

HEAT-STABLE CARBETOCIN

INJECTION, 100 MICROGRAMS/ML

GENERAL PRODUCT INFORMATION

Postpartum hemorrhage (PPH) is commonly defined as a blood loss of 500 mL or more within 24 hours after birth. PPH is the leading cause of maternal mortality in low- and middle-income countries (LMICs) and the primary cause of nearly one quarter of all maternal deaths globally. The majority of deaths due to PPH could be avoided through the use of prophylactic uterotonics during the third stage of labor and by timely and appropriate management.

Carbetocin is a long-acting synthetic agonist analogue of human oxytocin. It has a greater biological effect and longer half-life than oxytocin.¹ It has been used for the prevention of PPH following Caesarean section births since 1997. The original formulation requires refrigeration.²

Recently, a heat-stable formulation of carbetocin was developed to specifically address limitations in refrigeration and cold-chain transport of PPH medications in LMICs. The heat-stable formulation, consisting of 0.1 micrograms/mL carbetocin in sodium succinate buffer, mannitol, and methionine, is stable at temperatures up to 30°C.³ When used for PPH prevention after vaginal birth, heat-stable carbetocin has demonstrated non-inferiority to oxytocin for the prevention of blood loss of at least 500 mL or the use of additional uterotonic agents.⁴

¹ Dell-Kuster, S., Hoesli, I., Lapaire, O. et al. 2016. "Efficacy and safety of carbetocin applied as an intravenous bolus compared to as a short-infusion for caesarean section: study protocol for a randomized controlled trial." *Trials* 17: 155. <https://doi.org/10.1186/s13063-016-1285-5>.

² Widmer, M., Piaggio, G., Abdel-Aleem, H. et al. 2016. "Room temperature stable carbetocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally: study protocol for a randomized controlled trial." *Trials* 17: 143. <https://doi.org/10.1186/s13063-016-1271-y>

³ Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

⁴ Widmer, M., Piaggio, G., Nguyen, T.M., et al. 2018. "Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth." *New England Journal of Medicine* 379(8): 743-752. doi: 10.1056/NEJMoa1805489

Heat-stable carbetocin is included on the WHO Model List of Essential Medicines (EML), and in the WHO recommendations on uterotonics for the prevention of postpartum hemorrhage.⁵ WHO recommends the use of heat-stable carbetocin (100 micrograms/mL, intramuscularly or intravenously), along with misoprostol and ergometrine, for the prevention of PPH for all births in settings where oxytocin is unavailable or its quality cannot be guaranteed, and where its cost is comparable to other effective uterotonics.

It should be noted that the WHO recommendation applies only to the use of carbetocin for the prevention of PPH. Unlike oxytocin, misoprostol and ergometrine, carbetocin is not indicated for treatment of PPH, and it is contraindicated during pregnancy and must not be used for the induction or augmentation of labor.

Heat-stable carbetocin is available under the proprietary names Pabal®, Duratocin®, and Carbetocin Ferring. When cost is a concern, it should be noted that Carbetocin Ferring is made available by Ferring at an affordable and sustainable price for use in public-sector healthcare facilities in LMICs. This price is a subsidized price of \$0.31 ± 10% per ampoule of 100 micrograms Carbetocin Ferring, Ex Works.⁶ This is comparable to the current United Nations Population Fund (UNFPA) price for oxytocin of \$0.33 per unit (10 I.U.), making Carbetocin Ferring a cost-effective option in low-income settings.

KEY CONSIDERATIONS IN PROCUREMENT

1. Only the heat-stable formulation of carbetocin should be procured. Procurers should pay attention to the formulation declared by the manufacturer and product labeling for storage at room temperature (below 30°C).
2. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.
3. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use, as carbetocin is an injectable medicine.

⁵ WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at <http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1> Last accessed: August 2022

⁶ Ferring Pharmaceuticals. 2020. "Swissmedic approves Carbetocin Ferring for the prevention of postpartum haemorrhage in all births." Available at: <https://www.ferring.com/swissmedic-approves-carbetocin-fering-for-the-prevention-of-postpartum-haemorrhage-in-all-births/> Last accessed: August 2022

KEY QUALITY CONSIDERATIONS

Product formulation

The heat-stable formulation differs from the non-heat-stable (refrigerated) formulation only in its excipients. Comparison of the two existing formulations of carbetocin is shown in Table C-I below.

Table C-I. Composition of heat-stable carbetocin injection⁷

| CARBETOCIN HEAT-STABLE FORMULATION | | CARBETOCIN REFRIGERATED FORMULATION | |
|---------------------------------------|-------------------|--|-------------------|
| Component | Function | Component | Function |
| Carbetocin | Active ingredient | Carbetocin | Active ingredient |
| Succinic acid | Buffer | Sodium chloride | Isotonicity agent |
| Mannitol | Isotonicity agent | Glacial acetic acid | pH adjustment |
| L-methionine | Antioxidant | Water for injection | Solvent |
| Sodium hydroxide | pH adjustment | | |
| Water for injection | Solvent | | |

Procurement of carbetocin heat-stable formulation as per the WHO EML is recommended.

Product specification

Heat-stable carbetocin injection products must comply with the quality specifications suggested in “Product Specifications” section below.

Packaging and labeling

Heat-stable carbetocin injection is supplied in single-dose ampoules (e.g. Carbetocin Ferring) and single-dose vials (e.g. Pabal®, Duratocin®) containing 100 micrograms in 1 mL.

The container-closure system (ampoule/vial) must be sufficient to preserve sterility during the shelf life of the product.

Additional information about heat-stable carbetocin injection packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Heat-stable carbetocin does not need to be maintained in the cold chain, but should be stored below 30°C.

⁷ Widmer, M., Piaggio, G., Abdel-Aleem, H. et al. 2016. “Room temperature stable carbetocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally: study protocol for a randomized controlled trial.” *Trials* 17: 143. <https://doi.org/10.1186/s13063-016-1271-y>

Procurers must ensure that the product is stored safely so that the ampoule/vial cannot break or leak, which would compromise its sterility.

| | |
|--|---|
| Name of the Medicinal Product | Heat-stable carbetocin injection |
| Chemical Name | <p>Carbetocin</p> <p>I-desamino-I-monocarba-2-(0-methyl)-tyrosine oxytocin</p> <p>Carbetocin is a long-acting synthetic agonist analogue of human oxytocin, with antihemorrhagic and uterotonic activities. Upon administration, carbetocin binds to oxytocin receptors in the uterine smooth muscle, resulting in rhythmic contractions, increased frequency of existing contractions, and increased uterine tone.</p> |
| Chemical Structure | <p>$C_{45}H_{69}N_{11}O_{12}S$</p> $ \begin{array}{ccccccccccc} & & CH_2 & & & CH_2 & & & CH_2 & & \\ & & & & & & & & & & \\ O=C & - & Tyr & - & Ile & - & Gln & - & Asp & - & Cys & - & Pro & - & Leu & - & Gly & - & NH_2 \\ & & & & & & & & & & & & & & & & & & \\ & & Me & & & NH_2 & & NH_2 & & & & & & & & & & & \end{array} $ |
| Pharmaceutical Form | <p>Sterile solution for injection</p> <p>A clear, colorless solution</p> |
| Qualitative and Quantitative Composition | <p>Heat-stable carbetocin injection contains 100 micrograms of carbetocin per mL.</p> <p>List of typical excipients⁸:</p> <ul style="list-style-type: none"> ■ L-methionine |

⁸ Based on the formulation of an innovator product, Duratocin® / Pabal®.

Packaging and Presentation

- Succinic acid
- Mannitol
- Sodium hydroxide for pH adjustment
- Water for injection

The WHO EML states “carbetocin injection (heat stable) 100 micrograms/mL”, which does not preclude procurement of any particular presentation of carbetocin. Heat-stable carbetocin injection is packed in glass ampoules or vials.

SUPPLY



Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of August 2022, there is only one heat-stable carbetocin injection product prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>.

Table C-2. List of WHO-prequalified heat-stable carbetocin injection

| | |
|---------------------------------------|---|
| WHO REF. NUMBER | RH095 |
| MARKETING AUTHORIZATION HOLDER | Ferring International Center SA, Chemin de la Vergognausaz 50, St Prex, 1162, Switzerland |
| MANUFACTURING SITE | FPP manufacturing site: <ul style="list-style-type: none">- Ferring Pharmaceuticals (China) Co Ltd, No. 6 HuiLing Lu (Ferring Road), National Health Technology Park, Zhongshan City, Guangdong Province, China (People's Republic of)- Steril-Gene Life Sciences (P) Ltd., 45, Mangalam Main Road, Mangalam Village, Villianur Commune, Puducherry, 605 110, India API manufacturing site: PolyPeptide Laboratories France SAS, Buildings 1 and 2, 7 rue de Boulogne, Strasbourg, 67100, France |
| DOSAGE FORM AND STRENGTH | Solution for injection 100 micrograms/mL |

| | |
|-----------------------------------|--|
| PACKAGING AND PRESENTATION | Ampoule; Type I glass 1 mL x 10's |
| DATE OF PRE-QUALIFICATION | July 4, 2022 |
| SHELF LIFE | 48 months |
| STORAGE CONDITION | Do not store above 30°C. Do not freeze. Keep ampoules in the outer carton, in order to protect from light. |

SRA-approved products

Table C-3. Examples of SRA-approved heat-stable carbetocin injection

| PRODUCT NAME | SRA | MARKETING AUTHORIZATION HOLDER | REGISTRATION NUMBER | PACKAGING AND PRESENTATION | SHELF LIFE | STORAGE CONDITION |
|--|--------------------------|---------------------------------------|----------------------------|---|-------------------|--|
| PABAL 100 micrograms/mL solution for injection | UK MHRA | Ferring Pharmaceuticals Ltd, UK | PL 03194/0058 | Type I glass vials (2R) with type I bromobutyl stoppers with aluminum crimp cap | 3 years | Keep vials in the outer carton, in order to protect from light. Store below 30°C. Do not freeze. |
| Carbetocin Ferring Injektionslösung 100 µg/mL | Swissmedic (Switzerland) | Ferring AG, Switzerland | 67157 | Type I glass ampoule | Not specified | Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light. |
| PABAL Injektionslösung 100 µg/ml | Swissmedic (Switzerland) | Ferring AG, Switzerland | 58079 | Type I glass vials (2R) with type I bromobutyl stoppers with aluminum crimp cap | Not specified | Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light. |
| PABAL 100 microgrammes/mL, solution injectable | ANSM, France | Ferring SAS, France | 34009 550 109 2 0 | Type I glass vials (2R) with type I bromobutyl stoppers with aluminum crimp cap | 3 years | Store the vials in the original outer packaging, in order to protect from light. Store at a temperature not exceeding 30°C. Do not freeze. |
| PABAL 100 Mikrogramm/mL Injektionslösung | BfArM, Germany | Ferring Arzneimittel GmbH, Germany | 64579.00.00 | Type I glass vials (2R) with type I bromobutyl stoppers with aluminum crimp cap | 3 years | The vials should be kept in the original packaging in order to protect the contents from light. Do not store above 30°C. Do not freeze. |

| PRODUCT NAME | SRA | MARKETING AUTHORIZATION HOLDER | REGISTRATION NUMBER | PACKAGING AND PRESENTATION | SHELF LIFE | STORAGE CONDITION |
|--|---------------|--|----------------------------|---|-------------------|---|
| Pabal 100 mikrogram/mL injektionsvätska, lösning | MPA, Sweden | Ferring Läkemedel AB, Sweden | 24549 | Type I glass vials (2R) with type I bromobutyl stoppers with aluminum crimp cap | 3 years | Store the vials in the outer carton. Sensitive to light. Do not store above 30°C. Do not freeze. |
| DURATOCIN solution for injection, 100 micrograms/mL | Health Canada | Ferring INC, Canada | 02496526 | Colorless glass vials with bromobutyl rubber stoppers and aluminum crimp cap. | Not specified | Store at room temperature (15°C to 30°C). |
| DURATOCIN 100 micrograms/mL solution for injection | TGA Australia | Ferring Pharmaceuticals Pty Ltd, Australia | AUST R 233671 | 1 mL clear glass vial with a bromobutyl rubber stopper and an aluminum crimp cap with a tear-off over cap | 3 years | Store below 30°C. Once the vial has been opened, the product should be used immediately. |

Note: Carbetocin is not available in the United States.

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
- UK MHRA: <https://products.mhra.gov.uk/>
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: <https://www.swissmedicinfo.ch/>
- HealthCanada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>
- TGA Australia: <https://www.tga.gov.au/australian-register-therapeutic-goods>

Related products

Other presentations of carbetocin injection that exist in the market include:

- Carbetocin 100 micrograms/mL solution for injection in pre-filled glass syringe

It is used for the same indications, dosage and administration. However, it should be noted that carbetocin injection in pre-filled syringe is the non-heat-stable formulation, which contains sodium chloride, acetic acid for pH adjustment, and water for injections. It is typically labeled for storage under refrigerated conditions, between 2–8°C.⁹

STORAGE, STABILITY, AND DEGRADATION

⁹ Medicines & Healthcare Products Regulatory Agency (MHRA). 2021. Summary of Product Characteristics of Carbetocin 100 micrograms/mL solution for injection in pre-filled syringe. Available at: <https://mhraproducts4853.blob.core.windows.net/docs/a64a13c549a55f490a0b84f6db5be369b52c5a14> Last accessed: August 2022



Shelf life: 36–48 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table C-2 and Table C-3 above respectively.

Malm et al.¹⁰ reported that the main degradation routes of carbetocin are found to be deamidation, oxidation, and racemization. Deamidation of the amide side-chains of asparagine and glutamine and the amidated glycine C-terminus is favored by low pH (acid-catalyzed hydrolysis), and to some extent by high pH (direct base hydrolysis). The thioether linkage is sensitive to oxidation, which is accelerated by increasing pH. The racemization of the asparagine residue from the L to the D-form is an important degradation route at pH-values above ≈ 6 . Due to the presence of an antioxidant (methionine) in the heat-stable carbetocin formulation, degradation by oxidation was negligible at all pH-values. The optimum pH where the sum of remaining degradation pathways is minimized was determined to be pH 5.45.

PRODUCT SPECIFICATIONS



There is currently no published pharmacopeial specifications for heat-stable carbetocin 100 micrograms/mL injection. Therefore, the product should meet the in-house specifications established by the manufacturers, which should comply with the ICH Q6A guideline.¹¹ Some general factors that the procurers should consider when assessing the in-house specifications of heat-stable carbetocin injection are highlighted in this section. Additional considerations in quality assessment of heat-stable carbetocin are included in part 2 of the attached Annex.

The minimum parameters to be included in the product specifications of heat-stable carbetocin injection include appearance, pH, identification and assay of active pharmaceutical ingredient (API), impurities, identification and assay of methionine (antioxidant), bacterial endotoxins, sterility, extractable volume and particulate matter.

Due to the lack of compendial methods, any in-house analytical procedures (e.g. HPLC assay and impurity methods) used for routine testing of heat-stable carbetocin injection should be shown to be fully validated.

¹⁰ Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

¹¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1999. "Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A." Geneva: ICH. Available at: <https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf>

pH

The study from Malm et al. demonstrated the optimum pH of heat-stable carbetocin to control the amount of impurities as pH 5.45. Heat-stable carbetocin injection can therefore be expected to demonstrate a pH in the region of that value for optimum stability.

Assay of API (carbetocin)

The acceptable limit for the API content in the product release specifications is $\pm 5\%$ of the label claim (i.e. 95.0–105.0%), whereas it is $\pm 10\%$ of the label claim (i.e. 90.0–110.0%) in the shelf-life specifications.

Impurities

According to the study from Malm et al., known degradation products found in heat-stable carbetocin injection are shown in the below table:

Table C-4. Degradation products of carbetocin

| MATERIAL | PATHWAY |
|--|--------------|
| [Gly ³ -OH]carbetocin | Hydrolysis |
| [Asp ⁵]carbetocin | Hydrolysis |
| [β Asp ⁵]carbetocin | Hydrolysis |
| [Glu ⁴]carbetocin | Hydrolysis |
| Carbetocin sulfoxide isomer 1 | Oxidation |
| Carbetocin sulfoxide isomer 2 | Oxidation |
| [D-Asn ⁵]carbetocin | Racemization |

Tests and acceptance limits for those impurities as well as the total impurities should be included in the product specifications.

As carbetocin is a synthetic peptide that is beyond the scope of the ICH Q3B guideline¹², the impurities limits should be set based on thresholds for reporting, identification and qualification of organic impurities described in the European Pharmacopoeia (Ph. Eur.) General Monograph 'Substances for Pharmaceutical Use' as follows:

- reporting threshold above 0.10%
- identification threshold above 0.5%
- qualification threshold above 1.0%.

¹² ICH. 2006. "Impurities in new drug products Q3B(R2)." Geneva: ICH. Available at: <https://database.ich.org/sites/default/files/Q3B%28R2%29%20Guideline.pdf>

Therefore, any impurities observed above the identification threshold (0.5%) should be identified, and the limits above the qualification threshold (1.0%) should be qualified. A limit of no more than 0.5% for unspecified impurities should be included in the heat-stable carbetocin product specifications. Procurers need to verify from manufacturers that there is satisfactory data to justify the impurities limits.

Identification and assay of methionine

L-methionine is included in the heat-stable formulation of carbetocin as an antioxidant. Identification and content determination tests and limits for methionine should therefore be included in the product specifications, according to the Committee for Medicinal Products for Human Use (CHMP) 'Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product'.¹³ If the lower limit for the proposed acceptance criterion for the assay of methionine is below 90%, the adequacy of the specified limits should be justified on the basis of controlled conditions and stability testing, to ensure that sufficient antioxidant remains to protect the product throughout its entire shelf-life.

Tests required for parenteral product

Heat-stable carbetocin injection is a parenteral product, it should therefore meet pharmacopeial standards for sterility, bacterial endotoxins, and particulate matter as well.

¹³ Committee for Medicinal Products for Human Use (CHMP). 2007. "Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product." European Medicines Agency, Amsterdam. (EMA/CHMP/QWP/396951/2006). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-excipients-dossier-application-marketing-authorisation-medicinal-product-revision-2_en.pdf

PART 1: CLINICAL PARTICULARS¹⁴

Therapeutic indications

Prevention of postpartum hemorrhage due to uterine atony.

Posology, method, and duration of administration

Posology

Carbetocin must be administered as soon as possible after delivery of the infant and preferably before delivery of the placenta. It should be administered in an obstetric unit by appropriately skilled and trained health care providers

Caesarean section under epidural or spinal anesthesia:

A single dose of 100 micrograms carbetocin (1 mL) by slow intravenous injection (over 1 minute) after delivery of the infant.

There are limited data on the use of carbetocin with general anesthesia.

Vaginal delivery:

A single dose of 100 micrograms (1 mL) by slow intravenous injection (over 1 minute) or by intramuscular injection, after delivery of the infant.

Children and adolescents

Only limited data are available on the safety and efficacy of carbetocin in adolescents after the menarche. In adolescents from the age of 15 years, the same dose as in adults may be administered under adequate supervision, if indicated.

Carbetocin is not recommended in adolescents under 15 years of age, i.e. those who are not yet fully mature, due to lack of data.

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

Elderly

There is no indication for use in post-menopausal women.

Hepatic or renal impairment

¹⁴ Based on Carbetocin Ferring Summary of Product Characteristics published by WHO Prequalification (WHO reference number RH095) Available at: <https://extranet.who.int/pgweb/sites/default/files/RH095part4v1.pdf> Last accessed: March 2023

The pharmacokinetics of carbetocin in patients with hepatic or renal impairment have not been investigated. Therefore, carbetocin should not be used in these patients (see “Contraindications” section)

Method of administration

For intravenous or intramuscular administration. For intravenous administration carbetocin must be administered slowly, over 1 minute. Carbetocin is for single administration only. No further doses of carbetocin should be administered.

Contraindications

Carbetocin is contraindicated in the following circumstances:

- Pregnancy and labor before delivery of the infant
- For induction or augmentation of labor
- Serious cardiovascular disorders
- Epilepsy
- Renal or hepatic disorders
- Hypersensitivity to carbetocin, oxytocin or to any of the excipients in the product

Special warnings and precautions for use

Carbetocin should be used only in obstetric units by appropriately skilled and trained health care providers.

Persistent or excessive bleeding

If uterine bleeding persists, 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 after caesarean section, or disorders of blood coagulation.

If uterine hypotonia or atonia persists after administration of carbetocin, with consequent excessive bleeding, therapy with another uterotonic can be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persisting uterine atony after oxytocin administration.

Water retention

Animal studies show that carbetocin has some antidiuretic activity (vasopressin activity: <0.025 IU/vial) and there is, therefore, a risk of water intoxication with hyponatremia, especially in patients receiving large volumes of infusion solutions. Attention should be paid to the early signs of water intoxication or hyponatremia – such as drowsiness, listlessness and headache – to prevent complications such as convulsions and coma.

In the presence of migraine, asthma, cardiovascular disease, and other conditions in which a rapid increase in extracellular water may be hazardous for an already overburdened system, carbetocin should only be used after carefully weighing up of the benefits and risks and under appropriate supervision.

Cardiac risks (including QT prolongation)

Adverse cardiac effects such as bradycardia, QT prolongation, arrhythmias, and myocardial ischemia have occurred with oxytocin, especially after rapid intravenous injection. It is not known if these effects are caused by oxytocin treatment or were caused by other simultaneously administered medicines. There are no data on a possible pathophysiological mechanism. Because carbetocin is structurally closely related to oxytocin, carbetocin should be used with special caution in patients with long-QT syndrome or other risk factors for QT prolongation (such as co-medication with drugs with a risk of QT-prolongation).

Sodium

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

Further precautions

Carbetocin has not been investigated in patients with eclampsia. It should therefore be used 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.

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 has been administered in association with a number of analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anesthesia. No drug interactions were observed.

The following interactions have occurred involving oxytocin. Since carbetocin is structurally related to oxytocin, they might also occur with carbetocin:

- Prostaglandins potentiate the effect of oxytocin. Therefore, prostaglandins should not be used at the same time as carbetocin. If simultaneous use cannot be avoided, then the patient must be closely monitored.
- Inhalation anesthetics, e.g. halothane, can potentiate the hypotensive effect and reduce the effect of carbetocin on the uterus. In case of concomitant use of such anesthetics with oxytocin, arrhythmias have also been reported
- Hypertension has been reported when oxytocin was given 3 to 4 hours after a vasoconstrictor was administered in conjunction with caudal-block anesthesia.

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

Fertility, pregnancy and lactation

Pregnancy

Carbetocin is contraindicated during pregnancy and must not be used for the induction of labor (see “Contraindications” section above).

Breastfeeding

No relevant effects on milk let-down have been reported during clinical trials. Small amounts of carbetocin have been detected in breast milk of nursing women. The small amounts of carbetocin transferred into colostrum or breast milk after a single injection of carbetocin, and subsequently ingested by the infant, are likely to be degraded by enzymes in the gastrointestinal tract and therefore have probably no clinically relevant effects in the breastfed infant.

Breast-feeding can be started without restrictions after the use of carbetocin.

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.

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 the clinical trials after vaginal delivery were also comparable in frequency and severity to those of oxytocin.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as very common (at least 1 in 10); common (1 in 100 to 1 in 10); uncommon (1 in 1000 to 1 in 100); rare (1 in 10,000 to 1 in 1000); or very rare (less than 1 in 10,000).

Table C-5. Adverse events observed with carbetocin

| SYSTEM ORGAN CLASS | ADVERSE DRUG REACTION |
|--|---|
| Blood and lymphatic system disorders | Common: anemia |
| Immune system disorders | Not known: hypersensitivity reactions (including anaphylactic reactions) |
| Nervous system disorders | Very common: headache, tremor Common: dizziness |
| Cardiac disorders | Uncommon: tachycardia (see also “Special warnings and precautions for use” section above) |
| Vascular disorders | Very common: hypotension, flushing |
| Respiratory, thoracic, and mediastinal disorders | Common: dyspnea |
| Gastrointestinal disorders | Very common: nausea, abdominal pain Common: metallic taste, vomiting |
| Skin and subcutaneous tissue disorders | Very common: pruritus |
| Musculoskeletal and connective tissue disorders | Common: back pain |
| General disorders and administration site conditions | Very common: feeling of warmth Common: chills, pain, chest pain, sweating |

Reactions at the administration site were not specifically investigated. As with other drugs, local irritation is likely, especially with intramuscular administration.

Overdose

An overdose with uterotonic agents such as carbetocin can induce uterine hyperactivity. Symptoms of an overdose observed with oxytocin are also likely with carbetocin. If carbetocin is used before delivery of the infant (see “Contraindications” section), hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions can occur, with the risk of uterine rupture or increased postpartum hemorrhage.

An overdose may lead to hyponatremia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake.

Treatment of overdosage consists of symptomatic and supportive therapy. If signs or symptoms of overdosage occur, oxygen should be given. In the case of water intoxication, it is important to restrict fluid intake, initiate diuresis, correct electrolyte disturbances, and control convulsions if they occur.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of heat-stable carbetocin products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on heat-stable carbetocin injection.

API

As of August 2022, there is no carbetocin API prequalified by the WHO PQP. Certificate of suitability to monographs of the European Pharmacopeia (CEP) is not applicable since no Ph. Eur. monograph exists for carbetocin.

The WHO-prequalified heat-stable carbetocin injection (Carbetocin Ferring) has used carbetocin API manufactured by PolyPeptide Laboratories France SAS.¹⁵ This manufacturer can be considered as a trusted source as it has passed the assessment of WHO PQP team. However, it is recommended to check for updated information on the WHO PQP website at the time of quality assessment. Other manufacturers of carbetocin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines¹⁶ to support the quality assessment.

There is currently no published pharmacopeial specifications for carbetocin API. Therefore, in-house specifications should be established by the manufacturers and adhere to the ICH Q6A guideline. The typical specifications of carbetocin API include the following parameters: identification, assay, related substances, specific optical rotation, water content, acetic acid content, residual solvents, microbial limits, and bacterial endotoxins.¹⁷ If intended for use in the aseptic manufacture of heat-stable carbetocin injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

According to Malm et al.,¹⁸ [D-Cys6]carbetocin and [des-Gln4]carbetocin are known synthesis-related impurities of carbetocin API. They should therefore be appropriately controlled in the specifications of carbetocin API. Furthermore, any impurities above the identification threshold given in the Ph. Eur. General monograph 'Substances for pharmaceutical use' (0.5%) should be identified, and the limits above

¹⁵ WHO. 2022. Prequalified medicinal products: RH095. Available at: <https://extranet.who.int/pqweb/medicine/4419> Last accessed: August 2022

¹⁶ WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46th report. WHO Technical Report Series, No. 970. Geneva: WHO.

¹⁷ PolyPeptide Group. 2021. Carbetocin drug substance specification. Available at: <https://www.polypeptide.com/wp-content/uploads/2018/09/Carbetocin-web-spec-2021.pdf> Last accessed: August 2022

¹⁸ Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

the qualification threshold (1.0%) should be qualified. A limit of not more than 0.5% for unspecified impurities should be included in the carbetocin API specifications.

Carbetocin is hygroscopic.¹⁹ It should be stored in a tightly closed original container at 2–8°C and avoid exposure to light,²⁰ or in the conditions recommended by the API manufacturer.

Excipients

The typical excipients of heat-stable carbetocin injection are shown in the table below.²¹ There are no special concerns with the excipients. No excipient with the risk of transmitting TSE/BSE is used.

Table C-7. Excipients of heat-stable carbetocin injection

| INGREDIENT | FUNCTION |
|---------------------|-------------------|
| L-methionine | Antioxidant |
| Succinic acid | Buffer agent |
| Mannitol | Isotonicity agent |
| Sodium hydroxide | pH adjustment |
| Water for injection | Solvent |

Excipients should be controlled according to the requirements of the officially recognized compendial standard (Ph.Int., Ph.Eur./BP, USP), and include a test for bioburden or bacterial endotoxins.

If excipients not contained in the innovator product are used in any generic products, it is necessary to demonstrate compatibility with the carbetocin API through chromatographic results (assay, purity). The choice of excipients, their concentration and their characteristics can influence the heat-stable carbetocin product performance and therefore should be discussed relative to their respective functions.

Manufacturing process

The manufacturing process of heat-stable carbetocin injection is a standard process—conducted under appropriate aseptic conditions—including the solution preparation steps with adjustment of pH, pre- and sterile filtration, filling and sealing of the ampoules/vials. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

¹⁹ <https://www.trc-canada.com/product-detail/?C175925> Last accessed: August 2022

²⁰ PolyPeptide Group. 2019. Carbetocin safety data sheet. Available at: <https://www.polypeptide.com/wp-content/uploads/2018/09/Carbetocin-SDS-v10-UK.pdf> Last accessed: August 2022

²¹ Based on formulation of an innovator product, , Duratocin® / Pabal®.

The pH adjustment is crucial for heat-stable carbetocin stability because it was shown by Malm et al.²² that carbetocin is most stable at pH 5.45 with low degradation ($\leq 4\%$) after 12 months at 40°C/75% RH. Carbetocin was found to degrade mainly by deamidation of the glutamine residue and the amidated glycine C-terminus at pH-values below the optimum and by racemization of the asparagine residue at pH values above the optimum.

The filters used in the sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components.

The selection of the environment temperature conditions may depend on the length of each of the stages of production, the time between stages and how bulk solution is packed and stored.

Nitrogen purging should be carried out throughout the manufacturing and filling process to minimize contact with atmospheric and dissolved oxygen. If bulk solution storage is required, store the solution under a nitrogen blanket. The lid of the manufacturing tank should be opened and closed immediately after each addition.

Heat-stable carbetocin injection may be manufactured by aseptic technique for the whole process. When aseptic processing is used, all the ingredients must be sterile grade and comply with the test for sterility before use.

For the validation of aseptic processing, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

A manufacturing process validation protocol for the validation of the first three production scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. In cases where the manufacturer is already manufacturing production scale batches, full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D “Guideline for Elemental Impurities”. Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule or vial should be used.

Suitability of the container should be demonstrated, including the following properties:

Safety

- Glass ampoule/vial must meet compendial requirements such as USP<660> and USP<1660>.

²² Malm, M., Madsen, I., Kjellström, J. 2018 “Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries.” *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

- Rubber stopper (for vial) must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:

- One-time test reported as part of product development
- Routine leak testing performed as part of product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as sorption.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Pabal® (carbetocin 100 micrograms/mL injection, Ferring) and Duratocin® (carbetocin 100 micrograms/mL injection, Ferring). The composition of the proposed product should be the same as the comparator product.

Equivalence of any generic heat-stable carbetocin products with the comparator product should be demonstrated, and the applicant should provide comparative results of physicochemical properties (e.g. pH, density, osmolarity etc.) for both the generic and comparator products.