

DATA SHEET

SYNTOCINON® **Synthetic Oxytocin** **5 IU/mL and 10 IU/mL Concentrate for solution for infusion;** **Solution for injection**

Qualitative and quantitative composition

Active substance: synthetic oxytocin.

Concentrate for solution for infusion; Solution for injection (in 1 mL ampoule) containing 5 IU/mL.

Concentrate for solution for infusion; Solution for injection (in 1 mL ampoule) containing 10 IU/mL.

For a full list of excipients, see. List of excipients.

Pharmaceutical form

Concentrate for solution for infusion; Solution for injection. The ampoules have a single pink identification ring for 5 IU and double pink rings for 10 IU.

Clinical particulars

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).
- Enhancement of labour in selected cases of uterine inertia.
- Syntocinon® may also be indicated in early stage of pregnancy, as adjunctive therapy for management of incomplete, inevitable or missed abortion.

Postpartum

- During caesarean section, after the delivery of the child.
- Prevention and treatment of postpartum uterine atony and haemorrhage.

Dosage and method of administration

Induction or enhancement of labour

Syntocinon should be administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of Syntocinon 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 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 increased gradually at intervals not shorter than 20 minutes 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 of higher rates being 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 Syntocinon 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 labour should be terminated; it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute.

Note

Inadvertent paravenous infusion of oxytocin is not harmful.

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) or 5 to 10 IU i.m. after delivery of the placenta.

In women given Syntocinon 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.

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), 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.

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 or higher.

Contraindications

Known hypersensitivity to oxytocin or to any of the excipients of Syntocinon.

Hypertonic uterine contractions, foetal distress when delivery is not imminent.

Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contraindicated: e.g. significant cephalopelvic disproportion, foetal malpresentation; placenta praevia and vasa praevia, placental abruption, cord presentation or prolapse; overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy, polyhydramnios, grand multiparity and in the presence of a uterine scar resulting from major surgery including classical caesarean section.

Special warnings and precautions for use

The induction of labour 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.

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

Syntocinon should not be given as i.v. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

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.

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.

When Syntocinon is given for induction and enhancement of labour:

- It must only be administered as an i.v. infusion, and never by s.c., i.m. or i.v. bolus injection.
- 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.

- 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 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.

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.

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 hemodynamic 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.

Interaction with other medicinal products and other forms of interaction

Prostaglandins may potentiate the uterotonic effect of oxytocin and vice versa; therefore, concomitant administration requires very careful monitoring.

Some inhalation anaesthetics, e.g. cyclopropane or halothane, 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.

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

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

Pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

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.

Effects on ability to drive and use machines

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

Adverse effects

When oxytocin is used by i.v. infusion for the induction or enhancement of labour, 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.

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 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 hemodynamic form of acute pulmonary oedema without hyponatraemia (see Special warnings and precautions for use).

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 Special warnings and precautions for use). 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 labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see Special warnings and precautions for use).

With either mode of administration, oxytocin may cause the following adverse effects:

Adverse reactions (Table 1) 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.

Table 1

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

Overdose

The **symptoms and consequences of overdose** are those mentioned under Special warnings and precautions for use and Adverse effects. 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 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones (ATC code H01B B02)

The active substance of Syntocinon is a synthetic nonapeptide identical with oxytocin, a hormone released by the posterior lobe of the pituitary. It exerts a stimulatory effect on the uterine smooth muscle, 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 i.v. 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.

In addition to its effects on the uterus, oxytocin contracts the myoepithelial cells surrounding the mammary alveoli, thereby causing milk ejection and facilitating breast-feeding.

Being synthetic, Syntocinon does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid i.v. bolus injection, is a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia (see Special warnings and precautions for use).

Pharmacokinetic properties

Plasma levels and onset/duration of effect

Intravenous infusion. When Syntocinon 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.

Intravenous injection and intramuscular injection. When administered by i.v. or i.m. injection for prevention or treatment of postpartum haemorrhage, Syntocinon 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.

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 from 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 i.v. 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 per minute in men as well as in pregnant women. Less than 1% of a given dose is excreted unchanged in the urine.

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.

Effects (foetal loss in rats) in one pre-clinical study were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Acute toxicity

Single dose toxicity studies with oxytocin in rats and mice have been conducted by the oral, intravenous and subcutaneous application routes. Acute oral (and subcutaneous) toxicity was 20.5 mg/kg bodyweight in rats and exceeded 514 mg/kg bodyweight in mice. By the intravenous route, the lethal oxytocin dose amounted to 2.3 mg/kg bodyweight in rats and to 5.8 mg/kg bodyweight in mice. Thus, the intravenous lethal oxytocin dose in mice exceeds the usual intravenous dose in humans by a factor of greater than thousand.

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.

Carcinogenicity, teratogenicity and reproduction toxicity

Treatment of rats with oxytocin early in pregnancy in doses thousands of times greater than the dose used to induce labor in humans caused fetal loss in one study, but its relevance is

unknown. No standard teratogenicity, reproductive performance and carcinogenicity studies with oxytocin are available.

Pharmaceutical particulars

List of excipients

Sodium acetate trihydrate, acetic acid glacial, chlorobutanol, ethanol 94%, water for injections.

Incompatibilities

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

Shelf life

5 years

Special precautions for storage

For prolonged storage Syntocinon Concentrate for solution for infusion; Solution for injection: must be stored in a refrigerator (2-8°C). Do not freeze

Syntocinon may be stored at 30°C for 3 months. After this time Syntocinon must be discarded and not returned to the refrigerator

Syntocinon must be kept out of the reach and sight of children.

Information might differ in some countries.

Nature and contents of container

Each pack contains 5 x 1mL ampoules

Instructions for use and handling and disposal

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

Medicine classification

Prescription Medicine

Name and address

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Date of preparation

8 June 2009
(Ref: BPI 16 February 2009)