

## SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

*On the last page, the patient information leaflet is available by scanning the QR code.*

### 1. NAME OF THE MEDICINAL PRODUCT

Carbetocin Ferring 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

A clear, colourless, sterile solution for injection.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Carbetocin Ferring is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

#### 4.2 Posology and method of administration

##### Posology

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

##### Dosage

Caesarean section: 100 µg Carbetocin Ferring i.v.

Vaginal delivery: 100 µg Carbetocin Ferring i.v., alternatively 100 µg can also be administered i.m.

##### Method of administration

For intravenous or intramuscular administration.

For intravenous administration Carbetocin Ferring must be administered slowly, over 1 minute.

Carbetocin Ferring is intended for single administration only. No further doses of Carbetocin Ferring should be administered.

##### *Dosage recommendations in special populations*

*Children and adolescents:* Only limited data are available on the safety and efficacy of carbetocin in adolescents after the menarche (see "Pharmacological properties"). In adolescents from the age of 15 years, the same dose as in adults may be administered under adequate supervision, if indicated.

Use in adolescents <15 years of age, i.e. those who are not yet fully mature, is not recommended due

to lack of data.

There is no indication for use in pre-pubescent children.

*Elderly patients:* There is no indication for use in post-menopausal women.

*Hepatic or renal impairment:* The pharmacokinetics of carbetocin in patients with hepatic or renal impairment have not been investigated. Therefore Carbetocin Ferring should not be used in these populations (see “Contraindications”).

### **4.3 Contraindications**

- Pregnancy and labour before delivery of the infant,
- For induction or augmentation of labour,
- Serious cardiovascular disorders,
- Epilepsy,
- Renal or hepatic disorders,
- Hypersensitivity to carbetocin, oxytocin or any of the excipients according to the composition.

### **4.4 Special warnings and precautions for use**

Carbetocin Ferring should be used only in obstetric units with experienced and qualified staff.

The use of Carbetocin Ferring at any stage before delivery of the infant is not appropriate because its uterotonic activity persists for several hours.

In the case of persistent uterine bleeding after administration of Carbetocin Ferring, the cause must be determined. Possible causes are retained placental fragments, injuries to the perineum, vagina or cervix, inadequate emptying or repair of the uterus in the case of caesarean section, or disorders of blood coagulation.

Carbetocin Ferring is intended for single administration only. With intravenous administration the injection must be given slowly over 1 minute. If uterine hypotonia or atony persists and the consequent excessive bleeding occurs, additional therapy with another uterotonic can be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persistent uterine atony after oxytocin administration.

The risk of water intoxication with hyponatraemia cannot be excluded, especially in patients receiving large volumes of infusion solutions. Animal studies have shown carbetocin to possess some antidiuretic activity (vasopressin activity: <0.025 I.U./vial). Attention should be paid to the early signs of water intoxication or hyponatraemia - such as drowsiness, listlessness and headache - to prevent complications such as convulsions and coma.

In the presence of migraine, asthma or cardiovascular disease as well as in any state in which a rapid increase in extracellular water may be hazardous for an already overburdened system, carbetocin

should only be used after careful weighing up of the benefits and risks and under appropriate supervision.

Cases of transient asymptomatic QT-prolongation have been observed on rapid intravenous injection of oxytocin in doses of several I.U. as bolus. It is not known whether these changes are causally related to the oxytocin treatment, or were caused by simultaneously administered co-medication. There are no data on a possible pathophysiological mechanism. The occurrence of such QT prolongations also under carbetocin cannot be excluded. Therefore, carbetocin should only be used with special caution in patients with known long-QT syndrome or other risk factors for QT prolongation (such as co-medication with drugs with a known risk of QT-prolongation).

Carbetocin has not been investigated in patients with manifest eclampsia. It should therefore be used only with special caution in cases of eclampsia or pre-eclampsia, and patients should be carefully monitored.

Only limited data are available on the use of carbetocin in patients with (gestational) diabetes.

#### Excipients

This medicine contains less than 1 mmol sodium (23 mg) per 100 micrograms/ml, that is to say essentially 'sodium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been undertaken with carbetocin.

There is a risk of a cumulative effect with the use of methylergometrine or oxytocin after the administration of carbetocin.

During clinical trials, Carbetocin Ferring has been administered in association with analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anaesthesia. No drug interactions were observed.

The following interactions have been observed under oxytocin. Since carbetocin is structurally related to oxytocin, they cannot be excluded with carbetocin either.

Prostaglandins potentiate the effect of oxytocin. Therefore prostaglandins should not be used at the same time as carbetocin. If these substances are nevertheless used simultaneously, then the patient must be closely monitored.

Inhalation anaesthetics, e.g. halothane, can potentiate the hypotensive effect and reduce the effect of carbetocin on the uterus. In case of concomitant use of such anaesthetics with oxytocin, arrhythmias have also been reported.

Cases of severe hypertension have been reported when oxytocin was given 3 to 4 hours after prophylactic administration of a vasoconstrictor in conjunction with caudal-block anaesthesia.

Carbetocin can potentiate the hypertensive effect of ergot-alkaloids such as methylergometrine.

#### 4.6 Pregnancy and lactation

##### *Pregnancy*

Carbetocin Ferring is contraindicated during pregnancy, including 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 determined in the breast milk of nursing women (see Pharmacokinetics). The small amounts of carbetocin transferred into colostrum or breast milk after a single injection of Carbetocin Ferring and subsequently ingested by the infant are assumed to be degraded by enzymes in the gastrointestinal tract and therefore have probably no clinically relevant effects in the breastfed infant.

#### 4.7 Effects on ability to drive and use machines

No studies of the effect on the ability to respond, to drive and to use machines have been conducted. However, carbetocin can have undesirable effects such as dizziness that could impair the ability to drive.

#### 4.8 Undesirable effects

The following statements are based on clinical trials in which carbetocin was used in the context of a Caesarean section. However, a similar safety profile is to be expected on use after vaginal delivery. The undesirable effects observed with carbetocin during clinical trials after vaginal delivery or Caesarean section, were also comparable in frequency and severity to those of oxytocin.

##### *Tabulated summary of adverse reactions*

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10	Uncommon (≥1/1000 to <1/100)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Anaemia		
Immune system disorders				Hypersensitivity reactions (including anaphylactic reactions)
Nervous system disorders	Headache, tremor	Dizziness		
Cardiac disorders			Tachycardia	
Vascular disorders	Hypotension, flushing			

Respiratory, thoracic and mediastinal disorders		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, chest pain, sweating		

Possible reactions at the administration site were not specifically investigated. As with other drugs, the possibility of local irritation is likely, especially with i.m. administration.

#### 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 [SafetyMailboxCarbetocin@Ferring.com](mailto:SafetyMailboxCarbetocin@Ferring.com)

#### **4.9 Overdose**

An overdosage with uterotonic agents such as carbetocin can induce uterine hyperactivity. The following symptoms of an overdosage, as have been observed with oxytocin, are also likely with carbetocin. If carbetocin is used before delivery of the infant (see "Contraindications"), hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions can occur, with the risk of uterine rupture or increased postpartum haemorrhage.

An overdosage may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid administration.

Treatment of overdosage consists of symptomatic and supportive therapy. If signs and symptoms of overdosage occur, oxygen should be given. In the case of water intoxication it is important to restrict fluid administration, initiate diuresis, correct electrolyte disturbances 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, increases uterine tone, stimulates rhythmic contractions of the uterus and increases the frequency of existing contractions.

On the postpartum uterus, carbetocin is capable of increasing the frequency and force of spontaneous uterine contractions. The onset of uterine contractions following carbetocin is rapid after intravenous or intramuscular administration, with a first firm contraction obtained within 2 minutes.

A single 100 µg intravenous or intramuscular dose of Carbetocin Ferring administered after the delivery of the infant is sufficient to maintain adequate uterine contraction. This can reduce the risk of uterine atony and excessive bleeding.

#### *Clinical efficacy*

##### *Prevention of uterine haemorrhage due to postpartum uterine atony following caesarean section*

The efficacy of carbetocin was compared with oxytocin in a randomised, double-blind, double dummy study in n=659 patients. Healthy pregnant women in whom an elective Caesarean section had been performed under epidural anaesthesia were enrolled and received either 100 µg/ml carbetocin as an IV bolus dose or 25 I.U. oxytocin as an infusion over 8 h. The primary endpoint was the proportion of patients who required an additional dose of oxytocin. This was the case in 5% of the patients in the carbetocin group compared with 10% in the oxytocin group (p=0.031).

##### *Prevention of uterine haemorrhage due to postpartum uterine atony following vaginal delivery*

The efficacy of carbetocin compared with oxytocin was investigated in a randomised, double-blind trial in n= 29,645 patients. In addition to healthy pregnant women, patients with (gestational) diabetes or pre-eclampsia, as well as those with mild or moderate hepatic or renal impairment were included. Patients with risk factors for uterine atony (such as a history of postpartum haemorrhage, macrosomia or the use of uterotonics for induction or augmentation of labour), were also enrolled. Patients were given a single intramuscular dose of either carbetocin 100 µg or oxytocin 10 I.U. Primary endpoints were 1) the proportion of patients with a blood loss of ≥500 mL or given additional uterotonics, 2) the proportion of patients with a blood loss of ≥1000 mL.

Non-inferiority of carbetocin could be demonstrated for the first of the two co-primary endpoints. The proportion of patients with a blood loss ≥500 mL and/or given additional uterotonics on carbetocin was 14.37%, on oxytocin 14.29% (relative risk [RR] 1.01; 95% CL: 0.96 to 1.06), On the other hand, in the second of the two co-primary endpoints, the pre-defined criterion of non-inferiority was not achieved. A blood loss ≥1000 mL occurred with carbetocin in 1.52% of patients, with oxytocin in 1.44% (RR 1.05; 95% CL 0.88-1.27).

##### *Paediatric population*

In the pivotal study after vaginal delivery, 151 adolescents aged 12-18 years received carbetocin at the recommended dosage of 100 µg; 162 adolescents were treated with oxytocin. In this age group, the proportion of patients with a blood loss of ≥500 mL and/or given additional uterotonics (first co-primary endpoint) on carbetocin was 18.67%, on oxytocin 15.43%.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of carbetocin were investigated in healthy non-pregnant female subjects.

### *Absorption*

Following intravenous administration of 100 µg Carbetocin, the mean peak concentration was 7232 pg/mL.

Following intramuscular administration of a dose of 100 µg, peak concentrations were reached after 30 minutes. The bioavailability was 77%.

### *Distribution*

The mean distribution volume in pseudo-equilibrium ( $V_z$ ) was 22 L.

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

### *Metabolism*

Carbetocin is mainly degraded in the kidneys like endogenous proteins via peptidases. Metabolites were detected only in urine but not in plasma.

### *Elimination*

Carbetocin showed biphasic elimination after intravenous administration. The mean terminal half-life was 33 minutes after intravenous administration and 55 minutes after intramuscular administration. Only <1% of the injected dose was excreted unchanged by the kidney.

### *Kinetics in specific patient groups*

The pharmacokinetics of carbetocin have not been investigated in paediatric or geriatric patients or in patients with hepatic or renal impairment.

## 5.3 Preclinical safety data

In a modified and preliminary pre- and post-natal study in rats with daily injection after delivery until the 21st day of lactation, the only finding was a reduced body weight gain of the offspring in all groups compared to the controls. 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.

The product was not mutagenic in in-vitro and in-vivo tests.

## 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**

4 years.

Once the ampoule has been opened, the product must be used immediately. Unused solution must be discarded.

## **6.4 Special precautions for storage**

Keep ampoules in the outer carton, in order to protect from light.

Store below 30 °C. Do not freeze.

## **6.5 Nature and contents of container**

1ml One-point-cut (OPC), colourless Type I glass ampoules with a white OPC dot.

Packs of 10 ampoules.

## **6.6 Special precautions for disposal and other handling**

Only for i.m and i.v. use. Only particle-free, clear solutions must be used.

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7. APPLICANT/ MARKETING AUTHORISATION HOLDER & MANUFACTURER**

Made for Ferring International Center S.A., St Prex, Switzerland, by  
Ferring Pharmaceuticals (China) Co., Ltd.

No. 6 HuiLing Lu (Ferring Road), National Health Technology Park,  
Zhongshan City, Guangdong Province, People's Republic of China

and

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Steril-Gene, 45, Main Road, Mangalam Village,  
Villianur, Puducherry 605110, India

For Nigeria:  
IDA Foundation Nigeria.

## **8. WHO PREQUALIFICATION REFERENCE NUMBER**

RH095

*Please refer to the national marketing authorisation number/s available on the patient information leaflet.*

## **9. DATE OF PREQUALIFICATION**

To be confirmed.

**10. DATE OF REVISION OF THE TEXT**

03/2021