OXYTOCIN

OXYLA®

10 IU / mL Solution for Injection (I.M./I.V.)
Oxytocic

COMPOSITION :
Each mL contains :
Oxytocin, BP ..... 10 IU

PRODUCT DESCRIPTION :
Oxytocin (Oxyla®) Injection is a sterile aquaeous solution containing synthetic oxytocin. The solution is clear and colourless.

PHARMACODYNAMICS :
Mechanism of Action (MOA) and Pharmacodynamics
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 labor. Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labor, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased. The oxytocin receptors are G-proteins couple 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 labor. Being synthetic, it 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 desensitization of oxytocin receptors probably due to down-regulation of oxytocin-binding sites, destabilization of oxytocin receptors mRNA and internalization of oxytocin receptors.

Plasma levels and onset/duration of effect
Intravenous infusion :
When oxytocin (Oxyla®) is given by continuous I.V. infusion at doses appropriate for induction or enhancement of labor, 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 labor. 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.
Intravenous injection and intramuscular injection :
When administered by I.V. or I.M. injection for prevention or treatment of postpartum hemorrhage, oxytocin (Oxyla®) acts rapidly with a latency period of less than 1 minute by I.V. injection, and of 2 to 4 minutes by I.M. injection. The oxytocic response lasts for 30 to 60 minutes after I.M. administration, possibly less after I.V. injection.

PHARMACOKINETICS :
Absorption :
Oxytocin is rapidly absorbed from the I.M. site. Plasma levels of oxytocin following intravenous infusion at a rate of 4 milliunits/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 was 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 fetus. Liver and kidney plays a major role in metabolizing 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 metabolizing 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 (see section **Precautions and Warnings**).

INDICATIONS :
Antepartum
• Induction of labor for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia).
• Enhancement of labor in selected cases of uterine inertia.
• Also indicated in early stage of pregnancy, as adjunctive therapy for management of incomplete, inevitable or missed abortion.
Postpartum
• During caesarean section, but after the delivery of the child.
• Prevention and treatment of postpartum uterine atony and hemorrhage.

DOSAGE AND ROUTE OF ADMINISTRATION :
Dosage Regimens
Induction or enhancement of labour :
Oxytocin (Oxyla®) should only 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 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 **Precautions and Warnings**). 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 increased gradually 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 labor 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 of higher rates being required, as may occur in the management of fetal death in utero or for induction of labor at an earlier stage of pregnancy when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated solution, e.g. 10 IU in 500 mL.
When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, suitable concentration for infusion within the recommended dosage range must be calculated according to the specifications of the pump.
The frequency, strength and duration of contractions and also fetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or fetal 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 labor should be terminated, it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute.
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) or 5 to 10 IU I.M., 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 hemorrhage :
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, preferable, by means of a variable-speed infusion pump over 5 minutes) or 5 to 10 IU I.M. after delivery of the placenta.
In women given oxytocin (Oxyla®) for induction or enhancement of labor, the infusion should be continued at an increased rate during the third stage of labor and for the next few hours thereafter.
Treatment of postpartum uterine hemorrhage :
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), or 5 to 10 IU I.M., followed in severe cases by intravenous infusion of a solution containing 5 to 20 IU of oxytocin in 500 mL of an electrolyte-containing diluent, 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.
Pediatric patients :
No studies have been performed in pediatric patients.
Geriatric patients :
No studies have been performed in elderly patients (65 years old and over).

CONTRAINDICATIONS :
Known hypersensitivity to oxytocin or to any of the excipients.
Hypertonic uterine contractions, fetal distress when delivery is not imminent.
Any condition in which, for fetal or maternal reasons, spontaneous labor is unadvisable and/or vaginal delivery is contraindicated : e.g. :
• Significant cephalopelvic disproportion,
• Fetal malpresentation,
• Placenta praevia and vasa praevia,
• Placental abruption,
• Cord presentation of prolapse,
• Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy,
• Polyhydramnios,
• Grand multiparity and
• In the presence of a uterine scar resulting from major surgery including classical caesarean section.
Oxytocin (Oxyla®) must not be administered within 6 hours after vaginal prostaglandins have been given (see section **Drug Interactions**).

PRECAUTIONS AND WARNINGS :
Induction of labour :
The induction of labor by means of oxytocin should be attempted only when strictly indicated for medical reasons rather than for convenience. Administration should only be under hospital conditions and qualified medical supervision.
Oxytocin (Oxyla®) should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxemia or severe cardiovascular disoders.
Oxytocin (Oxyla®) should not be given as I.V. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.
Cardiovascular disorders :
Oxytocin (Oxyla®) should be used with caution in patients who have pre-disposition to myocardial ischemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy, vascular heart disease and/or ischemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.
QT Syndrome :
Oxytocin (Oxyla®) 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 QT interval (see section Drug Interactions).
When oxytocin (Oxyla®) is given for induction and enhancement of labor :
• It must only be administered as an I.V. infusion, and never by S.C., I.M or I.V. bolus injection.
• Fetal distress and fetal death : Administration of oxytocin at excessive doses results in uterine overstimulation which may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus.
Careful monitoring of fetal heart rate and uterine motility (frequency, strength and duration of contractions) is essential, so that the dosage may be adjusted to individual response.
• Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension of 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 labor 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 the 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 fetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labor 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 hemorrhage, may cause water intoxication associated with hyponatremia. The combined antidiuretic effect of oxytocin and the I.V. fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary edema without hyponatremia. 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 labor 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.

PREGNANCY AND LACTATION :

Pregnancy :

Pre-clinical data for oxytocin reveal no special hazard based on conventional studies of single dose acute toxicity, genotoxicity, and mutagenicity. No standard teratogenicity and reproductive performance studies with oxytocin are available. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of fetal abnormalities when used as indicated.

Lactation

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.

DRUG 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 **Contraindications**).

Drugs prolonging 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 **Precautions and Warnings**).

Interactions to be considered

Inhalation anesthetics :

Inhalation anesthetics (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.

Vasoconstrictors/Sympathomimetrics :

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetrics, even those contained in local anesthetics.

Caudal anesthetics :

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

ADVERSE DRUG REACTIONS :

When oxytocin is used by I.V. infusion for the induction or enhancement of labor, administration at excessive doses results in uterine overstimulation which may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions 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 **Precautions and Warnings**). These rapid hemodynamic changes may result in myocardial ischemia, 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 (i.e. incidence rate <0.0006), the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section **Precautions and Warnings**).

Water intoxication

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin have been administered together with large amounts of electrolyte-free fluid over a prolonged period of time (see section **Precautions and Warnings**).

The combined antidiuretic effect of oxytocin and the I.V. fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary edema without hyponatraemia (see section **Precautions and Warnings**).

The following adverse drug reactions have been reported regardless of the mode of administration.

Adverse reactions (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention :

very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliable estimate their frequency which is therefore categorized 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 the 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 ischemia, QTc prolongation
Vascular disorders	Not known : Hypotension
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 hyponatremia
Respiratory, thoracic and mediastinal disorders	Not known : acute pulmonary edema
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 fetus/neonate

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

OVERDOSE AND TREATMENT :

The symptoms and consequences of overdose are those mentioned under sections **Precautions and Warnings** and **Adverse Drug Reactions**). In addition, placental abruption and/or amniotic fluid embolism as a result of uterine overstimulation have been reported.

Treatment

When signs or symptoms of overdose occur during continuous I.V. administration of oxytocin (Oxyla®), the infusion must be discontinued at once and oxygen should be given to the mother. In the event of water intoxication, it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control possible convulsions.

INCOMPATIBILITIES :

In the absence of compatibility studies, oxytocin (Oxyla®) must not be mixed with other medicinal products.

STORAGE CONDITION :

Store in a refrigerator (2°C to 8°C).

SPECIAL PRECAUTIONS :

Use only once or discard any remaining portion.
Single use or single dose.
Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permits.

PACKAGING AVAILABLE (PACK SIZE) :

Type I (borosilicate) Clear Glass Ampoule in 1 mL (net content). Box of 10 ampoules.

CAUTIONS :

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING :

For suspected adverse drug reaction, report to the FDA : www.fda.gov.ph

REGISTRATION NUMBER :

DR-XY45566

DATE OF FIRST AUTHORIZATION :

19 August 2016

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November 2016

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