5 IU Injection **1ml Ampoule**

Syntomax

(Synthetic Oxytocin) Injection BP

DESCRIPTION AND COMPOSITION:

Pharmaceutical forms: Concentrate for Solution for infusion; Solution for injection.

Active substance: The active substance is synthetic oxytocin.

Composition: Each 1ml ampoule contains:
Synthetic Oxytocin 5 IU
(Equivalent to Oxytocin 8.333mcg/ml).
For IM injection or for IV infusion.
Finished Product Specs.: BP

INDICATIONS:

Antepartum:

- Induction of labor for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (preeclampsia).
- Enhancement of labor in selected cases of uterine inertia.
- Syntomax may also be indicated in early stage of pregnancy, as an adjunctive therapy for management of incomplete, inevitable or missed abortion.

Postpartum:

- During cesarean section but not until after the delivery of the child.
- Prevention and treatment of postpartum uterine atony and hemorrhage.

DOSAGE AND ADMINISTRATION:

Dosage: General target population: Induction or enhancement of labor: Syntomax should be administered as an intravenous (IV) drip infusion or, preferably, by means of a variable -speed infusion pump. For drip infusion it is recommended that 5 IU of Syntomax 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 WARNINGS AND PRECAUTIONS). 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 managment of foetal 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 Syntomax 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, 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 and also the foetal 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 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 labor should be terminated; it may be repeated on the following day, starting again from rate of 1 to 4 milliunits/minute.

Incomplete, inevitable, or missed abortion: 5 IU by IV 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 IM, if necessary followed by IV Infusion at a rate of 20 to 40 milliunits/minute.

Cesarean section: 5 IU by IV Infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or preferably by means of variable speed infusion pump over 5 minutes) immediately after delivery.

Prevention of postpartum uterine hemorrhage: The usual dose is 5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or preferably, by means of a variable-speed infusion pump over 5 minutes) or 5 to 10 IU IM after delivery of the placenta.

In women given Syntomax 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 IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or preferably, by means of a variable-speed infusion pump over 5 minutes), or 5 to 10 IU IM, followed in severe cases by IV 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.
- Hypertonic uterine contractions, foetal distress when delivery is not imminent.
- Any condition in which, for foetal or maternal reasons, spontaneous labor is unadvisable and/or vaginal delivery is contraindicated, e.g.
- Significant cephalopelvic disproportion.
- Foetal malpresentation.
- Placenta previa and vasa previa.
- Placental abruption.
- Cord presentation or prolapse.

- Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy.
- Polyhydramnios.
- Grand multiparity.
- Presence of a uterine scar resulting from major surgery, including classical cesarean section. Syntomax must not be administered within 6 hours after vaginal prostaglandins have been given (see section INTERACTIONS).

WARNINGS AND PRECAUTIONS: Induction of labor: 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.

Syntomax should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe preeclamptic toxemia, or severe cardiovascular disorders. Syntomax 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: Syntomax should be used with caution in patients who have a pre-disposition to myocardial ischemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy, valvular 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: Syntomax 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 INTERACTIONS). When Syntomax is given for induction and enhancement of labor:

- It must only be administered as an IV infusion and never by s.c. IM or IV bolus injection.
- 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 cesarean 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 foetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labor must be avoided, as it may causes amniotic fluid embolism.

Water intoxication: Because oxytocin possesses slight antidiuretic activity, its prolonged IV administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion, or in the management of postpartum 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 toa 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.

Renal Impairment: Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin (see section CLINICAL PHARMACOLOGY).

ADVERSE DRUG REACTIONS: When oxytocin is used by i.v. infusion for the induction or enhancement of labor, its administration 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.

Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied by flushing and reflex tachycardia (see section WARNINGS AND PRECAUTIONS). These rapid hemodynamic changes may result in myocardial ischemia, particularly in patients with pre-existing cardiovascular disease. Rapid IV bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

In rare circumstances (i.e. incidence rate <0.0006), the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum DIC (see section WARNINGS AND PRECAUTIONS).

Water intoxication: Water intoxication associated with maternal and neonatal hyponatremia 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 WARNINGS and PRECAUTIONS).

The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a hemodyanamic form of acute pulmonary edema without hyponatremia (see section WARNING AND PRECAUTIONS).

The following adverse drug reactions (ADRs) have been reported regardless of the mode of Administration: ADRs (Table 1, Table 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.

The ADRs tabulated below are based on clinical trial results as well as postmarketing reports. The ADRs erived from postrnarketing 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 categorized as not known. ADRs 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 disorder	Rare: anaphylactoid reaction associated with dyspnea and hypotension, anaphylactoid shock.
Nervous system disorders	Common headache
Cardiac disorders	Common: tachycardia bradycardia Uncommon:Arrhythmia Not known: myocardial ischemia Electrocardiogram: QTc prolongation
Vascular Disorder	Not known: Hypotension
Gastrointestinal disorders	Common: nausea,vomiting
Skin and subcutaneous tissue disorders	Rare: Rash
Pregnancy, puerperium and perinatal conditions	Not known: Uterine hypertonus, tetanic contractions of uterus, uterine rupture.
Metabolism and nutrition disorders	Not known: Water intoxication, hyponatraemia,
Respiratory, thoracic and mediastinal disorders.	Not known: Acute pulmonary oedema
General disorder 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 syndrome, asphyxia and death
Metabolism and nutrition disorders	Not known: Neonatal hyponatraemia

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 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 a history of long QT syndrome (see section WARNINGS AND PRECAUTIONS).

Interactions to be considered:

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/Sympathomimetics: Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, 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.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST- FEEDING AND FERTILITY:

Women of childbearing potential: Not applicable for Syntomax because of the targeted indications.

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.

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 where it undergoes rapid inactivation.

Fertility: Not applicable for Syntomax because of the targeted indications.

Overdosage: The symptoms and consequences of overdose are those mentioned under sections WARNINGS AND PRECAUTIONS 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 IV administration of Syntomax, 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.

CLINICAL PHARMACOLOGY: 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 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 labor. Being synthetic, oxytocin in Syntomax 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 Syntomax 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 IV or IM injection for prevention or treatment of postpartum hemorrhage, Syntomax acts rapidly with a latency period of less than 1 minute by' IV injection, and of 2 to 4 minutes by IM injection. The oxytocic response lasts for 30 to 60 minutes after IM administration, possibly less after IV Injection.

Pharmacokinetics: Absorption: Oxytocin is rapidly absorbed from the IM site. Plasma levels of oxytocin following IV infusion at 4 milliunits per minute in pregnant women at term were 2 to 5 microunits/mL.

Distribution: The steady-state volume of distribution determined in 6 healthy men after IV injection is 12. 2 L or 0.17 L/kg. Plasma protein binding is negligible for oxytocin. It crosses the placenta in both directions. Oxytocin may be found in small quantities in mother's breast milk.

Biotransformation/metabolism: Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. It is produced from both the mother and the foetus. Liver and kidney plays a major role in 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 20ml/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 antidiuretic properties, the possible accumulation of oxytocin can result in prolonged action (see section WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES: Oxytocin injection 5 IU is an established product. No recent clinical studies are available.

NON-CLINICAL SAFETY DATA: Preclinical data for oxytocin reveal no special hazard for humans based on conventional studies of single-dose acute toxicity, genotoxicity, and mutagenicity.

Mutagenicity: An in-vitro genotoxicity and mutagenicity study with oxytocin has been reported. Tests were negative for chromosomal aberration and sister chromatid exchange in human peripheral lymphocyte cultures. No significant changes in the mitotic index were noticed. Oxytocin had no genotoxic properties. The genotoxic potential of oxytocin has not been determined *in vivo*.

Carcinogenicity, teratogenicity, and reproductive toxicity: Treatment of rats with oxytocin in early pregnancy at doses considered sufficiently in excess of the maximum recommended human dose caused embryonic loss in one study. No standard teratogenicity, reproductive performance and carcinogenicity studies with oxytocin are available.

INCOMPATIBILITIES: In the absence of compatibility studies. Syntomax must not be mixed with other medicinal products.

Storage: Syntomax Concentrate for Solution for infusion; Solution for injection: Store in a refrigerator 2°C-8°C and protect from heat and light.
(See Pack)
Syntomax should not be used after the expiry date on the pack/ampoule.

SPECIAL PRECAUTIONS FOR DISPOSAL: Any unused product or waste material should be disposed off in accordance with local requirements.

PRESENTATION: 50x1ml Ampoule.

Keep all medicines out of the reach of children.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
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