HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 January 2007

PABAL 100 µg/ml, solution for injection
Pack of 5 ampoules of 1 ml (CIP: 569 644-5)

Applicant : FERRING SAS FRANCE

Carbetocin

List I

Medicinal product reserved for hospital use

Date of Marketing Authorisation: July 6, 2006

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Carbetocin

1.2. Background

Carbetocin is a synthetic human oxytocin analogue with a longer duration of action than oxytocin (approximately 5 hours instead of 90 minutes). The onset of uterine contractions following the administration of carbetocin is rapid and firm contractions are obtained within 2 minutes.

1.3. Indication

Prevention of uterine atony following delivery by Caesarean section under epidural or spinal anaesthesia.

1.4. Dosage

Withdraw 1 ml of PABAL containing 100 micrograms of carbetocin and administer only by intravenous injection, under adequate medical supervision in a hospital.

PABAL must be administered only after delivery of the infant by caesarean section. It should be given as soon as possible after delivery, preferably before expulsion of the placenta. No further doses of carbetocin should be administered.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

H: Systemic hormones (except sex hormone and insulins)
H01: Pituitary, hypothalamic hormones and analogues
H01B: Hormones of the posterior lobe of the pituitary gland
H01BB: Oxytocin and analogues
03: Carbetocin

2.2. Medicines in the same therapeutic category

Comparator drugs

There is only one medicinal product in the same pharmacotherapeutic class: SYNTOCINON 5 IU/1 ml (oxytocin). However, the two products are not strictly similar.
SYNTOCINON is a synthetic oxytocic with identical composition and pharmacological properties as natural oxytocin whereas carbetocin has a more prolonged action duration than natural oxytocin.

The indications of SYNTOCINON are:

- Insufficient uterine contractions at the start or during labour.
- Obstetric surgery (caesarean section, termination of pregnancy etc.): to ensure good uterine retraction
- Post-partum uterine atony due to haemorrhage.

2.3. Medicines with a similar therapeutic aim

There are other medicinal products that may induce uterine contractions and/or increase basal uterine tone though the wording of the indication is not the same as for carbetocin:

- Ergometrin derivative - METHERGIN (methylergometrin), when a switch to a parenteral oxytocic preparation is indicated after haemorrhage during delivery and post-partum in the case of uterine atony,

- Prostaglandin - NALADOR (sulprostone), indicated in the treatment of post-partum haemorrhage due to uterine atony resistant to first-line treatment by oxytocin.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Efficacy and safety of a single 100-µg dose of carbetocin after delivery by caesarean section under epidural or spinal anaesthesia were evaluated in three clinical studies including one versus placebo (Barton S.R) and two versus a reference treatment: oxytocin (Boucher M. et al., 1998 and Dansereau J. et al,. 1999).

3.1.1 Study versus placebo

Barton S.R (USA, unpublished)

Randomised, double-blind, placebo-controlled comparison of the efficacy and safety of a single 100-µg dose of carbetocin on uterine contractions after delivery by caesarean section in 119 women.

The primary endpoint was the need for further oxytocic therapy in the case of insufficient uterine contractions or excessive bleeding after delivery.

Results

Carbetocin was superior to placebo on the primary endpoint: 13% of patients treated by carbetocin versus 72% of patients on placebo needed an additional dose of oxytocic therapy, $p < 0.001$.

3.1.2 Studies versus oxytocin

Boucher M. et al. (Canada, 1998)[1]

Randomised, double-blind, comparative study versus ocytocin of the efficacy and safety of carbetocin on blood loss and maintenance of uterine contractions during delivery by caesarean section in 57 patients.

The patients received, after delivery and before expulsion of the placenta, either a single IV bolus dose of 100 µg of carbetocin (n=29), or an IV bolus of 2.5 IU of oxytocin followed by infusion of 30 IU over 16 hours (n=28).

[1] Boucher M. et al : Double–blind, Randomized Comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing caesarean section. J. Perinatol 1998; 18:202-7.

Outcome variables:
No primary endpoint was defined in this study, and there were many outcome variables:

- Blood loss during surgery,
- Uterine tone
- Type and amount of lochia
- Need for additional oxytocic therapy
- Position of uterine fundus

Results

- Patient characteristics:

Patient characteristics were similar in the two groups:
age 30.5 ± 4.6 years, body weight: 73.9 ±12.9 kg, previous pregnancies: 2.5 ± 1.1. previous caesarean sections: 1 ± 0.7.

- Blood loss during surgery:

Mean blood loss after the single dose of 100-µg of carbetocin was similar to that after 16 hours of oxytocin infusion.

Parameters	Carbetocin (29)	Ocytocin (28)	Difference
Mean blood loss	149 +/- 74 ml	190 +/-118 ml	NS
Proportion of women with blood losses ≤ 200 ml	79%	53%	p<0.05

Sub-group analysis (a post-hoc analysis as this was not planned in the protocol) showed that the proportion of women with bleeding ≤ 200 ml was significantly greater in the carbetocin group than in the oxytocin group.

- Uterine Tone, type and amount of lochia

No statistically significant difference was demonstrated between the two groups.

- Need for additional oxytocic therapy

No patient in the carbetocin group needed an additional dose of oxytocic therapy during the 16 hours of the study for uterine atony or excessive bleeding whereas 3 patients in the oxytocin group (11%) needed it.

Conclusion:
During this study, no statistically significant difference was demonstrated between a single IV injection of carbetocin and a bolus IV dose of 2.5 IU oxytocin followed by an infusion of 30 IU over 16 hours for the maintenance of uterine contractions and excessive blood loss during delivery by caesarean section.

Dansereau J. et al (Canada, 1999)[2]

Randomised, double-blind, comparative study versus oxytocin of the efficacy and safety of carbetocin in 694 women during elective delivery by caesarean section under epidural or spinal anaesthesia.

The patients received, after delivery and before expulsion of the placenta either a single IV bolus dose of 100-µg of carbetocin or an IV bolus of 5 IU of oxytocin followed by an infusion of 20 IU over 8 hours.

The primary endpoint was the proportion of patients requiring additional doses of oxytocin to obtain and maintain adequate uterine contractions.

Results

Patient characteristics

Parameters	Carbetocin (n = 317)	Oxytocin (n =318)
Age (years)	31±5	31±5
Bodyweight (kg)	79±21	81±19
Height (cm)	159±8	160±9
Number of pregnancies	2.7±1.3	2.8±1.2
Previous caesarean sections	1±0.8	1±0.8
Number of post partum haemorrhages n, (%)	2±0.6	5±1.5
Gestational diabetes n, (%)	11±2.3	28±8,5

Sequential analysis per protocol (n=635)
The proportion of patients who needed additional doses of oxytocic therapy was 4.7% (15/317) in the carbetocin group *versus* 10.1% (32/318) in the oxytocin group, p=0.031.

Post hoc analysis
In the population of randomised patients (ITT population) no statistically significant difference was demonstrated between the carbetocin group and the oxytocin group. The proportion of patients who needed additional doses of ocytocicic therapy was 10.1% in the ocytocin group versus 6.3% in the cabetocin group, OR =1.71 (CI 95% : 0.99-2.99).

The results of this study are difficult to interpret. On the one hand, on the primary endpoint was analysed for the per protocole population (which is contrary with the usual practice) with a sequential analysis, that it makes difficult the interpretation of the results for others populations. On the other hand, the results are non significant for the randomised patient population (n=694). Therefore this study does not allow for a conclusion regarding the superiority of carbetocin *versus* ocytocin.

Comments;
The oxytocin doses used in these two studies comply with Canadian recommendations, but they are much higher than those recommended in France (5 to 10 IU by the slow IV route).

[2] Dansereau J. et al;: Double –blind comparison of carbetocin versus oxytocin in preventing uterine atony post caesarean. Int. J. Gyn. Obs. 1999, 46 (suppl 2) : 77)

3.2. Adverse effects

Study versus placebo:

No serious or unexpected adverse effect was observed.

The most frequent adverse effects were: nausea (61% with carbetocin, vs 57% with placebo), hypotension (45% with carbetocin vs 38% with placebo), vomiting (41% with carbetocin vs 36% with placebo).

Boucher et al Study

No serious or unexpected adverse effect was reported.

No significant difference in terms of adverse effects was observed between the carbetocin group and the oxytocin group.

Dansereau et al. study

There was no significant difference in terms of severity and incidence of adverse effects between the two groups. The most frequent adverse effects were: abdominal pain, nausea, hot flushes, headache and vomiting.

Four serious adverse effects were reported, including two in each group.

- In the carbetocin group, one patient had an intense pain in the chest and another, a transient episode of confusion;
- In the oxytocin group, there was one neonatal death due to congenital malformations incompatible with life and one cardiac arrest with recovery in another child.

In addition, two patients in each group had postpartum haemorrhage (blood loss < 500 ml) and were excluded from the trial:

- In the carbetocin group (haemostasis hysterectomy after failure of prostaglandin F2 alpha in a patient with a uterus scarred from 3 previous pregnancies and one successful administration of prostaglandin F2 alpha)
- The two patients in the oxytocin group recovered under oxytocin infusion.

3.3. Conclusion

Three clinical studies conducted on a total sample of 872 patients evaluated the efficacy and safety of carbetocin in the prevention of uterine atony after delivery by caesarean section under epidural or spinal anaesthesia.

An intravenous bolus dose of 100 µg of carbetocin was better than placebo in reducing the proportion of patients needing additional oxytocic therapy in the event of insufficient uterine contractions or excessive bleeding after delivery (primary endpoint). The proportion of patients requiring additional doses of oxytocic therapy was reduced in the carbetocin group (13%) compared to the placebo group (72%).

During the two studies comparing carbetocin to oxytocin, no significant difference was demonstrated in terms of efficacy between a single injection of carbetocin of 100 µg and an IV bolus dose of 2.5 IU oxytocin followed by an infusion of 30 IU over 16 hours or an IV bolus dose of 5 IU followed by an infusion of 20 IU over 8 hours.

No study has provided any proof that carbetocin is superior to the reference treatment, oxytocin.

Consequently, the potential interest of carbetocin is to permit a simplification of the administration in comparison with ocytocin, to obtain a good uterine contractility with a single injection.

The safety profile of carbetocin was similar in these studies to that of oxytocin. The most frequent adverse effects were: nausea, abdominal pain, hot sensation, headaches, tremors, pruritis and hypotension.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Uterine atony remains the main cause of post-partum haemorrhage. Post-partum haemorrhage is defined by heavy bleeding of more than 500 ml within 24 hours after delivery and 1000 ml after a caesarean section. It is life-threatening.

This medicine provides symptomatic treatment.

Public Health Benefit

Post-partum haemorrhage, in the event of delivery by elective caesarean section, constitutes a low public health burden.

Although serious individual cases may occur, they do not constitute a priority public health problem. Moreover, the availability of effective treatment means that the improved prevention of post-partum haemorrhage cannot be considered to be a public health need.

A review of available data and existing treatments shows that this proprietary drug is not expected to have an impact in terms of morbidity and quality of life.

Accordingly, the proprietary drug PABAL is not expected to have an impact on public health.

Its efficacy/adverse effects ratio is high.
This medicinal product is used for first-line therapy.
There are alternative treatments.
The actual benefit of this product is substantial.

4.2. Improvement in actual benefit

In the indication: prevention of uterine atony following delivery by caesarean section under epidural or spinal anaesthesia, no statistically significant difference was demonstrated in terms of efficacy between PABAL and SYNTOCINON for the endpoint “proportion of patients needing further oxytocic therapy in the event of insufficient uterine contractions or excessive bleeding after delivery”.

Moreover, the safety profiles of these two proprietary drugs were similar.

The Transparency Committee therefore considers that PABAL does not provide an improvement in actual benefit (IAB V) compared to SYNTOCINON.

4.3. Therapeutic use[3]

The strategy of prevention of post-partum haemorrhage (PPH) is based on the recommendations of the French National Board of Gynaecologists-Obstetricians:

[3] French National Board of Gynaecologists-Obstetricians. Clinical Practice Recommendations 2004.

"Clinical and pharmacological prevention of PPH during delivery"
It is recommended to systematically conduct:

— Regular monitoring in the delivery room for two hours after delivery (expert consensus). This monitoring concerns the volume of blood loss, appearance of uterus, heart rate and measurement of blood pressure. This data must be noted in the patient record (expert consensus);

— Active management of delivery comprising a minimum number of clinical procedures: at the time of placental separation, controlled cord traction while applying supra-pubic counter-pressure using the abdominal hand. Moreover, a hypotonic uterus should be massaged after expulsion of the placenta (grade A);

— Examination of the placenta to check that it is complete. Retention of the placental cotyledons or membranes is an indication for uterine evacuation (expert consensus);

— Prophylactic oxytocin injection (grade B); this injection may be given immediately after delivery of the anterior shoulder of the child (active management of third stage) or after expulsion of the placenta (grade B). It involves direct slow intravenous (or intramuscular) injection of from 5 to 10 IU of oxytocin;

— Artificial placental delivery when the placenta is not expelled within a period of 30 minutes (grade C).

Early diagnosis is an essential element in the prognosis of any PPH. Quantification may be facilitated by placing a collection bag under the patient at the end of foetal expulsion (grade C). Its efficacy in reducing the risk or seriousness of PPH however remains to be established.

Blood losses are greater in the case of caesarean section than during delivery and are particularly difficult to estimate. It is recommended to provide active management of the third stage rather than immediate manual delivery (grade B).

Misoprostol is not recommended for prophylaxis of PPH: it is less effective than oxytocin in this indication and induces more adverse effects (grade A)."

The role of PABAL in the therapeutic strategy:
Carbetocin is a longer-acting synthetic oxytocin (5h) than natural oxytocin (90 min). Its potential value is that it maintains uterine contractions and prevents excessive bleeding after a single injection, whereas oxytocin treatment requires repeated injections or infusions over several hours.

According to the SPC, carbetocin must be administered in a single dose only after delivery of an infant born by caesarean section. It should be given as soon as possible after delivery, preferably before expulsion of the placenta. In the event of persistent hypotonia or uterine atony and excessive concomitant bleeding, combination of oxytocin and/or ergometrine should be considered. There are no data about the administration of additional doses of carbetocin or the use of carbetocin in the event of persistent uterine atony after oxytocin injection.

The efficacy of carbetocin was not evaluated after delivery.

4.4. Target population

According to INSEE (“2005 population survey”), approximately 807,400 infants are born every year in France.

The number of caesarean sections is estimated to be 20 %, i.e. approximately 162,000 per year.

Only 3 to 4% of these are carried out under general anaesthesia, giving a total of 157,000.

As there are no identified risk factors making it possible to select those patients who may benefit from preventive measures with a sufficient sensitivity and specificity, the target population of PABAL is certainly very close to 157,000.

However, given that the use of PABAL is restricted to caesarean sections under epidural or spinal anaesthesia, this target population is certainly over-estimated.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the posology in the Marketing Authorisation.