

**COMMON TECHNICAL DOCUMENT****PRODUCT: OXYTOCIN INJECTION BP****MODULE 1 : ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION**

1.3 Summary of product characteristics (SmPC) - Attached

SUMMARY OF PRODUCT CHARACTERISTICS**1. NAME OF THE PRODUCT:****OXYTOCIN INJECTION BP****2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml contains:

Oxytocin BP 10 IU

3. PHARMACEUTICAL FORM:

Solution for Injection

4. CLINICAL PARTICULARS**4.1. THERAPEUTIC INDICATIONS:**

Oxytocin BP 10 IU injection/infusion is indicated for:

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:**Posology****Induction or enhancement of labour:** Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins.

Oxytocin should be administered as an intravenous (i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump.

For drip infusion it is recommended that 10 IU (8.3 micrograms) 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. 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 2 to 8 drops/minute (1 to 4 milliunits/minute). It may be gradually increased at intervals not shorter than 20 minutes and increments of not more than 1 to 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 20 drops/minute (10 milliunits/minute), and the recommended maximum rate is 40 drops/minute (20 milliunits/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

COMMON TECHNICAL DOCUMENT**PRODUCT: OXYTOCIN INJECTION BP**

oxytocin, it is advisable to use a more concentrated oxytocin solution, e.g., 10 IU (16.7 micrograms) in 500 ml.

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 10 IU (8.3 micrograms), 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 2 to 8 drops/minute (1 to 4 milliunits/minute)

Incomplete, inevitable, or missed abortion: 10IU (8.3 micrograms) by i.v. infusion (10 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 10 IU (8.3 micrograms) by i.v. infusion (10IU diluted in physiological electrolyte solution and administered as an i.v. 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 IU (8.3 micrograms) by i.v. infusion (10 IU diluted in physiological electrolyte solution and administered as an i.v. 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: 10 IU (8.3 micrograms) by i.v. infusion (10 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), followed in severe cases by i.v. infusion of a solution containing 5 to 20 IU (8.3 to 33.4 micrograms) 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.

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 contraindicated: 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.

COMMON TECHNICAL DOCUMENT**PRODUCT: OXYTOCIN INJECTION BP**

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

Oxytocin must not be administered within 6 hours after vaginal prostaglandins have been given

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Oxytocin must only be administered as an i.v. infusion and never by i.v. 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

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.

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 i.v. 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 i.v. 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

COMMON TECHNICAL DOCUMENT**PRODUCT: OXYTOCIN INJECTION BP**

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a concomitant use not recommended

Prostaglandins and their analogues

Prostaglandins and their analogues facilitate contraction of the myometrium hence oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa

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.

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 & LACTATION:**Pregnancy**

The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons.

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.

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 oxytocin. The effects of oxytocin on fertility are unknown.

COMMON TECHNICAL DOCUMENT**PRODUCT: OXYTOCIN INJECTION BP****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 i.v. 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 i.v. bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia

These rapid haemodynamic changes may result in myocardial ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid i.v. 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.

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.

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

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 ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports; not known (cannot be estimated from the available data). The adverse reactions (ADRs) tabulated below are based on clinical trial results as well as post-marketing 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 Med DRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**COMMON TECHNICAL DOCUMENT****PRODUCT: OXYTOCIN INJECTION BP**

Table 1 Adverse drug reactions in mother

System organ class	Adverse drug reaction
Immune system disorders	Rare: 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
Gastrointestinal disorders	Common: Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Rash
Pregnancy, puerperium and perinatal conditions	Not known: Uterine hypertonicity, tetanic contractions, 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

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

Reporting of suspected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via.

COMMON TECHNICAL DOCUMENT**PRODUCT: OXYTOCIN INJECTION BP****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 section 4.8. 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 i.v. 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, by judicious use of diazepam. 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 Pharmacodynamics Properties:**

Systemic hormonal preparations, excl. sex hormones and insulins, oxytocin and analogues,

ATC code: H01BB02

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 this product 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 i.v. 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

**COMMON TECHNICAL DOCUMENT****PRODUCT: OXYTOCIN INJECTION BP**

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 i.v. 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 minutes. 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.



COMMON TECHNICAL DOCUMENT

PRODUCT: OXYTOCIN INJECTION BP

PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

24 months.

6.2 Special Precautions for Storage

Store between 2°C to 8 °C, Protect form light.

6.3 Nature and Contents of Container

1 ml amber glass ampoule, in packs containing 10 ampoules.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.

C-1101/1102, Lotus Corporate Park, Graham Firth Steel Compound,

Jay Coach Junction, Western Express Highway, Goregaon (E),

Mumbai-400 063, INDIA

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable