For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

ECBOSUERE

1. Generic Name:

Carbetocin Injection 100 mcg/ml

2. Qualitative and quantitative composition:

Each ml of solution for injection in vial contains:

Carbetocin……100 mcg

Excipients…….q. s.

Water for injection I.P……. q.s.to 1.0 ml

The excipients used are D-Mannitol, Mannitol, S-Methyl-L-Crysteine, L-Methionine, Sodium Hydroxide, Succinic Acid and Water for injection.

3. Dosage form and strength:

Dosage form: Injection

Strength: 100 mcg/ml

4. Clinical particulars:

4.1 Therapeutic indication:

It 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 ECBOSUERE containing 100 micrograms carbetocin and administer only by intravenous injection, under

adequate medical supervision in a hospital.

Vaginal delivery:

Withdraw 1 ml of ECBOSUERE 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.

ECBOSUERE 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.

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.
- 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 Drugs interactions

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

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. 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. Caution should be exercised when prescribing to pregnant women.

4.7 Effects on ability to drive and use machines:

None known.

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	
Nervous system disorders	Headache, tremor	Dizziness	
Cardiac disorders			Tachycardia, bradycardia***, arrhythmia***, myocardial ischaemia***, and QT
Vascular disorders	Hypotension,		
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 was 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		
Nervous system disorders	Headache, dizziness	Tremor	
Cardiac disorders	Tachycardia		Bradycardia***, arrhythmia***, myocardial ischaemia***, and QT prolongation***
Vascular disorders	Hypotension	Flushing	
Respiratory, thoracic and	Chest pain	Dyspnoea	
Gastrointestinal disorders	Nausea, abdominal pain, vomiting		
Skin and subcutaneous tissue disorders		Pruritus	
Musculoskeletal and	Back pain, muscular		
connective tissue disorders	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 side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

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 Mechanism of Action

Carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions, and increased uterine tone.

5.2 Pharmacodynamic properties:

Pharmacotherapeutic group**:** Oxytocin and analogues

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 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 oxytocin 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.

5.3 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.

6. Nonclinical properties:

6.1 Animal Toxicology or Pharmacology

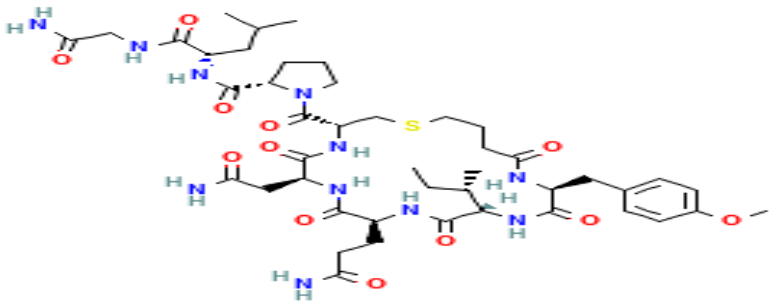
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and local tolerance. A reproductive toxicity study in rats with daily drug administration from parturition to day 21 of lactation, showed a reduction in offspring body weight gain. No other toxic effects were observed.

The indication did not warrant studies on fertility or embryo toxicity.

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

7. Description:

The chemical name is (2S)-N-[(2S)-1-[(2-amino-2-oxoethyl)amino]-4-methyl-1-oxopentan-2-yl]-1-[(3R,6S,9S,12S,15S)-6-(2-amino-2-oxoethyl)-9-(3-amino-3-oxopropyl)-12-[(2S)-butan-2-yl]-15-[(4-methoxyphenyl)methyl]-5,8,11,14,17-pentaoxo-1-thia-4,7,10,13,16-pentazacycloicosane-3-carbonyl]pyrrolidine-2-carboxamide having molecular weight of 988.2. Its empirical formula is $C_{45}H_{69}N_{11}O_{12}S$ with structural formula of



Carbetocin Injection 100 mcg/ml is clear colorless liquid free from visible particles filled in 2ml USP Type-I clear vial with 13 mm grey bormobutyl Rubber stopper and sealed with 13 mm flip off seal. The excipients used are D-Mannitol, Mannitol, S-Methyl-L-Crysteine, L-Methionine, Sodium Hydroxide, Succinic Acid and Water for injection.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than date of expiry

8.3 Packaging information:

ECBOSUERE is available in pack of 1 ml

8.4 Storage and handing instructions:

Store at up to 30^0C. Do not freeze. Keep the vials in the outer carton, in order to protect from light.

9. Patient Counselling Information

ECBOSUERE

Carbetocin Injection 100 mcg/ml

Read all of this leaflet carefully before you start taking 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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.3 How to take ECBOSUERE

9.4 Possible side effects.

9.5 How to store ECBOSUERE

9.6 Contents of the pack and other information.

9.1 What ECBOSUERE is and what it is used for

The active ingredient in ECBOSUERE is carbetocin. It is similar to a substance called oxytocin, which is naturally produced by the body to make the womb contract during childbirth.

It is used for the prevention of postpartum haemorrhage due to uterine atony

9.2 What you need to know before you take ECBOSUERE

Do not take ECBOSUERE if:

- 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
- 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.

Warnings and precautions

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

- 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.

ECBOSUERE may cause a buildup of water in the body which can lead to drowsiness, listlessness and headache.

Taking other medicines

Taking another medicine while you are taking ECBOSUERE can affect how it or the other medicine works. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including those you may have bought yourself without a prescription.

Pregnancy and breast-feeding

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

Driving and operating machines

ECBOSUERE do not affect the ability to drive or operate machinery.

9.3 How to take ECBOSUERE

Your doctor will decide the dose which is best for you. Always follow your doctor's instructions completely and also follow any special instructions or warnings which appear on the label which the pharmacist has put on the package. Contact your doctor if your symptoms worsen or do not improve. If you do not understand, or are in any doubt, ask your doctor or pharmacist.

Elderly

The experience with Elderly is limited.

Children

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

If you take more ECBOSUERE than you should

If you are accidentally given too much ECBOSUERE, 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.

9.4 Possible side effects.

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

When ECBOSUERE 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

Not known: frequency cannot be estimated from the available data

Fast heartbeat

Side effects seen with similar products that might be expected with carbetocin:

Slow heartbeat, irregular heartbeat, chest pain, fainting or palpitations which may mean the heart is not beating properly. Infrequently some women might experience sweating.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5 How to store ECBOSUERE

Store at up to 30^0C. Do not freeze. Keep the vials in the outer carton, in order to protect from light

9.6 Contents of the pack and other information. What ECBOSUERE contains

The active substances in ECBOSUERE is Carbetocin.

The other ingredients are D-Mannitol, Mannitol, S-Methyl-L-Crysteine, L-Methionine, Sodium Hydroxide, Succinic Acid and Water for injection

Contents of the pack: Available in pack of 1 ml

10 Details of manufacturer

Precise Biopharma pvt. Ltd.

At. Plot No 8, Pharmacity, Selaqui

Dehradun, Uttarakhand 248 011

11 Details of permission or licence number with date

Mfg. Licence No. 20/UA/LL/SC/P-2019 Issued on 02.05.2019

12 **Date of revision**

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ECBOSUERE 100 mcg/ml /Feb-23/01/PI