

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Oxytocin 10 IU/ml Concentrate for Solution for Infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin

Concentrate for solution for infusion (in 1ml ampoule) containing 10 IU/ml

Excipient(s) with known effect:

None

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

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

## 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 an 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

#### 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 5 IU of Oxytocin be added to 500ml 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 "Contra-indications").

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.

***Incomplete, inevitable, or missed abortion:*** 5 IU 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 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 5 IU 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) after delivery of the placenta.

***Treatment of postpartum uterine haemorrhage:*** 5 IU 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), followed in severe cases by i.v. 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.

#### Method 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 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 toxemia 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 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 (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 post partum 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 (see section 5.2 Pharmacokinetics).

This medicine contains less than 1mmol sodium (less than 23mg per ampoule), i.e. it is essentially sodium free.

### ***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 interactions**

### **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**

### **Pregnancy**

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.

One study has shown that treatment of rats with oxytocin in early pregnancy at doses considered sufficiently in excess of the maximum recommended human dose caused embryonic loss. No standard reproductive performance studies with oxytocin are available

### **Breast-feeding**

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 when it undergoes rapid inactivation.

### **Fertility**

Not applicable for oxytocin because of the targeted indications

#### 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 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 (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 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 (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 i.v. 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
Blood and lymphatic system disorders	Not known: disseminated intravascular coagulation
Immune system disorders	Rare: Anaphylactic/Anaphylactoid reaction associated with dyspnoea, hypotension or Anaphylactic/Anaphylactoid 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, Electrocardiogram QTc prolongation
Vascular disorders	Not known: Hypotension, haemorrhage
Respiratory, thoracic and mediastinal disorders	Not known: acute pulmonary oedema
Gastrointestinal disorders	Common: Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Rash Not known: Angioedema

System organ class	Adverse drug reaction
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

**Table 2 Adverse drug reactions in foetus/neonate**

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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 676 4971; Fax +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); Email; [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

**4.9 Overdose**

The fatal dose of oxytocin has not been established. Oxytocin is subject to inactivation by proteolytic enzymes of the alimentary tract. Therefore 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 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. 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 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 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 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 have 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**

Sodium acetate tri-hydrate, glacial acetic acid, sodium hydroxide and water for injections.

### **6.2 Incompatibilities**

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf life**

Three years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

### **6.4 Special precautions for storage**

Store between 2°C and 8°C. May be stored up to 30°C for 3 months, but must then be discarded.

Store in the original package in order to protect from light.

### **6.5 Nature and contents of container**

Clear, Type I, neutral glass, 1ml ampoules. Boxes of 10 or 5 ampoules. Not all packs sizes may be marketed.

### **6.6 Special precautions for disposal**

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

Snap ampoules: no file required.

Oxytocin is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: 6% dextran 60 or 70 (in glucose or sodium chloride), 10% dextran 40 (in glucose or sodium chloride), sodium/potassium chloride (103mmol Na<sup>+</sup> and 51mmol K<sup>+</sup>), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, Ringer's solution.

## **7 MARKETING AUTHORISATION HOLDER**

Pinewood Laboratories Ltd,  
Ballymacarbry  
Clonmel  
Co. Tipperary  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0281/239/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 18<sup>th</sup> July 2014

Date of last renewal: 20<sup>th</sup> April 2019

## **10 DATE OF REVISION OF THE TEXT**

December 2020