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.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH050 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10 units of oxytocin

Excipients with potential clinical effect

This medicine contains small amounts of ethanol (alcohol), less than 100 mg per dose (4.81 mg). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

A clear, colourless, sterile solution in 1ml clear glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Before childbirth

- 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

After childbirth

- During caesarean section, after delivery of the baby
- Prevention and treatment of uterine atony and haemorrhage

WHO treatment guidelines as well as national and other authoritative guidelines should be consulted on the use of oxytocin.

4.2 Posology and method of administration

Where possible, [RH050 trade name] should be given by intravenous infusion, preferably through a variable-speed infusion pump. It can also be given by intramuscular injection but intravenous use can produce more rapid activity and allow better control of dosing.

Induction or enhancement of labour

Oxytocin should be started at least 6 hours after use of any vaginal prostaglandins.

Oxytocin should be administered as an intravenous drip infusion or, if available, through a variable-speed infusion pump. For drip infusion, it is recommended that 2.5 units of oxytocin be added to 500 mL of glucose 5% solution (or sodium chloride 0.9% solution but 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 recommended infusion rates below assume 20 drops per mL.

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

The initial infusion rate of oxytocin should be set at 2.5 milliunits/minute (0.5 mL/minute or 10 drops/minute).

The infusion rate of oxytocin may be increased at 30-minute intervals until a contraction pattern similar to that of normal labour is established (i.e. 3 contractions in 10 minutes, each lasting 40 seconds). The rate should be increased in steps of 2.5 milliunits/minute (0.5 mL/minute or 10 drops/minute), i.e. increased to 5 milliunits/minute after 30 minutes, 7.5 milliunits/minute after another 30 minutes and so on. Once a good contraction pattern is established, the oxytocin infusion rate should be maintained.

The woman's pulse, blood pressure, and the frequency, strength, and duration of contractions as well as the fetal heart rate must be carefully monitored throughout the infusion. If there are more than 5 contractions in 10 minutes or if any contraction lasts longer than 60 seconds, the infusion must be stopped. If the fetal heart rate is less than 100 beats/minute or more than 180 beats/minute, the infusion must be stopped.

If a good contraction pattern has not been established with oxytocin infusion rate of 15 milliunits/minute (3 mL/minute or 60 drops/minute):

- The oxytocin concentration should be increased to 5 units in 500 mL of glucose 5% solution (or sodium chloride 0.9%)
- The oxytocin infusion rate should be adjusted to 15 milliunits/minute (1.5 mL/minute or 30 drops/minute)
- The oxytocin infusion rate may then be increased every 30 minutes in steps of 5 milliunits/minute (10 drops/minute) up to 30 milliunits/minute (3 ml/minute or 60 drops/minute)

In **multigravida women**, if a good contraction pattern has not been established with oxytocin infusion rate of 30 milliunits/minute a caesarean section should be arranged.

In **primigravida women**, if a good contraction pattern has not been established after 30 minutes with oxytocin infusion rate of 30 milliunits/minute:

- The oxytocin concentration should be increased to 10 units in 500 mL of glucose 5% solution (or sodium chloride 0.9%)
- The oxytocin infusion rate should be adjusted to 40 milliunits/minute (2 mL/minute or 40 drops/minute)
- The oxytocin infusion rate may then be increased after 30 minutes in steps up to a **maximum of** 60 milliunits/minute (3 ml/minute or 60 drops/minute)
- If a good contraction pattern has not been established after 1 hour at the maximum rate, a caesarean section should be arranged.

For rapid escalation of labour in **primigravida women only**, the infusion rate may be increased at 15-minute intervals until the infusion rate is 60 milliunits/minute.

Incomplete, inevitable or missed abortion

The usual dose is oxytocin 5 units by intravenous infusion (diluted in physiological electrolyte solution and given as a drip infusion or, preferably, through 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 oxytocin 5 units by intravenous infusion (diluted in physiological electrolyte solution and given as a drip infusion or, preferably, through 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 slow intravenous injection. If the woman already has intravenous access, oxytocin can be given slowly through this route in preference to intramuscular injection.

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

If the woman has an intravenous infusion running, oxytocin 10 to 40 units can be added to physiological electrolyte solution (maximum 40 units in 1 litre) and given as a drip at a rate of 10 to 20 units over 5 minutes, adjusted to sustain uterine contraction and control uterine atony.

Alternatively, if other options are not available, oxytocin 10 units can be given by intramuscular injection after the placenta has been delivered.

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.

[RH050 trade name] should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

4.4 Special warnings and precautions for use

Oxytocin should preferably be given by intravenous infusion, as intravenous bolus injection may cause short-lasting hypotension accompanied by flushing and reflex tachycardia.

Induction or enhancement of labour

[RH050 trade name] should be used for inducing labour only when strictly indicated for medical reasons. It should be given only under hospital conditions and qualified medical supervision.

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.

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.

Disseminated intravascular coagulation

Rarely, the induction of labour using uterotonic agents, including [RH050 trade name], increases the risk of postpartum disseminated intravascular coagulation (DIC). The risk is linked to induction of labour rather than to a particular medicine. 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, [RH050 trade name] or another uterotonic 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.

Cardiovascular disorders

[RH050 trade name] should be used with caution to avoid significant changes in blood pressure and heart rate in patients predisposed to myocardial ischaemia due to cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease and ischaemic heart disease including coronary artery vasospasm).

QT Syndrome

[RH050 trade name] should be given with caution to patients with long QT syndrome or with related symptoms and to patients taking medicines that prolong the QTc interval (see section 4.5).

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 may result from prolonged intravenous infusion at high doses with large volumes of fluid (e.g. for treating inevitable or missed abortion or for managing postpartum haemorrhage).

The combined antidiuretic effect of oxytocin and 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
- Low blood electrolyte concentration

To avoid this rare complication, the following precautions must be observed whenever high doses of [RH050 trade name] are given over a long time:

- an electrolyte-containing diluent must be used (not glucose);
- the volume of infused fluid should be kept low (by infusing [RH050 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 latex allergy. Due to the structural homology between oxytocin and latex, latex allergy or intolerance may predispose women to anaphylaxis with oxytocin.

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. Use of a prostaglandin at the same time as [RH050 trade name] can produce excessive uterotonic effects.

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

Drugs prolonging the QT interval

[RH050 trade name] is potentially arrhythmogenic; drugs which prolong the QT interval should be used with caution during treatment with oxytocin.

Other interactions

Inhalation anaesthetics

Inhalation anaesthetics (e.g. cyclopropane, desflurane, halothane, sevoflurane) relax the uterus and inhibit uterine tone and may diminish the uterotonic effect of [RH050 trade name]. Their concurrent use with [RH050 trade name] has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors and sympathomimetics

[RH050 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, [RH050 trade name] may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Based on the wide experience with oxytocin and its chemical structure and pharmacological properties, [RH050 trade name] is not expected to present a risk of fetal abnormalities when used as indicated.

Breast-feeding

Oxytocin may be present in small quantities in breast milk. However, it is not expected to harm the newborn because oxytocin is rapidly inactivated in the gut.

Fertility

Oxytocin has been used extensively but formal evidence on its effect on fertility is lacking.

4.7 Effects on ability to drive and use machines

[RH050 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, low doses of oxytocin may cause uterine spasm in some instances. When [RH050 trade name] is used for inducing or enhancing 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.

Adverse reactions to [RH050 trade name] are listed below by body system or organ. Frequencies are defined as follows: 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), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

The adverse reactions listed below are based on clinical trial results or derived from post-marketing experience with [RH050 trade name] 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.

Adverse drug reactions in mother

Blood and lymphatic system disorders

Not known	disseminated intravascular coagulation

Immune system disorders

Rare	anaphylactic or anaphylactoid reaction associated with dyspnoea, hypotension or shock

Metabolism and nutrition disorders

Not known	water intoxication, maternal hyponatraemia

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

Respiratory, thoracic and mediastinal disorders

Not known	acute pulmonary oedema

Gastrointestinal disorders

Common	nausea, vomiting

Skin and subcutaneous tissue disorders

Rare	Rash

Pregnancy, puerperium and perinatal conditions

Not known	uterine hypertonus, tetanic contractions of uterus, rupture of the uterus

General disorders and administration site conditions

Not known	Flushing

Adverse drug reactions in fetus or neonate

Metabolism and nutrition disorders

Not known	neonatal hyponatraemia

Pregnancy, puerperium and perinatal conditions

Not known	fetal distress syndrome, asphyxia and death

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

The fatal dose of oxytocin has not been established. Oxytocin is inactivated by proteolytic enzymes in the gut. Hence it is not absorbed from the intestine and is not likely to be toxic 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 [RH050 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 any convulsions that occur. In the case of coma, a free airway should be maintained with routine measures to care for an 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 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, [RH050 trade name] does not contain vasopressin, but even in its pure form oxytocin possesses weak vasopressin-like antidiuretic activity.

Laboratory studies suggest that prolonged exposure to oxytocin can desensitise oxytocin receptors probably by down-regulation of oxytocin-binding sites, destabilisation of oxytocin receptors mRNA and internalisation of oxytocin receptors.

Plasma levels and onset and duration of effect

After intravenous administration of oxytocin, uterine response occurs almost immediately and subsides within 1 hour. After intramuscular injection, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours.

When [RH050 trade name] is given by continuous intravenous infusion at doses appropriate for induction or enhancement of labour, the uterine response is gradual and usually reaches 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 present 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/minute in pregnant women Plasma half-life is 3 to 20 minutes; it may be shorter during labour
% of dose excreted in urine	< 1% as intact oxytocin
% 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; possible accumulation of oxytocin can prolong its action.
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, single-dose toxicity, genotoxicity and mutagenicity. No standard teratogenicity, reproductive performance and carcinogenicity studies with oxytocin are available.

In a study on rats, oxytocin caused embryonic loss when given in early pregnancy at doses exceeding the maximum recommended human dose. No standard reproductive performance studies with oxytocin are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol hemihydrate

Glacial acetic acid

Sodium acetate, anhydrous

Ethanol

Sodium chloride

Water for injection

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per *dosage unit*.

6.2 Incompatibilities

Oxytocin is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

24 months. Shelf life after first opening the container: the solution should be used immediately.

6.4 Special precautions for storage

Store between 2 and 8°C.

6.5 Nature and contents of container

Type I glass ampoules

Clear and colorless type I glass ampoule with a white color break. It has double orange rings and red vertical "SANBE" print containing 1 mL of solution for injections. The ampoules are inserted to plastic blister divider, each plastic blister contains 5 ampoules and each folding box (made of ivory paper 310 g) contains 2 plastic blisters.

6.6 Special precautions for disposal and other handling

Any unused product should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH050

9. DATE OF PREQUALIFICATION

30 June 2017

10. DATE OF REVISION OF THE TEXT

November 2024

References

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products