double-counting, which would make the oxytocin arm seem more expensive. However, additional results submitted by the company indicated only a slight reduction to the base case cost savings of carbetocin (from £18.70 to £17.52 per patient) when the extra routine use in 17% of patients was not included in the model.
- Likewise, including both the staff cost related to 1:1 observation during the additional time spent in recovery and also the hospitalisation cost, may potentially reflect double counting since staff costs are typically included in the hospitalisation costs to some extent. The company addressed this by submitting an additional set of results in which hospitalisation costs were removed from the analysis, leaving only the cost related to 1:1 staff observation. In this scenario the cost savings associated with carbetocin dropped from £18.70 to £8.52.
- Since the outcome of interest (additional use of uterotonics) differed between the two treatments, the analysis falls under the category of a cost-comparison analysis rather than a cost-minimisation analysis as described by the company. The latter type of analysis assumes that outcomes are achieved to the same extent between the two treatments, which is not the case in the current analysis. A cost-comparison analysis was considered sufficient to address the current decision problem since data on quality-of-life is generally lacking and there is no statistically significant difference between the two treatments in relation to other outcomes such as PPH.

Due to the uncertainties regarding the additional time spent in recovery associated with the additional use of uterotonics (which is the main driver of the savings attributed to carbetocin), the economic case has not been demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

A guideline (updated from 2009) entitled Prevention and management of postpartum haemorrhage, was published in 2016 on behalf of the Royal College of Obstetricians and Gynaecologists. It notes that a Cochrane review has addressed the use of carbetocin in the prevention of PPH and that there were no statistically significant differences between carbetocin and oxytocin in terms of risk of PPH.

The guideline states that for women delivering by CS, oxytocin (5 international units by slow IV injection) should be used to encourage contraction of the uterus and to decrease blood loss. Ergometrine plus oxytocin may be used in the absence of hypertension in women at increased risk of haemorrhage as it reduces the risk of minor PPH (500 to 1000mL). For women at increased risk of haemorrhage, it is possible that a combination of preventative measures might be superior to oxytocin alone to prevent PPH. Clinicians should consider the use of IV tranexamic acid (0.5 to 1g), in addition to oxytocin, at CS to reduce blood loss in women at increased risk of PPH.[4]

Additional information: comparators

Oxytocin 5 international units by slow IV injection is the relevant comparator.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per dose (£)
Carbetocin	**100 micrograms by slow IV injection**	**17.64**
Oxytocin	5 international units by slow IV injection	0.80

IV=intravenous; *Doses are for general comparison and do not imply therapeutic equivalence. Cost of carbetocin from online Dictionary of medicines and devices and cost of oxytocin from eVadis on 27.09.17. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration*

Additional information: budget impact

The submitting company estimated there would be 16,711 patients eligible for treatment with carbetocin in year 1 rising to 18,954 patients in year 5. The estimated uptake rate was 10% in year 1 (1,671 patients) and 30% in year 5 (5,686 patients) with a discontinuation rate of 16% applied.

The gross impact on the medicines budget was estimated to be £29k in year 1 rising to £100k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £27k in year 1 rising to £91k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 17 November 2017.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.