Proposed packaging material		
Code	PABA-I-MY,BN-05.01	
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Submission	☐NDA ☐Renewal ☒Variation change detail no.: #275119 #275120 #275121 CCDS v 5.0	
Code of previous version	PABA-I-MY,BN-04.01	
Changes	Update as per CCDS v 5.0	
	/ CCDS version: CCDS ver5.0 Nov 2025 ☐Core PIL version:	☐SPC country/version/date: ☐LAC no.:
Name & Date	- BRKH, 24-Feb-2026	

DURATOCIN® RTS 100mcg/ml Injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
Carbetocin 100 micrograms/ml.

List of excipients:
L-methionine
Succinic acid
Mannitol
Sodium hydroxide for pH adjustment
Water for injections

PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

THERAPEUTIC INDICATIONS
Prevention of postpartum haemorrhage due to uterine atony.

POSOLOGY AND METHOD OF ADMINISTRATION
Caesarean section under epidural or spinal anaesthesia:
Withdraw 1 ml of DURATOCIN RTS containing 100 micrograms carbetocin and administer only by intravenous injection, under adequate medical supervision in a hospital.

Vaginal delivery:
Withdraw 1 ml of DURATOCIN RTS 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 injection carbetocin must be administered slowly, over a period of 1 minute.
DURACTOCIN 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.

CONTRAINDICATIONS
During pregnancy and labour before delivery of the infant.
Carbetocin must not be used for the induction or augmentation of labour.
Hypersensitivity to carbetocin, oxytocin or to any of the excipients listed in section List of excipients.
Hepatic or renal disease.
Serious cardiovascular disorders.
Epilepsy.
The use of carbetocin at any stage before delivery of the infant is contraindicated 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.

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.

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	/ CCDS version: CCDS ver5.0 Nov 2025 ☐Core PIL version:	☐SPC country/version/date: ☐LAC no.:
Name & Date	- BRKH, 24-Feb-2026	

Carbetocin is intended for single administration only, intramuscular or intravenous. In case of intravenous administration, it must be administered slowly over a period of 1 minute. In case of persisting uterine hypotonia or atony 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 epilepsy, 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.

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 observed. 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.

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.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Carbetocin is contraindicated during pregnancy and must not be used for the induction or augmentation of labour. (See section CONTRAINDICATIONS).

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 Pharmacokinetic properties). 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Not relevant.

UNDESIRABLE EFFECTS
Summary of safety profile

Tabulated summary of adverse reactions

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Code	PABA-I-MY,BN-05.01	
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	/ CCDS version: CCDS ver5.0 Nov 2025 ☐Core PIL version:	☐SPC country/version/date: ☐LAC no.:
Name & Date	- BRKH, 24-Feb-2026	

Adverse reactions associated with carbetocin obtained from clinical studies and post-market surveillance are tabulated below. Frequencies are based on data from key randomized clinical trials involving 422 women who received 100 microgram carbetocin, i.v. during elective caesarean section under epidural anaesthesia.

The tabulation is primarily based on clinical trials in the context of caesarean section. However, a similar safety profile is observed following vaginal delivery. The type, frequency, and severity of adverse reactions observed with carbetocin after vaginal delivery or caesarean section were comparable to those reported with oxytocin.

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Frequency Not Known*
Blood and lymphatic system disorders		Anaemia		
Immune system disorders				Hypersensitivity (including anaphylactic reaction)
Nervous system disorders	Headache[1] , tremor	Dizziness		
Cardiac disorders		Tachycardia[2]	Palpitations	Bradycardia[3] Arrhythmia[3] Myocardial Ischaemia[3]
Vascular disorders	Hypotension[4] , Flushing[5]			
Respiratory, thoracic and mediastinal disorders		Chest Pain[6] , Dyspnoea		
Gastrointestinal disorders	Vomiting Nausea Abdominal pain[7]	Dysgeusia		
Skin and subcutaneous tissue disorders	Pruritus			
Musculoskeletal and connective tissue disorders		Back Pain		
General disorders and administration site conditions	Feeling hot	Chills	Pain[8]	

*The events listed in this column have been spontaneously reported and are by overall judgement considered possibly related to treatment with carbetocin. Frequencies of these adverse events cannot be estimated from the available data.
In the clinical trials sweating was reported as sporadic cases.
[1]'Headache' includes 'Headache', and 'Head discomfort'
[2]'Tachycardia' includes 'Tachycardia', and 'Heart rate increased'
[3]Reported with oxytocin (closely related in structure to carbetocin).
[4]'Hypotension' includes 'Hypotension', and 'Blood pressure decreased'
[5]'Flushing' includes 'Flushing', and 'Hot flush'
[6]'Chest pain' includes 'Chest pain', and 'Chest discomfort'
[7]'Abdominal pain' includes 'Abdominal pain', 'Abdominal tenderness', and 'Abdominal discomfort'
[8]'Pain' includes 'Uterine pain', and radiating pain when the listed pain radiates to other parts of the body

OVERDOSE
Overdosage of carbetocin may produce uterine hyperactivity whether or not due to hypersensitivity to this agent.

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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 givento 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

PHARMACODYNAMICS PROPERTIES

Pharmacotherapeutic group: Oxytocin and analogues
ATC code: H01BB03
Carbetocin is a long-acting synthetic nonapeptide analogue of oxytocin with agonist properties.
The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin, a posterior pituitary hormone.

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 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 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.

Cardiac Electrophysiology

QT trial

The effect of carbetocin on cardiac repolarisation was evaluated in a QT trial. At the high clinical exposure level, carbetocin did not cause a clinically significant QTc interval prolongation.

PHARMACOKINETICS 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

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micrograms. The terminal 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 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 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.

PRE-CLINICAL 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, embryotoxicity or carcinogenicity.

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

SHELF LIFE
3 years.Shelf life after first opening the vial: the solution must be used immediately.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Do not freeze.

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.

PACK SIZES
Pack of 5 vials.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
DURATOCIN RTS is for intravenous or 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.

Manufacturer
FERRING GmbH
Wittland 11, 24109 Kiel,
Germany

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