## 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 uterine atony following delivery of the infant by Caesarean section under epidural or spinal anaesthesia

### 4.2 Posology and method of administration

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

Method of administration
PABAL must be administered slowly, over 1 minute only after delivery of the infant by Caesarean section. It should be given as soon as possible after delivery, preferably before removal of the placenta.
PABAL is intended for single use only. No further doses of carbetocin should be administered.

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### 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.
- Cases of pre-eclampsia and eclampsia.
- 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 after a single bolus injection. This is in marked contrast to the rapid reduction of effect observed after discontinuation of an oxytocin infusion.

In case of persistent uterine bleeding after administration of carbetocin the cause must be determined. Consideration should be given to causes such as retained placental fragments, inadequate emptying or repair of the uterus, or disorders of blood coagulation.

Carbetocin is intended for single administration only. It must be administered slowly over 1 minute. In case of persisting uterine hypotonia or atonia and the consequent excessive bleeding, additional therapy with oxytocin and/or ergometrine 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.

Specific studies have not been undertaken in gestational diabetes mellitus.

The efficacy of carbetocin has not been assessed following vaginal delivery.

### 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.

### 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 when administered after Caesarean section under spinal or epidural anaesthesia.

| System Organ Class | Very common ≥ 1/10 | Common ≥ 1/100 and < 1/10 |
|---|---|---|
| Blood and lymphatic system disorders | | Anaemia |
| Nervous system disorders | Headache, tremor | Dizziness |
| 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 | |
| Musculosceletal and connective tissue disorders | | Back pain |
| General disorders and administration site conditions | Feeling of warmth | Chills, pain |

In the clinical trials sweating and tachycardia were reported as sporadic cases.

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 *http://forms.gov.il/globaldata/getsequence/getsequence.aspx? formType=AdversEffectMedic@moh.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, 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.

### 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 terminal elimination half-life is approximately 40 minutes. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney.

In 5 healthy nursing mothers, plasma carbetocin concentrations were detectable by 15 min and peaked at a maximum of 1035 ± 218 pg/ml within 60 min. Peak concentrations in milk were 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. 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.

### 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 bromobutyle 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 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

The leaflet format has been determined by the Ministry of health and the content thereof has been checked and approved **by it in March 2018**

**Date:** 13 Jun 2018

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|---|---|---|---|
| Title | Leaflet PABAL sol for inj vial 100mcg/ml 5x 1ml | | |
| Item N° | 2009053421 | Perigord N° | 343384 |
| Proof N° | 02 | Approving Country(ies) | IL |
| E-MS N° | 3093 | Dimensions | 150 x500mm |
| Barcode N° | 2009053421 | | |
| Colours | P. Black. | | |