MODULE III

OXYTOCIN

USAID
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Manual for Procurement & Supply of
Quality-Assured MNCH Commodities

OXYTOCIN

INJECTION 10 IU IN 1-ML

GENERAL PRODUCT INFORMATION

Postpartum hemorrhage (PPH) refers to excessive bleeding after childbirth. Left untreated, it can lead to anemia, shock, and also death. PPH is the leading cause of maternal death in low- and middle-income countries. Proper screening, prevention, and treatment of PPH can save women's lives and reduce global burden of maternal mortality.

Prevention and treatment for most cases of PPH require the use of an uterotonic medicine to increase muscle contractions in the uterus that compress the blood vessels. Oxytocin is recommended by WHO as the first-line medicine for the prevention and treatment of postpartum hemorrhage. It is also prioritized as an essential medicine by the UN Commission on Life-Saving Commodities for Women and Children.

Other uterotonic medicines, such as misoprostol, ergotamine and ergometrine, have some drawbacks. Misoprostol is the second-line medicine, recommended by the WHO for the prevention and treatment of PPH only when oxytocin use is not feasible. It is recommended for use in women giving birth outside of a health facility (e.g., home deliveries), as it is administered by pill rather than by injection. Ergotamine and ergometrine have more side effects, should only be given after the birth of the placenta, must be kept in the cold chain, and are contraindicated for many conditions, including pre-eclampsia.

Oxytocin is the safest and most effective uterotonic medicine for the prevention and treatment of PPH, which should be procured over other uterotonic medicines and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

KEY CONSIDERATIONS IN PROCUREMENT

1. 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.

2. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use as oxytocin is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Oxytocin injection products must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

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

Additional information about oxytocin injection packaging and labeling can be found in Annex A2 item 4.

Storage, transportation, and distribution

Oxytocin that is procured should be labeled and stored between 2˚C and 8˚C from the point of manufacture to the point of use to maintain the product quality.

Although some manufacturers state the product can be stored at controlled room temperature, between 20˚C and 25˚C, it should be noted that room temperatures in health facilities in tropical countries often exceed the controlled room temperature, which can put oxytocin quality at risk.

Oxytocin is temperature-sensitive and loses effectiveness after three months of storage at temperatures above 30˚C. Significant quality issues can stem from inappropriate transport and storage, which may expose the product to high temperatures that can degrade it and result in low potency.

Detailed records of all stages of transport from the date the oxytocin product leaves the FPP manufacturer to its arrival at the procurer facility should be provided to assure the product has not been subject to adverse temperatures for a potentially harmful length of time. The procurer should reach agreement with the FPP manufacturer and/or distributor to use the most suitable transport and handling to protect the product from exposure to high temperatures. Data loggers or suitable temperature-time integrators can be used to alert procurers of any excursions during transportation and be alert to possible degradation of oxytocin.

Name of the Medicinal Product

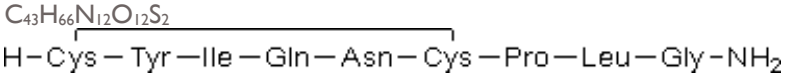
Oxytocin injection

Chemical Name

Oxytocin (L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide)
Oxytocin is a synthetic cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. Being wholly synthetic, it does not contain vasopressin and has a constant and reliable effect.

Chemical Structure

$C_{43}H_{66}N_{12}O_{12}S_2$



Pharmaceutical Form

Sterile solution for injection
A clear, colourless solution

Qualitative and Quantitative Composition

Oxytocin injection is a sterile solution of oxytocin or a sterile dilution of oxytocin concentrated solution in water for injection. It contains 10 IU of oxytocin per mL.

List of possible excipients[1]:
- Acetic acid
- Chlorobutanol
- Ethanol
- Sodium acetate trihydrate
- Water for injection

Packaging and Presentation

The WHO Essential Medicines List states "oxytocin injection 10 IU in 1-mL," which does not preclude procurement of any particular presentation of injectable oxytocin. Oxytocin injection is generally packed in glass ampoules. However, some manufacturers provide the product in glass or plastic vial.

[1] Based on the formulation of an innovator product, Syntocinon®.

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 February 2018, two oxytocin injections are prequalified by the WHO PQP, as shown below. It is recommended to check the updated information at the time of procurement, by going to https://extranet.who.int/prequal/content/prequalified-lists/medicines.

Table O-1. List of WHO Prequalified Oxytocin Injection

WHO REF. NUMBER	RH050	RH053(a)
MARKETING AUTHORIZATION HOLDER	PT Sanbe Farma, Jl. Taman Sari no. 10, Bandung, 40116, Indonesia	Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia
MANUFACTURING SITE	FPP manuf. site: PT Sanbe Farma, Sterile Preparation Plant, Unit 3, Jl. Industri Cimarene No. 8, Desa Cimareme, Kecamatan Ngamprah, Kabupaten Bandung Barat, 40553, Indonesia	FPP manuf. site: HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia
	API manuf. site: Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia	API manuf. site: Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia
DOSAGE FORM AND STRENGTH	Solution for injection 10 IU/mL	Solution for injection 10 IU/mL
PACKAGING AND PRESENTATION	Ampoule; Type I glass 1 mL x 10's	Ampoule; Type I glass 1 mL x 5's 1 mL x 10's
DATE OF PRE-QUALIFICATION	June 30, 2017	April 16, 2015
SHELF LIFE	18 months	48 months
STORAGE CONDITION	Store in refrigerator (2–8°C), do not freeze, protect from light.	Store in refrigerator (2–8°C), protect from light.

(a) Indicates SRA-approved product that has been prequalified based on abbreviated assessment.

Table O-2. Examples of SRA-Approved Oxytocin Injection 10 IU/mL in 1-mL

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDTION
Syntocinon® 10 IU/mL concentrate for solution for infusion	UK MHRA	Novartis Pharmaceuticals UK Ltd, UK	PL 00101/0960	Clear glass 1-mL ampoule	5 years	Store in refrigerator (2–8°C). May be stored up to 30°C for 3 months, but must then be discarded.
Oxytocin 10 IU/mL solution for infusion	UK MHRA	Peckforton Pharmaceuticals Ltd, UK	PL 15760/0036	Transparent Ph. Eur. type I glass 1-mL ampoule	4 years	Store in refrigerator (2–8°C). May be stored up to 30°C for 3 months but must then be discarded.
Oxytocin 10 IU/mL concentrate for solution for Infusion	UK MHRA	Hameln Pharmaceuticals Ltd, UK	PL 01502/0097, PL 01502/0102	Clear glass 1-mL ampoule	5 years	Store in refrigerator (2–8°C).
Oxytocin 10 IU/mL concentrate for solution for Infusion	UK MHRA	Wockhardt UK Ltd, UK	PL 29831/0625	Clear, type I, neutral glass, 1-mL ampoule	3 years	Store in refrigerator (2–8°C). May be stored up to 30°C for 3 months, but must then be discarded.
Oxytocin 10 IU solution for injection	UK MHRA	EVER Neuro Pharma GmbH, Austria	PL 40369/0006	Colorless glass (type I) 1-mL ampoule	3 years	Store in refrigerator (2–8°C). May be stored below 25°C for 6 months, but then must discarded.
Oxytocin Medipha Sante 10 IU/mL concentrate for solution for infusion	UK MHRA	Medipha Sante, France	PL 34760/0006	Clear glass 1-mL ampoule	3 years	Store in refrigerator (2–8°C).
Oxytocin injection, USP (synthetic)	US FDA	West-Ward Pharmaceutical, USA	NDA #018243	1-mL single-dose vial	Not specified	Store at 25°C; excursions permitted to 15–30°C [See USP Controlled Room Temperature.]* Do not freeze.
Oxytocin injection USP	US FDA	Fresenius Kabi, USA	NDA #018248	1-mL single-dose vial	Not specified	Store at 20°–25°C [See USP Controlled Room Temperature.]* Do not permit to freeze.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDTION
Pitocin® (oxytocin injection, USP)	US FDA	Par Sterile Products LLC, USA	NDA #018261	1-mL single-dose vial	Not specified	Store between 20° and 25°C [See USP Controlled Room
Pitocin® (oxytocin injection, USP)	US FDA	Par Sterile Products LLC, USA	NDA #018261	1-mL single-dose vial	Not specified	Store between 20° and 25°C [See USP Controlled Room
Oxytocin injection, USP	US FDA	Hikma Farmaceutica, USA	ANDA #200219	1-mL single-dose vial	Not specified	Store at 20°–25°C [See USP Controlled Room Temperature.]* Do not permit to freeze.
Syntocinon® 10 IU/mL injection ampoule	TGA Australia	Novartis Pharmaceuticals Australia Pty Ltd, Australia	AUST R 13383	Clear glass 1-mL ampoule	Not specified	Store in refrigerator (2–8°C). Do not permit to freeze.
Oxytocin Sandoz® 10 IU/mL injection ampoule	TGA Australia	Sandoz Pty Ltd, Australia	AUST R 162499	Clear glass 1-mL ampoule	Not specified	Store in refrigerator (2–8°C). Do not freeze.
Oxytocin Aspen® 10 IU/mL injection ampoule	TGA Australia	Aspen Pharmacare Australia Pty Ltd, Australia	AUST R 164131	Clear glass 1-mL ampoule	Not specified	Store in refrigerator (2–8°C). Do not freeze. Protect from light. Once removed from refrigerator the ampoules may be stored below 25°C for up to 4 weeks only, provided that the product is used before printed expiry date. Thereafter, ampoules must be discarded.

** Please note that this is the storage condition as approved for the US market. Since the room temperatures in low- and middle-income countries often exceed such controlled room temperature, it is recommended oxytocin supplied to those countries be included in the cold chain between 2 ℃ and 8 ℃ and be labeled as such.*

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 or equivalent, patient information leaflet or equivalent, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, 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
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: 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 oxytocin injection on the market include:

- Oxytocin injection 5 IU/mL in 1-mL ampoule
- Oxytocin injection 10 IU/mL in 10-mL multidose vial
- Oxytocin injection 2 IU/2mL in 2-mL ampoule

They are used for the same indications, dosage, and administration. However, it is important to note that the WHO EML recommends oxytocin injection 10 IU in 1-mL presentation for convenient use in prevention and treatment of PPH. According to the WHO recommendations for the prevention and treatment of PPH, for PPH prevention 10 IU is administered as intramuscular or slow intravenous injection and for PPH treatment 10–40 IU is administered as an intravenous (IV) infusion.

In certain markets, the price of the 5 IU/mL product may be attractive to meet local needs. However, as most dosing regimens for PPH are likely to require more ampoules of 5 IU/mL than 10 IU/mL, the cumulative costs may be substantively higher. It is therefore recommended to procure only oxytocin injection 10 IU/mL.

STORAGE, STABILITY, AND DEGRADATION

Oxytocin degrades when exposed to prolonged heat. It is therefore recommended that oxytocin products be kept refrigerated at 2-8˚C. Procurers and health facilities should have adequate cold-chain infrastructure for the transportation and storage of quality oxytocin.

Shelf life: 18–60 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Store in a refrigerator (2–8˚C). Do not freeze. Protect from light.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table O-1 and Table O-2 above.

PRODUCT SPECIFICATIONS

The product must meet pharmacopoeial specifications, such as those of the International Pharmacopoeia (IP), US Pharmacopoeia (USP), and British Pharmacopoeia (BP), depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopoeias are similar, except the pH, related substances, and/or bacterial endotoxin limits.

Table O-3. International Pharmacopoeia Specifications for Oxytocin Injection

Test	Acceptance Criteria	Analytical Method
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) TLC	The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.	1.14.1 TLC
b) HPLC	The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.	1.14.4 HPLC
pH	pH of the injection, 3.0 – 5.0	1.13 pH value
Assay	90.0–110.0%	1.14.4 HPLC
Related substances	In the chromatogram obtained with solution (1), the area of not more than one peak, other than the principal peak, is greater than the area of the principal peak obtained with solution (2) (2%). No such peak, other than the principal peak, is greater than 2.5 times the area of the principal peak obtained with solution (2) (5%).	1.14.4 HPLC

Test	Acceptance Criteria	Analytical Method
Bacterial endotoxins	Less than 0.5 IU of endotoxin per IU of oxytocin	3.4 Test for bacterial endotoxins
Sterility	Sterile	3.2 Test for sterility
Extractable volume	Comply	5.6 Extractable volume for parenteral preparations
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table O-4. US Pharmacopoeia Specifications for Oxytocin Injection

Test	Acceptance Criteria	Analytical Method
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) HPLC	The retention time of the oxytocin peak in the chromatogram of the *assay preparation* corresponds to that in the chromatogram of the *standard preparation* as obtained in the *assay*.	USP<621>
Perform one of the following two tests		
b) Nuclear magnetic resonance (NMR)	The NMR spectra from both the standard solution and the test solution are qualitatively and quantitatively similar, and all resonances from the spectrum of the standard solution are present in the spectrum of the test solution and have the same chemical shift values (±0.1 ppm).	NMR
c) Amino acid content	Aspartic acid: 0.90–1.10 Glutamic acid: 0.90–1.10 Proline: 0.90–1.10 Glycine: 0.90–1.10 Leucine: 0.90–1.10 Isoleucine: 0.90–1.10 Tyrosine: 0.7–1.05 Half-cystine: 1.4–2.1 Not more than traces of other amino acids are present.	USP<1052>
pH	3.0–5.0	USP<791>
Assay	90.0–110.0%	HPLC, USP<621>
Bacterial endotoxins	Not more than 35.7 endotoxin unit per USP oxytocin unit	USP<85>

Test	Acceptance Criteria	Analytical Method
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table O-5. British Pharmacopoeia Specifications for Oxytocin Injection

Test	Acceptance Criteria	Analytical Method
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) TLC	The principal spot in the chromatogram obtained with solution (1) corresponds in position, size, and intensity to that in the chromatogram obtained with solution (2).	As in Appendix III A
Identification b) HPLC	The chromatogram obtained with solution (1) exhibits a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).	As in Appendix III D
pH	3.5–4.5	As in Appendix V L
Assay	90.0–110.0%	HPLC, as in Appendix III D
Bacterial endotoxins	Comply	As in Ph.Eur. 2.6.14
Sterility	Sterile	As in Ph.Eur. 2.6.1
Extractable volume	Comply	As in Ph.Eur. 2.9.17
Particulate matter	Comply	As in Ph.Eur. 2.9.19

OXYTOCIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Antepartum

- Induction of labor for medical reasons—for example, in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia)
- Stimulation of labor in hypotonic uterine inertia
- Early stages of pregnancy as adjunctive therapy for the management of incomplete, inevitable, or missed abortion

Postpartum

- During cesarean section, but following delivery of the child
- Prevention and treatment of postpartum uterine atony and hemorrhage.

Posology, method, and duration of administration

Induction or stimulation of labor: Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor.

Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.

An intravenous infusion of a non–oxytocin containing solution should be started. Physiologic electrolyte solutions should be used except under unusual circumstances.

To prepare the usual solution for intravenous infusion, one mL (10 units) of oxytocin is combined aseptically with 1,000 mL of a non-hydrating diluent.

The combined solution, rotated in the infusion bottle to ensure thorough mixing, contains 10 milliunits (mU) of oxytocin per mL. Add the container with dilute oxytocic solution to the system through the use of a constant infusion pump or other such device to control accurately the rate of infusion.

The initial dose should be no more than 1–2 mU/minute. The dose may be gradually increased in increments of no more than 1–2 mU/minute, until a contraction pattern has been established which is similar to normal labor.

The fetal heart rate, resting uterine tone, and the frequency, duration, and force of contractions should be monitored.

The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and fetus must be evaluated by the responsible physician.

Incomplete, inevitable, or missed abortion: Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20–40 drops/minute.

Cesarean section: 5 IU by intravenous infusion after delivery of the fetus.

Prevention of postpartum uterine hemorrhage: 10 IU by intramuscular injection or intravenous infusion after delivery of the baby, after checking that there is no second (or third) child in utero. In women given oxytocin for induction or stimulation of labor, the infusion should be continued at an increased rate during the third stage of labor and for the next few hours thereafter.

Treatment of postpartum uterine hemorrhage: 10–40 units of oxytocin may be added to 1,000 mL of a non-hydrating diluent and given by intravenous infusion run at a rate necessary to control uterine atony.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the product
- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress

Any condition in which, for fetal or maternal reasons, spontaneous labor is inadvisable and/or vaginal delivery is contraindicated, such as:

- Significant cephalopelvic disproportion
- Fetal malpresentation
- Placenta previa and vasa previa
- Placental abruption
- Cord presentation or prolapse
- Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy
- Polyhydramnios
- Grand multiparity
- In the presence of a uterine scar resulting from major surgery, including classical cesarean section.

Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclampsia or severe cardiovascular disorders.

Oxytocin must not be administered within 6 hours after vaginal prostaglandins have been given (see "Interaction with other medicinal products and other forms of interaction" section below).

Special warnings and precautions for use

Oxytocin must only be administered as an intramuscular injection or intravenous infusion and never by intravenous bolus injection as it may cause an acute short-lasting hypotension accompanied by flushing and reflex tachycardia.

Induction of labor

The induction of labor by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Cardiovascular disorders

Oxytocin should be used with caution in patients who have a predisposition to myocardial ischemia due to preexisting cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease, and/or ischemic heart disease, including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT syndrome

Oxytocin should be given with caution to patients with known "long QT syndrome" or related symptoms and to patients taking medicines that are known to prolong the QTc interval (see "Interaction with other medicinal products and other forms of interaction" section below).

This guidance should be followed when oxytocin is given for induction and enhancement of labor:

- Fetal distress and fetal death: Administration of oxytocin at excessive doses results in uterine overstimulation, which may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, or rupture of the uterus. Careful monitoring of fetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.
- Borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy induced hypertension or cardiac disease, and in patients above 35 years of age or patients with a history of lower-uterine-segment cesarean section: Particular caution is required in these conditions.
- Disseminated intravascular coagulation: In rare circumstances, the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (DIC). The induction itself and not a particular agent is linked to such risk. This risk is increased in particular if the woman has additional risk factors for DIC, such as being 35 years of age or over, complications during pregnancy, and gestational age of more than 40 weeks. In these women, oxytocin or any other alternative medicine should be used with care, and the practitioner should be alerted by signs of DIC.

Intrauterine death

In the case of fetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labor must be avoided, as it may cause amniotic fluid embolism.

Water intoxication

Because oxytocin possesses slight antidiuretic activity, its prolonged intravenous administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum hemorrhage, may cause water intoxication associated with hyponatremia. The combined antidiuretic effect of oxytocin and the intravenous fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary edema without hyponatremia. To avoid this rare complication, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labor at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

Renal impairment

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin.

Interaction with other medicinal products and other forms of interaction

Prostaglandins and their analogues

Prostaglandins and their analogues facilitate contraction of the myometrium; therefore oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see "Contraindications" section above).

Medicines prolonging the QT interval

Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for torsades de pointes, such as medicines which prolong the QT interval or in patients with history of long QT syndrome (see "Special warnings and precautions for use" section above).

Inhalation anesthetics

Inhalation anesthetics (e.g., cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and produce a notable inhibition of uterine tone, which may in turn diminish the uterotonic effect of oxytocin. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors/sympathomimetics

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those contained in local anesthetics.

Caudal anesthetics

When given during or after caudal block anesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

Pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this medicine and its chemical structure and pharmacological properties, it is not expected to present a risk of fetal abnormalities when used as indicated.

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

Effects on ability to drive and use machines

Oxytocin can induce labor; therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

Undesirable effects

As there is wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by intravenous infusion for the induction or enhancement of labor, administration at too high a dose may result in uterine overstimulation, which may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage, or rupture of the uterus.

Rapid intravenous bolus injection of oxytocin at doses amounting to several IUs may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see "Special warnings and precautions for use" section above). These rapid hemodynamic changes may result in myocardial ischemia, particularly in patients with preexisting cardiovascular disease. Rapid intravenous bolus injection of oxytocin at doses amounting to several IUs may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see "Special warnings and precautions for use" section above).

Water intoxication

Water intoxication associated with maternal and neonatal hyponatremia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see "Special warnings and precautions for use" section above). The combined antidiuretic effect of oxytocin and the intravenous fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary oedema without hyponatremia (see "Special warnings and precautions for use" section above).

Symptoms of water intoxication include:

- Headache, anorexia (loss of appetite), nausea, vomiting, and abdominal pain
- Lethargy, drowsiness, unconsciousness, and grand-mal type seizures
- Low blood electrolyte concentration

Undesirable effects in the tables below are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports; frequency not known (cannot be estimated from the available data). The adverse drug reactions (ADRs) tabulated below are based on clinical trial results as well as post-marketing reports.

The ADRs related to post-marketing experience with oxytocin come from spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency—which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in the Medical Dictionary for Regulatory Activities (MedDRA). Within each system organ class, ADRs are presented in order of decreasing seriousness.

Adverse Drug Reactions in Mother

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Immune system disorders	Rare: anaphylactic/anaphylactoid reaction associated with dyspnoea, hypotension, or anaphylactic/anaphylactoid shock
Nervous system disorders	Common: headache
Cardiac disorders	Common: tachycardia, bradycardia Uncommon: arrhythmia Frequency not known: myocardial ischemia, electrocardiogram QTc prolongation
Vascular disorders	Frequency not known: hypotension, hemorrhage
Gastrointestinal disorders	Common: nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: rash
Pregnancy, puerperium, and perinatal conditions	Frequency not known: uterine hypertonus, tetanic contractions of uterus, rupture of the uterus
Metabolism and nutrition disorders	Frequency not known: water intoxication, maternal hyponatremia
Respiratory, thoracic, and mediastinal disorders	Frequency not known: acute pulmonary edema
General disorders and administration site conditions	Frequency not known: flushing
Blood and lymphatic system disorders	Frequency not known: disseminated intravascular coagulation
Skin and subcutaneous tissue disorders	Frequency not known: angioedema

Adverse Drug Reactions in Fetus/Neonate

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Pregnancy, puerperium, and perinatal conditions	Frequency not known: fetal distress syndrome, asphyxia, death
Metabolism and nutrition disorders	Frequency not known: neonatal hyponatremia

Overdose

The fatal dose of oxytocin has not been established. Oxytocin is subject to inactivation by proteolytic enzymes of the alimentary tract. Therefore it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under the "Special warnings and precautions for use" and "Undesirable effects" sections above. In addition, as a result of uterine overstimulation, placental abruption, and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous intravenous administration of oxytocin, the infusion must be discontinued at once and 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. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

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 oxytocin injection products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on oxytocin injection.

API

As of February 2018, there is no oxytocin API prequalified by the WHO PQP.

There are five manufacturers of oxytocin API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Manufacturers of Oxytocin API with CEP Certificate

Substance	Certificate Holder	Certificate Number	Issue Date	Type
Oxytocin (monograph number 780)	Aspen Oss B.V. NL 5349 AB Oss, The Netherlands	R1-CEP 2000-150-Rev 03	04/07/2016	Chemistry
Oxytocin (monograph number 780)	Hemmo Pharmaceuticals Pvt. Ltd. In 400 613 Mumbai, India	R1-CEP 2008-029-Rev 00	10/16/2015	Chemistry
Oxytocin (monograph number 780)	Shanghai Soho-Yiming Pharmaceuticals Co., Ltd. CN 201 707 Chonggu Town, China	R1-CEP 2011-003-Rev 00	8/25/2017	Chemistry
Oxytocin (monograph number 780)	Joint Stock Company "Grindeks" LV 1057 Riga, Latvia	R1-CEP 2002-200-Rev 01	1/10/2014	Chemistry
Oxytocin (monograph number 780)	Shenzhen Jymed Technology Co., Ltd. Cn 518 057 Shenzhen, China	R0-CEP 2015-376-Rev 00	11/27/2017	Chemistry

Other manufacturers of oxytocin API should provide evidences for GMP compliance and API quality documentation as per the WHO guideline.[1]

The specifications of oxytocin API should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP), with additional tests/limits for residual solvents and bacterial endotoxins. If intended for use in the aseptic manufacture of oxytocin injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

Oxytocin is hygroscopic. It should be kept in an airtight container, protected from light, at a temperature of 2–8°C or if sterile, in a sterile, airtight, tamper-evident container.

Excipients

The excipients of oxytocin injection are as follows.[2] There are no special concerns on the excipients.

Excipients of Oxytocin Injection

Ingredient	Function
Acetic acid	pH adjustment
Chlorobutanol	Preservative
Ethanol	Co-solvent
Sodium acetate trihydrate	Buffering agent
Water for injection	Vehicle

Acetic acid is mainly used for pH adjustment. Some formulations may also include sodium hydroxide for such purpose. The pH adjustment is crucial for oxytocin stability because it was shown by Nachtmann et al.[3] that oxytocin is most stable between pH 3 and 5. Hawe et al.[4] also reported that the degradation of oxytocin was pH- and temperature-dependent and followed (pseudo) first order kinetics. Degradation was fastest at pH 9.0, followed by pH 7.0, pH 2.0, and pH 4.5. Oxytocin degradation in formulations between pH 2.0 and 9.0 follows Arrhenius kinetics, with the pH 4.5 formulation being the most stable. This information is important for formulation development of oxytocin injection.

Chlorobutanol may not be present in some formulations because oxytocin injection 10 IU in 1-mL is intended for a single-dose use, which generally does not require an antimicrobial preservative. However, some manufacturers may add a preservative as an adjunct in aseptic processing of product where there may be product exposure during transfer, filling, and

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

[2] Based on the formulation of an innovator product, Syntocinon®.

[3] Nachtmann, F., K. Krummen, F. Maxl, and E. Reimer. 1981. "Oxytocin. Analytical profiles of drug substances." *Analytical Profiles of Drug Substances* 10: 563–600.

[4] Hawe, A., R. Poole, S. Romeijn Piotr Kasper, R. van der Heijden, and W. Jiskoo. 2009. "Towards Heat-stable Oxytocin Formulations: Analysis of Degradation Kinetics and Identification of Degradation Products." *Pharm Res* 26(7): 1679–88.

packing operations. Thus, should trace contamination occur during the manufacturing process, the added preservative may render the product sterile.

Where chlorobutanol is included in the formulation as an antimicrobial preservative, the assay of chlorobutanol (preservative content) should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of chlorobutanol is less than 90.0%, its effectiveness should be established by appropriate studies (e.g., USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP containing a concentration of chlorobutanol corresponding to the lower proposed acceptance criteria.

A single primary-stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

Manufacturing process

Oxytocin injection is a straightforward medicine to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.

The manufacturing process of oxytocin injection is a standard process—conducted under appropriate aseptic conditions—including the steps of preparation of the solution 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.

Since oxytocin is susceptible to degradation by heat, terminal steam sterilization cannot be used. Oxytocin injection should be manufactured by aseptic technique for the whole process or sterile filtration of the bulk solution followed by aseptic filling.

When the aseptic processing is used, all the ingredients must be in sterile grade and comply with the test for sterility before use.

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.

Oxytocin injection is prepared by dissolving oxytocin API in the diluent (solution of excipients). Since oxytocin API is hygroscopic (i.e. tend to absorb moisture from the air), it should be kept under the control of relative humidity before introducing into the diluent to avoid degradation. Maintain the temperature of dispensed oxytocin between 2°C and 8°C with the help of frozen-gel ice packs and thermometer in a thermo cool box. The API, after being dispensed, should be used as soon as possible to avoid exposure to light and oxygen.

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. Suggested conditions for production are temperature not more than 25°C.

Nitrogen purging should be carried out throughout the manufacturing and filling process to minimize the 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. The temperature of the bulk solution should be maintained below 10°C ± 5°C until filtration.

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.

Packaging

Neutral type I glass ampoule or vial should be used.

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

Safety

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

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

Compatibility

- Extractables/leachables data of the rubber stopper 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.
- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers, such as PVC, may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, 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 Syntocinon® (oxytocin 10 IU/mL injection, Novartis), Pitocin® (oxytocin 10 IU/mL injection, PAR Sterile Products LLC, USA), and oxytocin 10 IU/mL injection (Eurohealth International SARL or Fresenius Kabi LLC, USA). The composition of the proposed product should be the same as the comparator product.