

SUMMARY OF PRODUCT CHARACTERISTICS

1.7.1.1 Name of the Medicinal Product

- a) Name Of The Product : RELICIN 10 (Oxytocin Injection BP 10 IU/mL)
b) Strength : 10 IU/mL
c) Pharmaceutical Dosage Form : Solution for injection

1.7.1.2 Quantitative and Qualitative Composition:

Composition:

Each ml of solution for injection contains

| | | |
|---------------------|---------|----------|
| Oxytocin | Ph. Eur | 10IU |
| Chlorobutanol | BP | 0.5% w/w |
| Water for Injection | BP | q.s |

| S.No | Ingredients |
|------|---------------------------|
| 1. | Oxytocin * |
| 2. | Ethanol 96% |
| 3. | Chlorobutanol ** |
| 4. | Sodium Acetate trihydrate |
| 5. | Sodium Chloride |
| 6. | Glacial Acetic Acid |
| 7. | Water for injection |
| 8. | Nitrogen gas \$ |

Legends:

Ph. Eur.: European Pharmacopeia

BP: British Pharmacopeia

USP: United States Pharmacopeia-National Formulary

mg: Milligrams

mL: Millilitre

IU: International unit

%: Percentage

Qs: quantity sufficient

1 mg of Oxytocin peptide is equivalent to 600 IU.

*Denotes that the API has been taken as 100% Assay and 0% Water and Acetic Acid Content. The quantity of Oxytocin shall vary based on the Assay, Water and Acetic Acid Content.

**Denotes that the Chlorobutanol has been taken as 100% Assay and 0% Water Content. The quantity of Chlorobutanol shall vary based on the Assay and Water content. \$ for blanketing

The actual quantity of **Oxytocin** to be taken is calculated using the below given formula,

$$= \text{Standard Quantity} \times \frac{100}{\text{Assay (anhydrous, acetic acid free basis)}} \times \frac{100}{(100 - \text{Water} + \text{Acetic acid Content})}$$

The actual quantity of **Chlorobutanol** to be taken is calculated using the below given formula

$$= \text{Standard Quantity} \times \frac{100}{\text{Assay (anhydrous basis)}} \times \frac{100}{(100 - \text{Water Content})}$$

Overages: No overages of active pharmaceutical ingredient has been used in the formulation

Container Closure System:

Oxytocin Injection BP 10 IU/mL is packed in 1mL clear glass ampoules USP type I. 10 such ampoules are packed in a plastic ampoule tray, pre – folded literature will be placed in plastic ampoule tray and one ampoule tray in one printed carton along with leaflet.

1.7.1.1 Pharmaceutical Forms:

Liquid Injection

1.7.1.2 Clinical Particulars:

4.1 Therapeutic indication:

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

Oxytocin 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).

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 5 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 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 5 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: 5 IU (8.3 micrograms) by i.v. infusion (5 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: 5 IU (8.3 micrograms) by i.v. infusion (5 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) 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 mean of a variable-speed infusion pump), over 5 minutes after delivery of the placenta. In women given oxytocin for induction of enhancement of labor, the infusion should be continued at an increased rate during the third stage of labor 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 mean 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 diluents, run at the rate necessary to control uterine atony.

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

There are no indications for use of Oxytocin in children or adolescents.

Older people (65 years and over)

There are no indications for use of Oxytocin in elderly.

Method of administration

For IM/IV use

4.3 Contraindication:

Hypersensitivity to the active substance or to any of the excipients.

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.

Oxytocin Injection BP 10 IU/mL should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxemia or severe cardiovascular disorders.

Oxytocin Injection BP 10 IU/mL must not be administered within 6 hours after vaginal prostaglandins have been given.

4.4 Special Warning And Special Precaution 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 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 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 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.

4.5 Interaction With Other Medicaments 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 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 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 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).

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: 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 |

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.

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.

1.7.1.3 Pharmacological Properties:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones, 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 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 Pharmacokinetics 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.

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.

1.7.1.4 Pharmaceutical Particulars:

6.1 List of Excipients

Ethanol 96%, Chlorobutanol, Sodium Acetate trihydrate, Sodium Chloride, Glacial Acetic Acid, Water for injections

6.2 Incompatibilities:

Oxytocin Injection BP 10 IU/mL should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Oxytocin Injection BP 10 IU/mL is incompatible with solutions containing sodium metabisulphite as a stabilizer.

6.3 Shelf Life:

24 months.

6.4 Special Precaution for Storage:

Store the ampoule refrigerated (2-8°C) in the original cartons protected from light. Do not freeze. Single use only. Keep out of reach of Children

6.5 Nature and contents of container

A Clear colorless solution free from visible particulate filled in USP Type I 1 mL clear glass Ampoule. Such 10 labeled Ampoules are packed in Plastic Ampoule Tray. Such Plastic Ampoule Tray placed in Printed Carton along with Literature.

6.6 Special precautions for disposal

Oxytocin Injection BP 10 IU/mL is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium/potassium chloride (103 mmol Na⁺ and 51 mmol K⁺), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution for 48 hours at 25°C.

Discard unused portion in accordance with local requirements.

1.7.1.5 Manufacturer:

Registered Office:

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