SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PABAL 100 micrograms/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carbetocin 100 micrograms/ml.
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, and as soon as possible after delivery, preferably before the delivery 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
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

* Based on studies in caesarean section

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

Blood and lymphatic system disorders	Anaemia	
Nervous system disorders	Headache, dizziness	Tremor
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	Flushing
Respiratory, thoracic and mediastinal disorders	Chest pain	Dyspnoea
Gastrointestinal disorders	Nausea, abdominal pain, vomiting	
Skin and subcutaneous tissue disorders		Pruritus
Musculosceletal 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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 or intramuscular administration, 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 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 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 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.

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

3 years.
Shelf life 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

Keep vials in the outer carton, in order to 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 and other handling

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. MARKETING AUTHORISATION HOLDER

[To be completed nationally]
{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

PABAL 100 micrograms/ml solution for injection
Carbetocin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Carbetocin 100 micrograms

3. LIST OF EXCIPIENTS

L-Methionine
Succinic acid
Mannitol
Sodium hydroxide
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection. 5 vials of 1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous and intramuscular injection

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND SIGHTOF CHILDREN

Keep out of sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only. Once open use immediately

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep vials in the outer carton in order to protect from light.
Store below 30 ºC. Do not freeze

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
{Name and address}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. MANUFACTURERS BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PABAL 100 micrograms/ml injection
Carbetocin
For IV and IM use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Carbetocin 100 micrograms in 1ml

PACKAGE LEAFLET

Package leaflet: Information for the patient

PABAL 100 micrograms/ml solution for injection
carbetocin

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, midwife or nurse.
- If you get any side effects, talk to your doctor, midwife or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
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What is in this leaflet

1. What PABAL is and what it is used for

The active ingredient in PABAL is carbetocin. It is similar to a substance called oxytocin, which is naturally produced by the body to make the womb contract during childbirth.
PABAL is used to treat women who have just had a baby.
In some women, after delivery, the womb (uterus) doesn't contract (shrink) quickly enough. This makes it more likely that they'll bleed more than normal. PABAL makes the womb contract and so reduces the risk of bleeding.

2. What you need to know before you are given PABAL

PABAL must not be given until after the baby has been delivered.

Before giving you PABAL, your doctor needs to know about any medical conditions you may have. You should also tell your doctor about any new symptoms that develop while you are being treated with PABAL.

You must not be given PABAL

- if you are pregnant.
- if you are in labour and the baby has not been delivered.
- to induce labour.
- if you are allergic to carbetocin or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to oxytocin (sometimes given as a drip or injection during or after labour).
- if you have any disease of the liver or kidneys.
- if you have any serious heart disease.
- if you have epilepsy.

If any of these apply to you, tell your doctor, midwife or nurse.

Warnings and precautions

Talk to your doctor, midwife or nurse before you are given PABAL

- if you get migraines.

- if you have asthma.
- if you have pre-eclampsia (high blood pressure in pregnancy) or eclampsia (toxaemia of pregnancy).
- if you have problems with your heart or your circulation (such as high blood pressure).
- if you have any other medical condition.

If any of these apply to you, tell your doctor, midwife or nurse.

PABAL may cause a build up of water in the body which can lead to drowsiness, listlessness and headache.

Children and adolescents
Not relevant in children below 12 years of age.
The experience with adolescents is limited.

Other medicines and PABAL
Tell your doctor, midwife or nurse if you are taking, have recently taken or might take any other medicines – .

Pregnancy and breast-feeding
Do not use PABAL during pregnancy and labour until after the baby has been delivered.
Small amounts of carbetocin have been shown to pass from the nursings mother's blood into the breast milk, but it is assumed to be degraded in the infant's bowels. Breastfeeding does not need to be restricted after the use of PABAL.

3. How you are given PABAL

PABAL is given as an injection into one of your veins or into one of your muscles, immediately after your baby has been delivered. The dose is one vial (100 micrograms).

If you are given more PABAL than you should have been given

If you are accidentally given too much PABAL, your womb may contract strongly enough to become damaged or to bleed heavily. You may also suffer drowsiness, listlessness and headache, caused by water building up in your body. You will be treated with other medication, and possibly surgery

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When PABAL is given into one of your veins after caesarian section

Very common: may affect more than 1 in 10 people
- nausea
- pain in the stomach
- itching
- flushing (red skin)
- feeling of warm
- low blood pressure
- headaches
- shakiness

Common: may affect up to 1 in 10 people
- vomiting
- dizziness

- pain in the back or chest
- a metallic taste in the mouth
- anaemia
- breathlessness
- chills
- General pain

Infrequently some women might experience rapid heartbeat or sweating.

When PABAL is given into one of your muscles after vaginal delivery

Uncommon: may affect up to 1 in 100 people
- nausea
- pain in the stomach
- vomiting
- low blood pressure
- anaemia
- headaches
- dizziness
- rapid heartbeat
- pain in the back or chest
- muscle weakness
- chills
- fever
- General pain

Rare: may affect less than 1 in 1,000 people
- flushing (red skin)
- itching
- breathlessness
- shakiness
- difficulty to pass urine

Reporting of side effects
If you get any side effects, talk to your doctor, midwife or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PABAL

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Keep the vials in the outer carton in order to protect from light. Store below 30 ºC. Do not freeze.

The solution should be used immediately after opening of the vial.

6. Contents of the pack and other information

What PABAL contains

The active substance is carbetocin. Each millilitre contains 100 micrograms of carbetocin.
The other ingredients are L-methionine, succinic acid, mannitol, sodium hydroxide and water for injections.

What PABAL looks like and contents of the pack

Pabal is clear colourless solution for injection, ready for intravenous or intramuscular injection, supplied in packs of five vials of 1 ml.

PABAL should be used only in well-equipped specialist obstetrics units.

Marketing Authorisation Holder

[To be completed nationally]

Manufacturer

Ferring GmbH, Wittland 11, D-24109 Kiel, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

PABAL/DURATOCIN/DURATOBAL [To be completed nationally]

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

[To be completed nationally]