PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PABAL® solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Carbetocin (anhydrous acetic acid free): 100 micrograms/ml.

PABAL® is sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for Injection.

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

PABAL® is indicated for the prevention of postpartum haemorrhage due to uterine atony following delivery of the infant by caesarean section under epidural or spinal anaesthesia and following vaginal delivery of the infant.

4.2 Posology and method of administration

Posology

PABAL® should be administered as a single dose only, when delivery of the infant has been completed. There are no efficacy or safety data on repeat doses of PABAL® following delivery of the infant. The use of carbetocin should occur in the context of other measures to prevent PPH and associated morbidity, including uterine massage, detection and correction of coagulopathies (refer to

local clinical guidelines). Other uterotonic agents should be administered if additional treatment is required to reduce excessive postpartum bleeding and increase uterine tone.

Caesarean section:

A single dose of 100 micrograms (1 ml) of PABAL® (carbetocin injection) should be administered intravenously as a bolus injection, slowly over 1 minute after delivery of the infant.

Vaginal delivery:

A single dose of 100 micrograms (1 ml) of PABAL® (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.

Method of administration

For intravenous or intramuscular administration.

PABAL® must only be administered after delivery of the infant, and as soon as possible after delivery, preferably before the delivery of the placenta.

PABAL® should not be mixed with other infusion fluids. PABAL® should be inspected visually for particulate matter and discoloration prior to administration. The product should not be used if particulate matter or discoloration is observed.

Caesarean section under epidural or spinal anaesthesia:

Withdraw 1 ml of PABAL® containing 100 micrograms carbetocin and administer only by intravenous injection slowly, over 1 minute.

Vaginal delivery:

Withdraw 1 ml of PABAL® containing 100 micrograms carbetocin and administer by intramuscular injection.

For intravenous administration, PABAL® must be administered slowly, over 1 minute.

Paediatric Population

PABAL® is not intended for use in children below 12 years of age.

4.3. Contraindications

PABAL® is contraindicated in the following conditions:

- During pregnancy and labour before delivery of the infant.
- Hypersensitivity to carbetocin, oxytocin or any of the excipients listed in section 6.1.
- Hepatic or renal disease.
- Induction of labour.
- Serious cardiovascular disorders.
- Epilepsy.

4.4 Special warnings and precautions for use

The use of PABAL® at any stage before delivery of the infant is not appropriate because its uterotonic activity persists for several hours. This is in marked contrast to the rapid reduction of effect observed after discontinuation of an oxytocin infusion.

In case of persistent vaginal or uterine bleeding after administration of PABAL® the cause must be determined. Consideration should be given to causes such as retained placental fragments, perineal, vaginal and cervix lacerations, inadequate repair of the uterus, or disorders of blood coagulation.

PABAL® is intended for single administration only, intramuscular or intravenous injection. In case of intravenous administration, it must be administered slowly over 1 minute. In case of persisting uterine hypotonia or atonia and the consequent excessive bleeding, additional therapy with another uterotonic should be considered. There are no data on additional doses of carbetocin or on the use of carbetocin

following persisting uterine atony after oxytocin.

The risk of water intoxication cannot be excluded. Animal studies have shown carbetocin to possess some antidiuretic activity and therefore the possibility of hyponatraemia cannot be excluded, particularly in patients also receiving large volumes of intravenous fluids. The early signs of drowsiness, listlessness and headache should be recognised to prevent convulsions and coma.

In general, PABAL® 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 a hazard for an already overburdened system. The decision of administering PABAL® can be made by the medical practitioner after carefully weighing the potential benefit PABAL® may provide in these particular cases.

No data is available on the use of carbetocin (e.g., PABAL®) in patients with eclampsia. Patients with eclampsia and pre-eclampsia should be carefully monitored.

Specific studies have not been undertaken in gestational diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

During clinical trials, PABAL® has been administered in association with a number of analgesics, spasmolytics and medicines used for epidural or spinal anaesthesia, and no drug interactions have been identified. Specific interaction studies have not been undertaken.

Since PABAL® is closely related in structure to oxytocin, the occurrence of interactions known to be associated with oxytocin cannot be excluded: severe hypertension has been reported when oxytocin was given 3 to 4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal-block anaesthesia.

During combination with ergot-alkaloids, such as methylergometrine, oxytocin and carbetocin may enhance the blood pressure enhancing effect of these medicines. If oxytocin or methylergometrine are administered after PABAL® there may be a risk of cumulative exposure.

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is expected that this can also occur with carbetocin. Therefore, it is not recommended that prostaglandins and PABAL® be used together. If they are concomitantly administered, the patient should be carefully monitored.

Some inhalation-anaesthetics, such as halothane and cyclopropane may enhance the hypotensive effect and weaken the effect of carbetocin e.g. PABAL® on the uterus. Dysrhythmias have been reported for oxytocin during concomitant use.

4.6 Fertility, pregnancy and lactation

Pregnancy

PABAL® is contraindicated during pregnancy and must not be used for the induction of labour (see section 4.3).

Breastfeeding

Small amounts of PABAL® have been shown to pass from plasma into breast milk of nursing women (See section 5.2).

The small amounts transferred into colostrum or breast milk after a single injection of PABAL®, and subsequently ingested by the infant are assumed to be degraded by enzymes in the gut.

Breastfeeding does not need to be restricted after the use of PABAL®.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The adverse events observed with PABAL® during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin:

Intravenous Administration - Tabulated summary of adverse reactions:*

System Organ Class	**Very common** **≥ 1/10**	**Common** **≥ 1/100 and < 1/10**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders		Anaemia	
Immune system disorders			Hypersensitivity (including anaphylactic reaction)
Nervous system disorders	Headache, tremor	Dizziness	
Cardiac disorders			Dysrhythmia**, Bradycardia tachycardia** myocardial ischaemia**, and QT prolongation**
Vascular disorders	Hypotension, flushing		
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea	
Gastrointestinal disorders	Nausea, abdominal pain	Metallic taste, vomiting	
Skin and subcutaneous tissue disorders	Pruritus		

Musculoskeletal and connective tissue disorders		Back pain	
General disorders and administration site conditions	Feeling of warmth	Chills, pain	

*Based on studies in caesarean section.

** Reported with oxytocin (closely related in structure to carbetocin).

In the clinical trials sweating was reported as sporadic cases.

*Intramuscular administration** – Tabulated summary of adverse reactions*

System Organ Class	**Uncommon** **≥ 1/1 000 and < 1/100**	**Rare** **≥ 1/** **10 000 and < 1/** **1 000**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders	Anaemia		
Immune system disorders			Hypersensitivity (including anaphylactic reaction)
Nervous system disorders	Headache, dizziness	Tremor	
Cardiac disorders	Tachycardia		Bradycardia dysrhythmia***, myocardial ischaemia***, and QT prolongation***

Vascular disorders	Hypotension	Flushing	
Respiratory, thoracic and mediastinal disorders	Chest pain	Dyspnoea	
Gastrointestinal disorders	Nausea, abdominal pain, vomiting		
Skin and subcutaneous tissue disorders		Pruritus	
Musculoskeletal and connective tissue disorders	Back pain, muscular weakness		
Renal and urinary disorders		Urinary retention	
General disorders and administration site conditions	Chills, pyrexia, pain		

** Based on studies in vaginal delivery.

*** Reported with oxytocin (closely related in structure to carbetocin).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdosage of PABAL® may produce uterine hyperactivity whether or not due to hypersensitivity to this medicine.

Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contraction resulting from PABAL® overdose can lead to uterine rupture or postpartum haemorrhage.

As carbetocin is an analogue of oxytocin, the possibility of an overdosage of PABAL® leading to hyponatraemia and water intoxication, especially when associated with excessive concomitant fluid intake, cannot be excluded.

Treatment of overdosage of PABAL® consists of symptomatic and supportive therapy. When signs or symptoms of overdosage occur oxygen should be given to the mother. In cases of water intoxication, it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 19 Oxytocics.

Pharmacotherapeutic group: Oxytocin and analogues.

ATC code: H01BB03.

The pharmacological and clinical properties of carbetocin are those of a long acting oxytocin agonist.

Carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus, stimulates rhythmic contraction of the uterus, increases the frequency of existing contractions, and raises the tone of the uterus musculature.

On the postpartum uterus, carbetocin is capable of increasing the rate and force of spontaneous uterine

contractions. The onset of uterine contraction following carbetocin is rapid, with a firm contraction being obtained within 2 minutes.

A single 100 micrograms intravenous or intramuscular dose of carbetocin administered after the delivery of the infant is sufficient to maintain adequate uterine contraction that prevents uterine atony lasting for several hours without the need for an infusion.

Clinical efficacy and safety

The efficacy of carbetocin in the prevention of postpartum haemorrhage due to uterine atony following Caesarean section was established in a randomised, active controlled, double-blind, double dummy, parallel-group trial designed to establish the efficacy and safety of carbetocin compared to oxytocin 25 IU. Six-hundred fifty-nine healthy pregnant women undergoing elective Caesarean section under epidural anaesthesia received either carbetocin 100 µg/ml as an IV bolus dose or oxytocin 25 IU as an 8 h IV infusion.

The results of analysis of the primary endpoint, the need for additional oxytocic intervention, showed that additional oxytocic intervention was required in 15 (5 %) of the subjects receiving carbetocin 100 µg IV compared with 32 (10 %) of the subjects in the oxytocin 25 IU group (p = 0,031).

The efficacy of carbetocin in the prevention of postpartum haemorrhage following vaginal delivery was established in one randomised, active controlled, double-blind trial. In total 29 645 subjects were randomised to receive a single intramuscular dose of either carbetocin 100 µg or oxytocin 10 IU. For the primary endpoint of blood loss of ≥ 500 ml or use of additional uterotonics, similar rates were obtained in both treatment groups (carbetocin: 2 135 subjects, 14,47 %; oxytocin: 2 122 subjects, 14,38 %; relative risk [RR] 1,01; 95 % CI: 0,95 to 1,06), demonstrating non-inferiority of carbetocin compared with oxytocin with regard to the primary endpoint.

Paediatric population

In the clinical development of carbetocin for prevention of postpartum haemorrhage following vaginal

delivery 151 women between 12 and 18 years of age received carbetocin at the recommended dosage of 100 μg and 162 received oxytocin 10 IU. Efficacy and safety were similar for the two treatment arms in these patients.

5.2 Pharmacokinetic properties

Carbetocin shows a biphasic elimination after intravenous administration with linear pharmacokinetics in the dose range of 400 to 800 micrograms. The median terminal elimination half-life is 33 minutes after intravenous administration and 55 minutes after intramuscular administration. After intramuscular administration, peak concentrations are reached after 30 minutes and the mean bioavailability is 77 %. The mean volume of distribution at pseudo-equilibrium (Vz) is 22 L. Renal clearance of the unchanged form is low, with < 1 % of the injection dose excreted unchanged by the kidney.

After intramuscular administration of 70 μg carbetocin in 5 healthy nursing mothers, carbetocin concentrations were detectable in milk samples. Mean peak concentrations in milk were below 20 pg/ml, which was approximately 56 times lower than in plasma at 120 min.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and local tolerance. A reproductive toxicity study in rats with daily drug administration from parturition to day 21 of lactation, showed a reduction in offspring body weight gain. No other toxic effects were observed. The indication did not warrant studies on fertility or embryotoxicity or carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-methionine

Mannitol

Sodium hydroxide 2M for pH adjustment

Succinic acid

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 Months.

Once the vial has been opened, the product must be used immediately.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store at or below 30 °C. Keep vials in outer carton, in order to protect from light. Once the vial has been opened, the product must be used immediately. Do not freeze.

PABAL® should be inspected visually for particulate matter and discoloration prior to administration. The product should not be used if particulate matter or discoloration is observed (see section 6.3).

6.5 Nature and contents of container

PABAL® is a 1 ml solution containing 100 micrograms carbetocin in colourless, Type I glass vials (2R) with Type I bromobutyl stoppers and an aluminium crimp cap. PABAL® is presented as 5 vials per unit carton.

6.6 Special precautions for disposal and other handling

Only clear solutions practically free from particles should be used.

Any unused product or waste material should be disposed of. Contact Ferring (Pty) Ltd or your pharmacist.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ferring (Pty) Ltd.

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8. REGISTRATION NUMBER(S)

A42/19/0383

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 20 June 2013

10. DATE OF REVISION OF THE TEXT

29 January 2024

MANUFACTURER:

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