

SYNTOCINON® Injection

(synthetic oxytocin)

NAME OF THE MEDICINE

Oxytocin BAN, INN. The active substance of Syntocinon is a synthetic nonapeptide identical with oxytocin, a hormone released by the posterior lobe of the pituitary. Being wholly synthetic, it does not contain vasopressin and has a constant and reliable effect.

DESCRIPTION

Oxytocin injection is a sterile aqueous solution containing synthetic oxytocin. The solution is clear and colourless.

Syntocinon is available in ampoules containing 5 IU in 1 mL and 10 IU in 1 mL.

Excipients: sodium acetate, glacial acetic acid, chlorobutanol hemihydrate, ethanol, water for injections.

PHARMACOLOGY

Pharmacodynamics

Oxytocin stimulates the smooth muscle of the uterus, producing rhythmic contractions, particularly towards the end of pregnancy, during labour, after delivery and in the puerperium, i.e. at times when the number of specific oxytocin receptors in the myometrium is increased. When given by low-dose intravenous infusion, Syntocinon elicits rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour. At higher infusion dosages, or when given by single injection, the drug is capable of causing sustained tetanic uterine contractions. Upon discontinuation of the infusion or following a substantial reduction in the infusion rate (e.g. in the event of over stimulation), uterine activity declines rapidly but may continue at an adequate lower level.

Oxytocin also causes contraction of the myo-epithelial cells surrounding the mammary alveoli. It therefore facilitates lactation in women experiencing difficulty in breast feeding. Synthetic oxytocin has only very slight pressor and anti-diuretic activity (absence of vasopressin).

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid intravenous bolus injection, is a transient direct relaxing effect on

vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia (see “PRECAUTIONS”).

Oxytocin, being a polypeptide, is largely inactivated in the alimentary tract and, therefore, virtually ineffective when ingested.

Pharmacokinetics

Plasma levels and onset/duration of effect:

Intravenous infusion: When Syntocinon is given by continuous intravenous infusion at doses appropriate for induction or augmentation 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 an intravenous infusion at a rate of 4 milliunits/minute, were 2 to 5 microunits/mL.

Intravenous injection and intramuscular injection: When administered by intravenous or intramuscular injection for prevention or treatment of post-partum haemorrhage, Syntocinon acts rapidly, with a latency period of less than 1 minute by intravenous injection and of 2 to 4 minutes by intramuscular injection. The oxytocic response lasts for 30 to 60 minutes after intramuscular administration and possibly less after intravenous injection.

Distribution:

Oxytocin distributes throughout the extracellular fluid, with minimal amounts reaching the foetus. The steady-state distribution volume determined in 6 healthy men after intravenous injection was 12.2 L or 0.17 L/kg. Plasma protein binding is very low. Oxytocin may be found in small quantities in mother’s breast milk.

Biotransformation:

A glycoprotein aminopeptidase, oxytocinase, is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. Enzyme activity increases gradually until term approaches, at which time it rises steeply to high levels. Enzyme activity then declines after delivery. Enzyme activity in the placenta and in the uterine tissue is also high during this period. There is little or no degradation of oxytocin by plasma in men, non-pregnant women or cord blood.

Elimination:

The relative ease with which the rate and force of uterine contractions can be regulated by the intravenous infusion of Syntocinon is due to the short half-life of oxytocin. Values reported by various investigators range from 3 to 20 minutes. Removal of oxytocin from plasma is

accomplished mainly by the liver and the kidneys. The metabolic clearance rate amounts to about 20 mL/kg/min in men as well as in pregnant women. Less than 1% of a given dose is excreted unchanged in the urine.

INDICATIONS

Induction of labour; inadequate uterine effort; management of third stage of labour; post-partum haemorrhage.

CONTRAINDICATIONS

- Foetal distress.
- Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contraindicated: e.g. cephalo-pelvic disproportion, abnormal presentation, cord presentation or prolapse, excessive distension or impaired resistance of the uterus to rupture (e.g. multiple pregnancy, polyhydramnios), parity greater than 4, elderly multiparae, grand multiparity and in the presence of uterine scar resulting from major surgery including previous caesarean section or other surgery involving the uterus.
- Severe toxemia, predisposition to amniotic fluid embolism (foetal death-in-utero, abruptio placentae), hypertonic contractions, placenta praevia and vasa praevia, placental abruption
- Hypersensitivity to oxytocin or to any of the excipients in the formulation.
- Syntocinon must not be administered within 6 hours after vaginal prostaglandins have been given.

PRECAUTIONS

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

Induction or augmentation of labour:

The induction of labour by means of oxytocic agents should be attempted only when strictly indicated for medical reasons rather than for convenience. Administration should only be under hospital conditions, and all patients receiving intravenous oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications must be immediately available.

When Syntocinon is given for the induction and augmentation of labour, it must only be administered as an intravenous infusion, preferably by means of a motor-driven variable speed infusion pump, and not by subcutaneous, intramuscular or intravenous bolus injection as it may cause an acute short-lasting hypotension accompanied by flushing and reflex tachycardia.

Foetal distress and foetal death: Administration of oxytocin at excessive doses results in uterine over-stimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring is essential (foetal heart rate, uterine response - by tocometry if possible, blood pressure), so that dosage may be titrated to individual response.

When Syntocinon is used for the induction of labour, there is a chance that infants with unanticipated prematurity may be delivered. To reduce this risk, it is recommended that, in women with uncertain obstetric dating, the maturity of the foetus be assessed by ultrasonic measurement of foetal biparietal diameter.

Third stage of labour and puerperium:

When Syntocinon is used for prevention or treatment of uterine haemorrhage, rapid intravenous bolus injection of oxytocin at high doses should be avoided, as it may cause acute short-lasting hypotension accompanied by flushing and reflex tachycardia. These rapid haemodynamic 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.

When Syntocinon is used for the management of the third stage of labour, multiple pregnancy must be excluded before the drug is injected.

Use caution in the following circumstances:

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 (note: use is contraindicated in elderly multiparae), or with a history of lower-uterine-segment caesarean section.

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 (see “CONTRAINDICATIONS”).

Syntocinon should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia or severe cardiovascular disorders. In patients with cardiovascular disorders, the infusion volume should be kept low by using a more concentrated solution.

Cardiovascular disorders: Syntocinon 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: Syntocinon 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.

In situations where more prolonged periods of administration may be required, such as in the treatment of inevitable or missed abortion, in the management of postpartum haemorrhage, or earlier in gestation when the uterus is less sensitive to Syntocinon, special precautions must be taken to avoid water intoxication.

Water intoxication:

Water intoxication associated with maternal and neonatal hyponatraemia, which is potentially fatal, 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. The weak anti-diuretic activity of oxytocin, acting to increase water reabsorption from the glomerular filtrate, may be a contributing factor, but the major cause is the use of large amounts of electrolyte-free fluids. The combined antidiuretic effect of oxytocin and the intravenous fluid administration may also cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia.

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

The symptoms and signs of water intoxication are:

1. Headache, anorexia, nausea, vomiting and abdominal pain.
2. Lethargy, drowsiness, unconsciousness and grand mal type seizures.
3. Low blood electrolyte concentration including maternal and neonatal hyponatraemia.
4. Possible acute pulmonary oedema without hyponatraemia.

Therefore, if high doses or a more prolonged period of administration is expected, the following precautions must be observed:

1. A strict fluid balance chart must be kept
2. Low-sodium infusion fluids should be avoided
3. Syntocinon should be infused in small volumes of isotonic diluent (not dextrose), using higher concentrations than recommended for the induction and augmentation of labour at term in non-complicated cases
4. Fluid intake by mouth must be restricted
5. Maternal serum electrolytes should be measured at regular intervals e.g. 8-12 hourly.

Treatment of Water Intoxication:

1. Discontinue oxytocin
2. Restrict fluid intake
3. Promote diuresis
4. Correct electrolyte imbalance
5. Control convulsions, e.g. with judicious use of diazepam
6. If coma is present: maintain a free airway and carry out the routine measures for care of an unconscious patient.

Disseminated intravascular coagulation:

In rare circumstances (i.e. incidence rate < 0.0006), the pharmacological induction of labour using uterotonic agents, including dinoprostone or 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 other risk factors for DIC such as 35 years of age or over, complications during the pregnancy and gestational age more than 40 weeks. In these women, Syntocinon or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC (fibrinolysis).

Anaphylaxis in women with latex allergy

There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

Effects on ability to drive and use machines

Syntocinon can induce uterine contractions and, therefore, caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

Carcinogenicity and Genotoxicity

No carcinogenicity studies with oxytocin are available. Oxytocin did not induce chromosomal aberration and sister chromatid exchange in human peripheral lymphocytes in vitro.

Effects on Fertility

There are no studies on the potential effect of oxytocin on fertility.

Use in Pregnancy (Category A)

Use of oxytocin has contributed significantly to the safety of parturition. However, there have been instances of idiosyncratic sensitivity of the uterus resulting in foetal anoxia.

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. Treatment of rats with oxytocin early in pregnancy, in doses approximately three thousand times the dose used to induce labour in humans, caused embryonic foetal loss in one study. No standard embryofoetal development studies with oxytocin are available.

Use in Lactation

Endogenous 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.

Special Populations

No studies have been performed in renally-impaired patients, hepatically-impaired patients, paediatric patients and elderly patients (65 years and over).

INTERACTIONS WITH OTHER MEDICINES

Prostaglandins and their analogues

Prostaglandins and their analogues facilitate contraction of the myometrium hence may potentiate the uterotonic effect of oxytocin and vice versa. Very careful monitoring is, therefore, recommended in cases of concomitant administration.

Inhalation anaesthetics

Some inhalation anaesthetics, e.g. cyclopropane, enflurane, halothane, sevoflurane, desflurane or isoflurane, have a relaxing effect on the uterus and produce a notable inhibition of uterine tone and thereby may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

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 "PRECAUTIONS"). Oxytocin should be given with caution in patients taking drugs that are known to prolong the QTc interval.

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.

ADVERSE EFFECTS

Adverse reactions from clinical trials (Table 1) are ranked 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.

Table 1: Adverse drug reactions in the mother reported during clinical trials

Immune system disorders	
Rare:	anaphylactoid reaction associated with dyspnoea, hypotension or shock
Nervous system disorders	
Common:	headache*
Cardiac disorders	
Common	tachycardia, bradycardia
Uncommon:	arrhythmia
Gastrointestinal disorders	
Common:	nausea, vomiting
Skin and subcutaneous tissue disorders	
Rare:	Rash

* Headaches can be associated with fluid overload (see “PRECAUTIONS – Water intoxication”).

Post-marketing experience

The adverse drug reactions derived from post-marketing experience with Syntocinon 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, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions in the mother

Immune system disorders

anaphylactic reaction and shock
Cardiac disorders
myocardial ischaemia, QTc prolongation
Vascular disorders
Hypotension
Pregnancy, puerperium and perinatal disorders
uterine hypertonicity, tetanic contractions, rupture of the uterus
Metabolism and nutrition disorders
water intoxication, maternal hyponatraemia
Respiratory, thoracic and mediastinal disorders
acute pulmonary oedema
General disorders and administration site conditions
Flushing
Blood and lymphatic system disorders
disseminated intravascular coagulation
Skin and subcutaneous tissue disorders
Angioedema

Table 3: Adverse drug reactions in the foetus/neonate

Pregnancy, puerperium and perinatal disorders
foetal distress, asphyxia and death
Metabolism and nutrition disorders
neonatal hyponatraemia

Other adverse events that have been reported include ECG changes following intravenous administration of concentrated solutions, hypertension, neonatal jaundice, neonatal convulsions, oedema, cardiovascular spasm and collapse.

Water intoxication associated with maternal and neonatal hyponatraemia, which is potentially fatal, can result from high doses or prolonged periods of infusion of oxytocin in electrolyte-free fluids. The combined antidiuretic effect of oxytocin and the intravenous fluid administration may also cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia (see “PRECAUTIONS”).

When oxytocin is used by intravenous infusion for the induction or augmentation of labour, its administration at excessive doses results in uterine over stimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus.

Rapid intravenous bolus injection of oxytocin at doses as little as 2 IU may result in acute short-lasting hypotension accompanied by flushing and reflex tachycardia (see “PRECAUTIONS”). These rapid haemodynamic changes may result in myocardial ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid intravenous bolus injection of oxytocin at these doses may also lead to QTc prolongation.

Amniotic fluid embolism (in association with pre-disposing factors, e.g. tumultuous labour, foetal death-in-utero, meconium-stained amniotic fluid) has been reported.

Increases in post-partum bleeding have been observed rarely in conjunction with oxytocin. This effect probably relates more to abnormality of uterine action rather than to side effects of the drug.

There are rare reports of post-partum disseminated intravascular coagulation following the induction of labour using oxytocin (see “PRECAUTIONS”).

DOSAGE AND ADMINISTRATION

Dosage regimens

Induction or augmentation of labour:

Syntocinon should only be administered as an intravenous infusion, preferably by means of a variable speed infusion pump, or by drip infusion. It should not be administered by subcutaneous, intramuscular or intravenous bolus injection.

The initial infusion rate should be set at 1-4 milliunits/min. This rate may be gradually increased at intervals of not shorter than 20 min, 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/min. The recommended maximum rate is 20 milliunits/min. The increments in infusion rate should not be as high once contractions have been established, as those used to initiate contractions. Once an adequate level of uterine activity is attained, the infusion rate can often be reduced.

The frequency and duration of contractions and foetal heart rate must be carefully monitored during oxytocin administration, the latter preferably by electronic means, and the infusion must be discontinued immediately in the event of uterine hyperactivity, foetal distress or foetal heart abnormalities.

If regular contractions are not established after the infusion of 5 IU oxytocin, the attempt to induce labour should be terminated. It can generally be repeated on the following day, starting again from a rate of 1-4 milliunits/min.

In general, the dose of Syntocinon required for the augmentation of labour is less than that required for induction. Therefore, the initial infusion rate should be at the lower end of the recommended range.

Third stage of labour and puerperium (haemorrhage, subinvolution of the uterus):

5-10 IU by intramuscular injection or 5 IU by slow bolus intravenous injection. In patients given Syntocinon by drip to induce or stimulate labour, the infusion should be continued during the third stage.

Caesarean section:

5 IU by intravenous infusion or slow bolus intravenous injection after delivery of the foetus.

Instructions for use and handling

Infusion fluids:

Compatibility of Syntocinon has been demonstrated with 0.9 % saline and 5 % dextrose solutions. Syntocinon is not compatible with solutions containing bisulphites and metabisulphites as preservatives.

Due attention should be paid to the choice of infusion fluid in individual patients. Generally, Syntocinon should be administered in a combination of dextrose and an electrolyte solution (such as 4 % dextrose in N/5 saline), or in an isotonic electrolyte solution. The use of 5 % dextrose in water is not recommended.

Due to the absence of compatibility studies, Syntocinon must not be mixed with other medicinal products.

Preparation of infusion solution:

For drip infusion, the preparation of a solution containing 10 IU Syntocinon per 1 litre infusion fluid is recommended. To ensure even mixing of the drip solution, the bottle or bag must be turned upside down several times before use. Using this concentration, the recommended initial infusion rate of 1-4 mU/min corresponds to 0.1-0.4 mL/min, and the recommended maximum rate of 20 mU/min is reached at a rate of 2 mL/min.

When using a mechanical infusion pump which delivers smaller volumes than those given by drip infusion, a more concentrated oxytocin solution will be required. The concentration suitable for infusions within the recommended dosage range (1-20 mU/min) must be calculated according to the specification of the pump used.

OVERDOSAGE

Symptoms:

Overdosage may give rise to the following complications:

- foetal distress (foetal bradycardia, meconium staining of the amniotic fluid, foetal asphyxia)
- uterine hypertonicity, tetanic contraction or rupture
- placental abruption
- amniotic fluid embolism
- water intoxication (see “PRECAUTIONS”)

Treatment:

Contact the Poisons Information Centre on 131 126 for advice on management.

When signs or symptoms of overdosage occur during continuous intravenous administration of Syntocinon, 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 by judicious use of diazepam (see “PRECAUTIONS – Water intoxication”).

PRESENTATION & STORAGE CONDITIONS**Presentations:**

Ampoules 5 IU	5 x 1 mL
Ampoules 10 IU	5 x 1 mL

Not all strengths and pack sizes may be marketed.

Storage:

Store at 2° to 8°C. Refrigerate. Do not freeze.
Keep out of the reach and sight of children.

NAME & ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

21 August 1991

DATE OF MOST RECENT AMENDMENT

27 September 2018
