

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Oxytocin Injection 10IU/1ml

2. Qualitative and quantitative composition

Each 1ml ampoule contains 10 IU of oxytocin

3. Pharmaceutical form

Solution for injection

A clear, colourless liquid.

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 the 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, but following delivery of the child
- Prevention and treatment of postpartum uterine atony and haemorrhage

4.2 Posology and method of administration

Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Oxytocin should be administered as an IV (intravenous) drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU 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% dextrose solution may be used as the diluent (see section 4.4 Special warnings and

precautions for use). To ensure even mixing, the 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). It may be gradually increased at intervals not shorter than 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 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 foetal death in utero or for induction 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 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump.

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

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute (see section 4.3 Contraindications).

Incomplete, inevitable, or missed abortion: 5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), if necessary followed by IV infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV 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 5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV 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 thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), followed in severe cases by IV infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

Route of administration: Intravenous infusion.

Special populations

Renal impairment

No studies have been performed in renally impaired patients.

Hepatic impairment

No studies have been performed in hepatically impaired patients.

Paediatric population

No studies have been performed in paediatric patients.

Elderly population

No studies have been performed in elderly patients (65 years old and over).

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, foetal distress.

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

- Significant cephalopelvic disproportion
- Foetal malpresentation
- Placenta praevia and vasa praevia
- 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 caesarean section.

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

Oxytocin must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

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

Induction of labour

The induction of labour 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 pre-disposition to myocardial ischaemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease and/or ischaemic 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 drugs that are known to prolong the QTc interval (see section 4.5 Interaction with other medicinal products and other forms of interaction).

When Oxytocin is given for induction and enhancement of labour:

- Foetal distress and foetal death: Administration of oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus.

Careful monitoring of foetal 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 degrees of 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: In rare circumstances, the pharmacological induction of labour using uterotonic agents, including oxytocin 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 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 more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.

Intrauterine death

In the case of foetal death in utero, and/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 possesses slight antidiuretic activity, its prolonged IV 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 haemorrhage, may cause water intoxication associated with hyponatraemia. The combined antidiuretic effect of oxytocin and the IV fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia. To avoid these rare complications, 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 labour 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 (see section 5.2 Pharmacokinetics).

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

Interaction resulting in a concomitant use not recommended

Prostaglandins and their analogues

Prostaglandins and its analogues facilitate contraction of the myometrium hence oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see section 4.3 Contraindications).

Drugs prolonging the QT interval

Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for Torsades de Pointes such as drugs which prolong the QT interval or in patients with history of long QT syndrome (see section 4.4 Special warnings and precautions for use).

Interactions to be considered

Inhalation anaesthetics

Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and produce a notable inhibition of uterine tone and thereby, may 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 anaesthetics.

Caudal anaesthetics

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

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. 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.

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.

4.7 Effects on ability to drive and use machines

Oxytocin can induce labour, therefore caution should be exercised when driving or operating machines. 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 what are normally considered to be low doses. When oxytocin is used by IV infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Rapid IV bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see section 4.4 Special warnings and precautions for use). These rapid haemodynamic changes may result in myocardial ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid IV bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and precautions for use).

Water intoxication

Water intoxication associated with maternal and neonatal hyponatraemia 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 section 4.4 Special warnings and precautions for use). The combined antidiuretic effect of oxytocin and the IV fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia (see section 4.4. Special warnings and precautions for use).

Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.
2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.
3. Low blood electrolyte concentration.

Undesirable effects (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$), including isolated reports; not known (cannot be estimated from the available data). The ADRs tabulated below are based on clinical trial results as well as postmarketing reports.

The adverse drug reactions derived from post-marketing experience with Oxytocin 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. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 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 Not known: Myocardial ischaemia, Electrocardiogram QTc prolongation
Vascular disorders	Not known: Hypotension, haemorrhage
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
Metabolism and nutrition disorders	Not known: Water intoxication, maternal 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
Skin and subcutaneous tissue disorders	Not Known: Angioedema

Table 2 Adverse drug reactions in foetus/neonate

System organ class	Adverse drug reaction
Pregnancy, puerperium and perinatal conditions	Not known: foetal distress, asphyxia and death
Metabolism and nutrition disorders	Not known: Neonatal hyponatraemia

4.9 Overdose

The fatal dose of Oxytocin has not been established. Oxytocin is subject to inactivation 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 Special warnings and precautions for use and 4.8 Undesirable effects. 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 IV 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones

ATC code: H01B B02

Mechanism of action

Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released 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-proteins coupled receptors. Activation of receptor by oxytocin triggers release of calcium from intracellular stores and thus leads to myometrial contraction.

Oxytocin elicits rhythmic contractions in upper segment of uterus, similar in frequency, force and duration to those observed during labour.

Being synthetic, oxytocin in Oxytocin does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Based on in vitro studies, prolonged exposure of oxytocin had been reported to cause desensitisation of oxytocin receptors probably due to down-regulation of oxytocin-binding sites, destabilisation of oxytocin receptors mRNA and internalisation of oxytocin receptors.

Plasma levels and onset/duration of effect

Intravenous infusion. When Oxytocin is given by continuous IV 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 a 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

Plasma levels of oxytocin following intravenous infusion at 4 milliunits per minute in pregnant women at term were 2 to 5 microunits/mL.

Distribution

The steady-state volume of distribution determined in 6 healthy men after IV injection is 12.2 L or 0.17 L/kg. Plasma protein binding is negligible for oxytocin. It crosses the placenta in both directions. Oxytocin may be found in small quantities in mother's breast milk.

Biotransformation/Metabolism

Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. It is produced from both the mother and the foetus. Liver and kidney plays a major role in metabolising and clearing oxytocin from the plasma. Thus, liver, kidney and systemic circulation contribute to the biotransformation of oxytocin.

Elimination

Plasma half-life of oxytocin ranges from 3 to 20 min. The metabolites are excreted in urine whereas less than 1% of the oxytocin is excreted unchanged in urine. The metabolic clearance rate amounts to 20 mL/kg/ min in the pregnant woman.

Renal impairment

No studies have been performed in renally impaired patients. However, considering the excretion of oxytocin and its reduced urinary excretion because of anti-diuretic properties, the possible accumulation of oxytocin can result in prolonged action.

Hepatic impairment

No studies have been performed in hepatically impaired patients. Pharmacokinetic alteration in patients with impaired hepatic function is unlikely since metabolising enzyme, oxytocinase, is not confined to liver alone and the oxytocinase levels in placenta during the term has significantly increased. Therefore, biotransformation of oxytocin in impaired hepatic function may not result in substantial changes in metabolic clearance of oxytocin.

5.3 Preclinical safety data

Pre-clinical data for oxytocin reveal no special hazard for humans based on conventional studies of single dose acute toxicity, genotoxicity, and mutagenicity.

6. Pharmaceutical particulars

6.1 List of excipients

Chlorobutanol

Glacial Acetic Acid

Water for injection

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. n.

6.3 Shelf life

36 months

Once opened, use immediately and discard any unused contents.

6.4 Special precautions for storage

Store between 2~8 °C.

6.5 Nature and contents of container

Clear glass 1ml ampoules. Boxes of 10 ampoules.

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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Bazreal Global Limited

2 Ogunyomi street , Olopo meji bus stop , Oworo Lagos, Nigeria.