1. NAME OF THE MEDICINAL PRODUCT

PABAL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carbetocin 100 micrograms/ml.
Oxytocic activity: approximately 50 IU of oxytocin/vial
For a 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.

4.2 Posology and method of administration

Posology:
Caesarean section under epidural or spinal anaesthesia:
Withdraw 1 ml of PABAL containing 100 micrograms carbetocin and administer only by intravenous injection, under adequate medical supervision in a hospital.
Vaginal delivery:
Withdraw 1 ml of PABAL containing 100 micrograms carbetocin and administer by intravenous injection or intramuscular injection, under adequate medical supervision in a hospital.

Method of administration
For intravenous or intramuscular administration.
Carbetocin must only be administered after delivery of the infant, preferably before removal of the placenta.
For intravenous administration carbetocin must be administered slowly, over 1 minute. PABAL is intended for single use only. No further doses of carbetocin should be administered.
Paediatric population

There is no relevant use of carbetocin in children below 12 years of age.

The safety and efficacy of carbetocin in adolescents has not yet been established.

Currently available data are described in section 5.1 but no recommendation on a posology can be made.

4.3 Contraindications

- During pregnancy and labour before delivery of the infant.
- Carbetocin must not be used for the induction of labour.
- Hypersensitivity to carbetocin, oxytocin or to any of the excipients listed in section 6.1.
- Hepatic or renal disease.
- Serious cardiovascular disorders.
- Epilepsy.

4.4 Special warnings and precautions for use

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

The use of carbetocin 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 carbetocin 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.

Carbetocin is intended for single administration only intramuscular or intravenous. 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.

Animal studies have shown carbetocin to possess some antidiuretic activity (vasopressin activity: <0,025 IU/vial) 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, 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. The decision of administering carbetocin can be made by the physician after carefully weighing the potential benefit carbetocin may provide in these particular cases.

No data is available on the use of carbetocin 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 medicinal products and other forms of interaction

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

Since carbetocin 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 agents. If oxytocin or methylergometrine are administered after carbetocin 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 carbetocin be used together. If they are concomitantly administered, the patient should be carefully monitored.

Some inhalation-anesthetics, such as halothane and cyclopropane may enhance the hypotensive effect and weaken the effect of carbetocin on the uterus. Arrhythmias have been reported for oxytocin during concomitant use.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

No significant effects on milk let-down have been reported during clinical trials. Small amounts of carbetocin 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 carbetocin, and subsequently ingested by the infant are assumed to be degraded by enzymes in the gut.

Breast-feeding does not need to be restricted after the use of carbetocin.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The adverse events observed with carbetocin 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			Tachycardia, bradycardia which can lead to cardiac arrest,, arrhythmia***, 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 and tachycardia were 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***, arrhythmia***, 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form *https://sideeffects.health.gov.il/*

4.9 Overdose

Overdosage of carbetocin may produce uterine hyperactivity whether or not due to hypersensitivity to this agent.
Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions resulting from oxytocin overdose can lead to uterine rupture or postpartum haemorrhage.
Overdosage of oxytocin may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake. As carbetocin is an analogue of oxytocin, the possibility of a similar event cannot be excluded.
Treatment of overdosage of carbetocin 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

Pharmacotherapeutic group: Oxytocin and analogues
ATC code: H01BB03
The pharmacological and clinical properties of carbetocin are those of a long acting oxytocin agonist.

Like oxytocin, carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus, stimulates rhythmic contractions 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 after intravenous administration, with a firm contraction being obtained within 2 minutes.
A single 100 micrograms intravenous dose of carbetocin administered after the delivery of the infant is sufficient to maintain adequate uterine contraction that prevents uterine atony and excessive bleeding comparable with an oxytocin infusion lasting for several hours.

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 carbetocine 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 oxyctocin 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 29645 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: 2135 subjects, 14.47%; oxytocin: 2122 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 was similar for the two treatment arms in these patients.

5.2 Pharmacokinetic properties

The pharmacokinetics of carbetocin have been investigated in healthy female subjects. 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 injected dose excreted unchanged by the kidney.

After intramuscular administration of 70 µg carbetocin inn 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 toxicicology and 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.

Carcinogenicity studies have not been performed with carbetocin due to the single dose nature of the indication

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-methionine
Succinic acid
Mannitol
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After first opening the vial: the solution should be used immediately.
From a microbiological point of view, unless the method of opening/reconstitution/dilution 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

Protect from light. Store below 30°C . Do not freeze.

6.5 Nature and contents of container

Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminium crimp cap containing 1 ml of solution for injection.
Packs of 5 vials

6.6 Special precautions for disposal

PABAL is for intravenous and intramuscular use only.
Only clear solutions practically free from particles should be used.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. **MANUFACTURER** Ferring GmbH, Kiel Germany

8. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceutical ltd, 8 Hashita St. Industrial Park, Caesarea

9 MARKETING AUTHORISATION NUMBER 160-34-35090

This leaflet was revised in April 2024.

תאריך הגשת עדכון עלון	פרקים שהתעדכנו	אסמכתא לעדכון
11/2019	4.3; 4.4; 4.6; 4.8; 5.1; 5.2; 6.3	Pabal SPC approved in UK on 10/2019
09/2022	4.1; 4.2; 4.4; 4.8; 5.1; 5.2; 6.6	Pabal SPC approved in UK on 10/2019 and MoH approval of additional indication and related posology
04/2024	4.8	Pabal SPC approved in UK on 10/2023 (PRAC recommendation (endorsed by CMDh) on bradycardia and hypersensitivity due to PSUSA outcome)