WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

[RH079 trade name]*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10 units of oxytocin

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless, solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antepartum:

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

Postpartum:

- During caesarean section, following delivery of the child
- Prevention and treatment of postpartum uterine atony and haemorrhage

4.2 Posology and method of administration

[RH079 trade name] should be administered as an intravenous infusion or preferably, by means of a variable-speed infusion pump. It can also be given by intramuscular injection (but intravenous use can produce more rapid onset of action and allow better control of dosing).

Attention should be paid to the oxytocin cold chain (i.e. the requirements of a temperature-controlled supply chain, see Section 6.4).

Induction or enhancement of labour:

If vaginal prostaglandins have been used, oxytocin should be started at least 6 hours after use of vaginal prostaglandins. Oxytocin should be administered as an intravenous drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion, it is recommended that 5 units of oxytocin be added to 500 mL of a physiological electrolyte solution (such as sodium chloride 0.9%). For patients in whom infusion of sodium chloride must be avoided, 5% glucose solution may be used as the infusion fluid (see Section 4.4 Special warnings and precautions for use).

To ensure even mixing, the infusion bottle or bag must be turned upside down several times before use.

The initial infusion rate should be set at 1 to 4 milliunits/minute (2 to 8 drops/minute).

The infusion rate may be gradually increased at intervals of at least 20 minutes and increments of not more than 1–2 milliunits/minute, until a contraction pattern similar to that of normal labour is established. In pregnancy near term, this can often be achieved with an infusion rate of less than 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event that higher rates are required, as may occur in the management of fetal death or for induction

* Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

of labour at an earlier stage of pregnancy when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated oxytocin solution, e.g. 10 units in 500 ml.

When using a motor-driven infusion pump which delivers smaller volumes than with drip infusion, the concentration suitable for infusion must be calculated according to the specifications of the pump.

With either method of infusion, the frequency, strength, and duration of contractions as well as the fetal heart rate must be carefully monitored throughout the infusion. Once the level of uterine activity is adequate, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity or fetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after a total dose of 5 units, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again at an infusion rate of 1 to 4 milliunits/minute.

Incomplete, inevitable or missed abortion:

The usual dose is 5 units by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes, followed if necessary by an intravenous infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section:

The usual dose is 5 units by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes immediately after delivery.

Prevention of postpartum uterine haemorrhage:

The usual dose is 10 units by intramuscular or intravenous injection. Alternatively, 5 units can be given by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes after delivery of the placenta. In women given oxytocin for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours.

Treatment of postpartum uterine haemorrhage:

The usual dose is 10 units by intramuscular or intravenous injection. Alternatively, 5 units can be given by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes, followed in severe cases by infusion of a solution containing 5 to 20 units of oxytocin in 500 mL of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress.

Any condition in which, for fetal or maternal reasons, spontaneous labour is inadvisable or vaginal delivery is contra-indicated: e.g.:

- Significant cephalopelvic disproportion
- Fetal malpresentation
- Placenta praevia and vasa praevia
- Placental abruption
- Cord presentation or prolapse
- Over-distension or impaired resistance of the uterus to rupture, as in multiple pregnancy
- Polyhydramnios
- Grand multiparity
- Presence of a uterine scar from major surgery including classical caesarean section.

[RH079 trade name] should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

[RH079 trade name] must be administered at least 6 hours after vaginal prostaglandins have been given (see section 4.5).

4.4 Special warnings and precautions for use

Attention should be paid to the oxytocin cold chain (i.e. the requirements of a temperature-controlled supply chain, see Section 6.4).

Oxytocin via intravenous infusion is preferred, as intravenous bolus injection may cause short-lasting hypotension accompanied by flushing and reflex tachycardia.

Induction of labour:

The induction of labour by [RH079 trade name] should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

[RH079 trade name] should not be infused via the same apparatus as blood or plasma, because it is rapidly inactivated by oxytocin-inactivating enzymes.

Cardiovascular disorders:

[RH079 trade name] should be used with caution in patients who have a predisposition to myocardial ischaemia due to cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease and ischaemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT Syndrome:

[RH079 trade name] should be given with caution to patients with 'long QT syndrome' or related symptoms and to patients taking drugs that prolong the QTc interval (see section 4.5).

Use for induction and enhancement of labour:

Fetal distress and fetal death: Excessive doses of oxytocin can result 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.

Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.

Disseminated intravascular coagulation: Rarely, the pharmacological induction of labour using uterotonic agents, including [RH079 trade name] increases the risk of postpartum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is particularly increased if the woman has additional risk factors for DIC such as being over 35 years of age, complications during pregnancy and gestational age more than 40 weeks. In these women, [RH079 trade name] or another alternative drug should be used with care, and the practitioner should be alert for signs of DIC, such as bleeding from multiple sites, internal bleeding, purpura of extremities, severe malaise and fever.

Intrauterine death:

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

Water intoxication:

Because oxytocin has mild antidiuretic activity, water intoxication associated with hyponatraemia may result from prolonged intravenous infusion at high doses with large volumes of fluid (e.g. in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage).

The combined antidiuretic effect of oxytocin and the intravenous fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia.

Features of water intoxication include:

- Headache, anorexia, nausea, vomiting and abdominal pain.
- Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

To avoid this rare complication, the following precautions must be observed whenever high doses of [RH079 trade name] are administered over a long time:

- an electrolyte-containing diluent must be used (not glucose);
- the volume of infused fluid should be kept low (by infusing [RH079 trade name] at a higher concentration than recommended for the induction or enhancement of labour at term);
- fluid intake by mouth must be restricted and 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 (see section 5.2).

Anaphylaxis in women with latex allergy

There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Due to the existing structural homology between oxytocin and latex, latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Prostaglandins and their analogues

Prostaglandins and their analogues facilitate contraction of the myometrium. They should not be used concomitantly with [RH079 trade name] because [RH079 trade name] can potentiate the uterine action of prostaglandins and analogues and vice versa (see section 4.3 Contraindications).

Note: Misoprostol may be used with oxytocin for the prevention and treatment of postpartum haemorrhage.

Drugs prolonging the QT interval

[RH079 trade name] is potentially arrhythmogenic; concomitant drugs which prolong the QT interval should be used with caution (see section 4.4).

Other interactions

Inhalation anaesthetics

Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) relax the uterus and inhibit uterine tone and thereby, may diminish the uterotonic effect of [RH079 trade name]. Their concurrent use with [RH079 trade name] has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors and sympathomimetics

[RH079 trade name] may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those in local anaesthetics.

Caudal anaesthetics

When given during or after caudal block anaesthesia, [RH079 trade name] may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

The induction of labour by means of [RH079 trade name] should be attempted only when strictly indicated for medical reasons (see section 4.4).

Animal reproduction studies have not been conducted with [RH079 trade name]. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

Breastfeeding

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.

Fertility

Animal reproduction studies have not been conducted with [RH079 trade name]. The effects of oxytocin on fertility are unknown.

4.7 Effects on ability to drive and use machines

[RH079 trade name] can induce labour. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by low doses. When [RH079 trade name] is used for the induction or enhancement of labour, excessive doses can 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.

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

The adverse drug reactions derived from post-marketing experience with [RH079 trade name] are via 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 categorised as not known. Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Adverse drug reactions in mother

System Organ Class	Adverse reaction
Immune system disorders	*Rare:* anaphylactic or anaphylactoid reaction associated with dyspnoea, hypotension or shock
Nervous system disorders	*Common:* headache
Cardiac disorders	*Common:* tachycardia, bradycardia *Uncommon:* arrhythmia *Not known:* myocardial ischaemia, QTc prolongation
Vascular disorders	*Not known:* hypotension, haemorrhage, angioedema
Gastrointestinal disorders	*Common:* nausea, vomiting
Skin	*Rare:* rash
Pregnancy, puerperium and perinatal conditions	*Not known:* uterine hypertonus, tetanic contractions of uterus, rupture of the uterus
Metabolism and nutrition disorders	*Not known:* water intoxication, hyponatraemia
Respiratory, thoracic and mediastinal disorders	*Not known:* acute pulmonary oedema
General disorders and administration site conditions	*Not known:* flushing
Blood and lymphatic system disorders	*Not known:* disseminated intravascular coagulation

Adverse drug reactions in fetus/neonate

Not known: fetal distress, asphyxia and death

Not known: neonatal hyponatraemia

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

The fatal dose of oxytocin has not been established. Oxytocin is inactivated by proteolytic enzymes of the alimentary tract. Hence 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 sections 4.4 and 4.8. In addition, as a result of uterine overstimulation, placental abruption and amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous intravenous administration of [RH079 trade name], 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 occur. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones

ATC code: H01BB02

Mechanism of action

Oxytocin is a synthetic cyclic nonapeptide that is identical to the natural hormone that is released by the posterior pituitary into the systemic circulation, in response to suckling and labour.

Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased. The oxytocin receptors are G-protein coupled receptors. Activation of receptors by oxytocin triggers release of calcium from intracellular stores leading to myometrial contraction. Oxytocin elicits rhythmic contractions in the upper segment of the uterus, similar in frequency, force and duration to those in labour.

Being synthetic, [RH079 trade name] does not contain vasopressin, but even in its pure form oxytocin possesses weak vasopressin-like antidiuretic activity.

Plasma levels and onset and duration of effect

When [RH079 trade name] is given by continuous intravenous infusion at doses appropriate for induction or enhancement of labour, the uterine response sets in gradually and usually reaches a steady state within 20 to 40 minutes. The corresponding plasma levels of oxytocin are comparable to those measured during spontaneous first-stage labour. For example, oxytocin plasma levels in 10 pregnant women at term receiving a 4 milliunits per minute intravenous infusion were 2 to 5 microunits/ml. Upon discontinuation of the infusion, or following substantial reduction in the infusion rate, e.g. in the event of overstimulation, uterine activity declines rapidly but may continue at an adequate lower level.

5.2 Pharmacokinetic properties

Absorption	
Oral Bioavailability	0%. Completely degraded in the gastrointestinal tract
Food effect	Not applicable.

Distribution	
Volume of distribution (mean)	0.17 L/kg
Plasma protein binding *in vitro*	Negligible
Tissue distribution	Widely distributed. Crosses placenta in both directions. Small quantities excreted in breast milk
Elimination	
General note	Degraded in the liver and kidney by non-specific peptidases
Mean systemic clearance (Cl/F)	Metabolic clearance rate is 20 mL/kg/min in pregnant women Plasma half-life is 3 to 20 minutes
% of dose excreted in urine	< 1% intact
% of dose excreted in faeces	Nil
Pharmacokinetic linearity	Not available
Drug interactions *(in vitro)*	Not available
Metabolising enzymes	Oxytocinase is produced during pregnancy and degrades oxytocin in the bloodstream
Special populations	
Renal impairment	No pharmacokinetic data available.
Hepatic impairment	No pharmacokinetic data available; not expected to influence pharmacokinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and mutagenicity. No standard teratogenicity, reproductive performance and carcinogenicity studies with oxytocin are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol hemihydrate
Acetic acid glacial
Water for injections

6.2 Incompatibilities

Oxytocin should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Oxytocin is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life.

36 months.

Shelf life after first opening the container: from a microbiological point of view, the product should be used immediately

6.4 Special precautions for storage

Store in the refrigerator (2°C-8°C). Do not freeze.

Single use ampoules. Discard unused portion.

6.5 Nature and contents of container

UAB Santonika: Clear type I glass ampoule with break ring or blue open point cut containing 1mL of solution for injection.
HBM Pharma s.r.o: Clear type I glass ampoule with colour rings (lower turquoise and upper red) and red open point cut containing 1mL of solution for injection.
Pack size: 5, 10 or 100 ampoules per PVC film liner.

6.6 Special precautions for disposal and other handling

Oxytocin is compatible with the following infusion fluids: sodium chloride 0.9 %, dextrose 5 %, Ringer's solution, acetated Ringer's solution.

Single use ampoules and discard unused portion. Any unused product should be disposed of in accordance with local requirements.

7. SUPPLIER

AS GRINDEKS.
Krustpils iela 53, Rīga, LV-1057, Latvia
Tel: + 371 67083205
Fax: + 371 67083505
e-mail: grindeks@grindeks.lv

WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH079

8. DATE OF PREQUALIFICATION

14 October 2019

10. DATE OF REVISION OF THE TEXT

February 2020

Section 6.5 updated in May 2021

References

WHO recommendations for augmentation of labour. World Health Organization: Geneva. 2014
https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/augmentation-labour/en/

WHO recommendation on the use of oxytocin alone for treatment of delay in labour. 2014
https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/care-during-childbirth/care-during-labour-1st-stage/who-recommendation-use-oxytocin-alone-treatment-delay-labour

WHO recommendations for the prevention and treatment of postpartum haemorrhage. World Health Organization: Geneva. 2012
https://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf?sequence=1

WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage Web annex 7: Choice of uterotonic agents World Health Organization: Geneva. 2018
https://apps.who.int/iris/bitstream/handle/10665/277283/WHO-RHR-18.34-eng.pdf

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Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .