

## Syntocinon® concentrate for solution for infusion / solution for injection

### Syntocinon® nasal spray

#### Composition

Active substance: Oxytocin

#### Excipients:

Concentrate for solution for infusion / solution for injection:

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

Nasal spray: Propyl parahydroxybenzoate, methyl parahydroxybenzoate, chlorobutanol hemihydrate, disodium phosphate anhydrous, citric acid anhydrous, sodium chloride, sorbitol 70%, glycerol, water purified. Information might differ in some countries.

#### Pharmaceutical form and quantity of active substance per unit

Concentrate for solution for infusion / solution for injection:

1 ml contains 5 IU oxytocin.

Concentrate for solution for infusion / solution for injection:

1 ml contains 10 IU oxytocin.

Nasal spray: 1 ml contains 40 IU oxytocin.

#### Indications / Potential uses

Concentrate for solution for infusion / solution for injection (parenteral administration)

#### Antepartum:

Induction of labour for medical reasons (e.g. postmaturity, premature rupture of the membranes, pre-eclampsia). Augmentation of labour in selected cases of uterine inertia. Syntocinon may also be indicated in the early stages of pregnancy as an adjunctive therapy for the management of incomplete, inevitable or missed abortion.

#### Postpartum:

Caesarean section but not until after delivery of the child. Prevention and treatment of postpartum uterine atony and haemorrhage.

#### Nasal spray

Stimulation of milk ejection and prevention of mastitis.

#### Dosage / Administration

Concentrate for solution for infusion / solution for injection (parenteral administration)

Depending on the indication, Syntocinon may be administered by the intravenous (i.v. – as an infusion or short infusion) or intramuscular (i.m.) route.

1. *Continuous infusion for induction or augmentation of labour*  
Syntocinon is administered as an intravenous (i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump. For preparation of the continuous infusion, see *Instructions for use and handling*.

Close monitoring of the infusion rate is essential. The initial rate should be 1-2 mIU/minute (= 0.1-0.2 mIU/minute, or 2-4 drops/minute). It may be increased gradually – under close monitoring of fetal heart rate and the frequency and duration of contractions – at intervals of no less than 20 minutes and increments of no more than 1-2 mIU/minute until a contraction pattern similar to that of spontaneous labour is achieved. In women at or near term, this can often be achieved with an infusion of less than 10 mIU/minute (= 1 mIU/minute, or 20 drops/minute). The maximum recommended infusion rate is 20 mIU/minute (= 2 mIU/minute, or 40 drops/minute). In exceptional cases where higher infused doses are required, such as intrauterine fetal death or 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. 2x5 IU in 500 ml (= 20 mIU/ml).

When using a variable-speed infusion pump instead of drip infusion, the appropriate concentration of the solution for the recommended dosage range must be calculated according to the specifications of the pump.

The frequency, strength and duration of contractions and also the fetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, the infusion rate can be reduced. In the event of uterine hyperactivity and/or at the first sign of fetal distress, the infusion must be discontinued immediately.

If, in women who are at or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is advisable to discontinue the attempt to induce labour; the attempt may be repeated on the following day, again with an initial infusion rate of 1-2 mIU/minute.

Note: Inadvertent paravenous infusion of oxytocin is not harmful.

#### Incomplete, inevitable or missed abortion

5 IU as a 5-minute i.v. infusion, or 5-10 IU by the intramuscular route, followed if necessary by i.v. infusion at a rate of 20-40 mIU/minute.

2. *Short infusion for postpartum use* (for preparation of the short infusion, see *Instructions for use and handling*).

#### Caesarean section

5 IU as a 5-minute i.v. infusion immediately after delivery of the child.

#### Prevention of postpartum uterine haemorrhage

The usual dose is 5 IU as a 5-minute i.v. infusion after expulsion of the placenta. As an alternative, 5-10 IU may be administered by the intramuscular route. In women who have been given Syntocinon to induce or augment labour, the infusion should be

continued during the third stage of labour and for a few hours thereafter at an increased rate (20-40 mIU/minute).

#### Treatment of postpartum uterine haemorrhage

5 IU as a 5-minute i.v. infusion, or 5-10 IU i.m., followed in severe cases by i.v. infusion of 5-20 IU oxytocin in 500 ml of an electrolyte solution, at the rate necessary to control uterine atony.

#### Nasal spray

One actuation of the spray (0.1 ml nasal spray solution containing 4 IU oxytocin) in one nostril 5 minutes before the infant is put to the breast or milk is expressed.

#### Special dosage recommendations

**Paediatric patients:** Syntocinon has only been studied in women aged 18 and over. There is no indication in pre-pubertal children. No dosage recommendations can be given for use in pregnancies in adolescents aged <18 years owing to a lack of specific data.

**Elderly patients:** There is no indication in post-menopausal women.

**Renal impairment:** No studies have been performed in renally impaired patients. Owing to the renal excretion of oxytocin and its antidiuretic properties, accumulation is to be anticipated in patients with renal impairment. Syntocinon should thus be used with particular caution in patients with renal impairment.

**Hepatic impairment:** No studies have been performed in hepatically impaired patients. No dosage recommendations can therefore be made.

**Instructions for use:** See *Instructions for use and handling* under **'Other information'**.

#### Contraindications

Hypertonic uterine contractions; fetal distress (unless delivery is imminent).

Severe toxæmia; predisposing factors for amniotic fluid embolism (intrauterine fetal death, placental abruption).

All conditions in which, for fetal or maternal reasons, spontaneous labour must be avoided and/or vaginal delivery is contraindicated, e.g. significant cephalopelvic disproportion, fetal malpresentation; placenta praevia, vasa praevia, placental abruption, umbilical cord entanglement or prolapse; overdistension or reduced resistance of the uterus (risk of rupture) as in multiple pregnancy, hydramnios, multiparity involving more than four births, multiparity in older women, or in the presence of a uterine scar resulting from major surgery, including classic caesarean section.

Syntocinon must not be administered within 6 hours after vaginal prostaglandins have been given (see **'Interactions'**). Hypersensitivity to the active substance or to any of the excipients indicated under **'Composition'**.

Syntocinon should not be infused over prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclampsia or severe cardiovascular disorders.

Syntocinon nasal spray is contraindicated during pregnancy and labour.

#### Warnings and precautions

Oxytocin should only be administered under hospital conditions and with qualified medical supervision. Intravenous (i.v.) bolus injection should be avoided, as it may result in acute short-lasting hypotension accompanied by flushing and reflex tachycardia, as well as QT prolongation.

Rapid i.v. injection of Syntocinon at doses of several IU may increase the risk of arrhythmia and cardiac arrest. One study showed that rapid i.v. bolus injection of oxytocin at doses of several IU may lead to transient asymptomatic QT prolongation. It is not known whether the observed cases of QT prolongation are caused by oxytocin treatment or by concomitantly administered medicinal products. No data are available regarding a possible pathophysiological mechanism.

Syntocinon should be used with particular caution in patients with a history of cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease, coronary heart disease or coronary artery spasm) to avoid substantial changes in blood pressure and heart rate.

Syntocinon should be used with particular caution in patients with known long QT syndrome or other risk factors for QT prolongation, including comedication with medicinal products for which there is a known risk of QT prolongation (see **'Interactions'**).

When Syntocinon is given to induce or augment labour, the following must be borne in mind:

- Induction of labour with oxytocin should be attempted only when strictly indicated for medical reasons, and not for reasons of convenience.
- Syntocinon must only be administered as a continuous 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 fetal distress, asphyxia and intrauterine fetal death, or uterine hypertonicity, tetanic contractions and rupture of the uterus. Careful monitoring of fetal heart sounds and the frequency, strength and duration of contractions is essential so that the rate of infusion can be adjusted to the individual situation.
- Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild to moderate hypertension, cardiac disorders or previous lower uterine segment caesarean section, and in patients over 35 years of age.
- In rare circumstances, the pharmacological induction of labour using uterotonic agents (including oxytocin) increases the risk of postpartum disseminated intravascular coagulation (DIC). Pharmacological induction itself, and not a particular agent, is linked to this risk, which is particularly elevated if the pregnant woman has additional risk factors for DIC, e.g. age > 35 years, complications during the pregnancy, or gestational age > 40 weeks. In such women, oxytocin and other similar drugs must be used with caution, and the physician should be alert for any signs of DIC.
- In cases of intrauterine fetal death, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided due to the risk of amniotic fluid embolism.

Caution is required when coadministering sulprostone and/or methylethergometrine in the treatment of postpartum atonic uterine haemorrhage (see **'Interactions'**).

#### Water-electrolyte imbalances

Because oxytocin possesses slight antidiuretic activity, prolonged i.v. infusion at high doses in conjunction with excessive volumes of fluid (e.g. in the treatment of inevitable or missed abortion, or in the management of postpartum haemorrhage) may cause water intoxication associated with hyponatraemia (in both the mother and the neonate).

The combination of the antidiuretic effect of oxytocin and i.v. fluid administration may cause hypervolaemia and a haemodynamic form of acute pulmonary oedema without hyponatraemia.

To avoid these rare complications, the following precautions must be taken whenever high doses of oxytocin are given over prolonged periods:

An electrolyte infusion solution (not a glucose solution!) should be used; the volume of infused fluid should be kept as low as possible (by infusing oxytocin at a higher concentration); oral fluid intake should be restricted; the fluid balance should be monitored; and serum electrolytes should be measured if changes in electrolyte levels are suspected.

In patients with severe hepatic or renal impairment, there is an increased risk of water retention or accumulation of oxytocin. Particular caution is therefore required when treating such patients.

Syntocinon parenteral and nasal spray solutions must not be given concomitantly.

#### Interactions

Possible pharmacokinetic interactions with oxytocin have not been studied. The following pharmacodynamic interactions have been reported in connection with the infusion and injection of Syntocinon.

#### Prostaglandins and their analogues:

Prostaglandins and their analogues also facilitate contraction of the myometrium, and can therefore potentiate the uterine action of oxytocin and vice versa. Syntocinon may therefore only be used following an interval of at least 6 hours after prostaglandin administration (see **'Contraindications'**).

#### Drugs that prolong the QT interval:

Concomitant administration of oxytocin with drugs known to potentially prolong the QT interval increases the risk of QT prolongation (see **'Warnings and precautions'**).

#### Regional anaesthesia:

When given during or after caudal anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictors. There are insufficient data regarding possible interactions between Syntocinon and sympathomimetics in epidural or spinal anaesthesia.

#### Inhalation anaesthesia:

Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and may therefore diminish the uterotonic effect of oxytocin.

#### Vasoconstrictors / sympathomimetics:

Oxytocin may enhance the pressor effect of vasoconstrictors and sympathomimetics. This also applies to vasoconstrictors contained in drugs used for local anaesthesia.

Oxytocin may potentiate the effects of antihypertensive drugs. Patients undergoing concomitant treatment with such drugs must therefore be monitored particularly carefully.

In the treatment of postpartum atonic uterine haemorrhage, there have been reports of sometimes fatal ventricular tachycardia/fibrillation and myocardial infarction/cardiac arrest in connection with concomitant administration of sulprostone and/or oxytocin and/or methylethergometrine.

#### Pregnancy / Lactation

There is no indication for oxytocin in pregnancy, except for medically indicated induction or augmentation of labour, and use in spontaneous or indicated abortion. There is clear evidence of risks to the human fetus, including bradycardia, arrhythmia, CNS and/or brain damage and intrauterine fetal death.

There have been no reproductive studies of oxytocin in animals.

Syntocinon nasal spray is contraindicated during pregnancy. Small amounts of oxytocin are excreted in the breast milk; no adverse effects are expected in the infant.

#### Effects on ability to drive and use machines

No relevant studies have been carried out. Syntocinon can induce labour. As women with uterine contractions should not drive or use machines, appropriate caution should be exercised following use of Syntocinon. The ability to drive and to use machines may also be limited by possible adverse effects of oxytocin, such as changes in heart rate and blood pressure.

#### Adverse effects

The serious adverse effects of oxytocin are described in the 'Warnings and precautions' section (please refer to there).

In induction and augmentation of labour, i.v. infusion of excessive doses results in uterine overstimulation, which may cause fetal distress and, in extreme cases, fetal asphyxia and intrauterine fetal death, or uterine hypertonicity, tetanic contractions and rupture of the uterus.

Irrespective of the route of administration, the following adverse effects have been reported:

#### Frequencies:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known: spontaneous post-marketing reports and literature cases.

#### Blood and lymphatic system disorders

Not known: Disseminated intravascular coagulation.

#### Immune system disorders

Rare: Anaphylactoid reactions associated with dyspnoea, hypotension or shock. Administration must be discontinued immediately if such reactions occur.

#### Nasal spray: Allergic dermatitis.

#### Metabolism and nutrition disorders

Not known: Water intoxication, maternal hyponatraemia.

#### Nervous system disorders

Common: Headache.

#### Cardiac disorders

Common: Tachycardia, bradycardia.

Uncommon: Arrhythmia (see **'Warnings and precautions'** and **'Interactions'**).

Not known: Myocardial ischaemia, QTc prolongation.

#### Vascular disorders

Very rare: Hypertension.

Not known: Hypotension.

#### Respiratory disorders

Not known: Nasal discomfort, acute pulmonary oedema.

#### Gastrointestinal disorders

Common: Nausea, vomiting.

#### Skin and subcutaneous tissue disorders

Rare: Rash.

#### Reproductive system and breast disorders

Uncommon: Nasal spray: abnormal uterine contractions.

Not known: Uterine hypertonicity, tetanic contractions, rupture of the uterus.

#### General disorders

Not known: Flushing.

#### Adverse effects in the fetus / neonate

#### Metabolism and nutrition disorders

Not known: Neonatal hyponatraemia.

#### Cardiovascular disorders

Not known: Fetal distress, asphyxia (possibly with a fatal outcome).

#### Overdose

The symptoms and consequences of overdose correspond to the adverse effects described above. In addition, cases of placental abruption and/or amniotic fluid embolism have been reported.

**Management:** When signs or symptoms of overdose occur during i.v. infusion of Syntocinon, the infusion must be discontinued immediately. Treatment of overdose is symptomatic. It is recommended to give oxygen to the mother. In the event of water intoxication, it is important to restrict fluid intake, promote diuresis and correct any electrolyte imbalances. Patients should also be monitored for possible convulsions.

#### Properties / Actions

ATC code: H01BB02

#### Mechanism of action

The oxytocin contained in Syntocinon is a synthetic nonapeptide identical to the posterior pituitary hormone. Oxytocin is released primarily towards the end of pregnancy and postpartum, and its secretion is stimulated by suckling.

As the number of oxytocin receptors in the uterus increases during pregnancy, oxytocin stimulates the smooth muscle of the uterus particularly towards the end of pregnancy, during labour and immediately postpartum.

When given as a continuous i.v. infusion during parturition, oxytocin elicits rhythmic contractions in the upper segment of the uterus, similar in frequency, strength and duration to those observed during spontaneous labour.

Oxytocin has a rapid onset of action, with a latency period of less than 1 minute following i.v. injection and 2-4 minutes following i.m. administration.

The duration of effect is 30-60 minutes following i.m. injection; it may be shorter after i.v. administration.

When Syntocinon is given by i.v. infusion at doses appropriate for induction or augmentation of labour, the uterine response sets in gradually and normally reaches the steady state achievable at the given infusion rate within 20-40 minutes. The resulting plasma levels of oxytocin are comparable to those measured in the first stage of spontaneous labour.

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. It may continue at an adequate lower level.

Desensitization of oxytocin receptors has been observed with prolonged exposure *in vitro*.

In addition to its effect on the uterus, oxytocin facilitates the release of milk and aids breast-feeding by contracting the myoepithelial cells surrounding the mammary alveoli. It does not, however, possess any galactopoietic action.

Synthetic oxytocin does not contain vasopressin, but still possesses weak intrinsic vasopressin-like antidiuretic activity.

Oxytocin also induces transient relaxation of vascular smooth muscle. Particularly when high doses are injected rapidly by the intravenous route, this can cause hypotension, flushing and reflex tachycardia (see **'Warnings and precautions'**).

#### Pharmacokinetics

##### Absorption

Following intramuscular injection, oxytocin is rapidly absorbed from the muscle tissue. Plasma levels of oxytocin following intravenous infusion of 4 mIU/min in pregnant women at term were 2-5 mIU/ml.

Oxytocin (nasal spray) is rapidly and sufficiently well absorbed from nasal mucosa.

##### Distribution

The steady-state volume of distribution determined in 6 healthy men after i.v. injection was 12.2 litres (5.8-20.7 litres) or 0.17 litres/kg.

Plasma protein binding is negligible for oxytocin. Oxytocin crosses the placental barrier in both directions. It may be found in small quantities in the breast milk.

##### Metabolism

Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy and appears in the plasma. It is produced by both the mother and the fetus. Oxytocinase is the main enzyme responsible for metabolizing oxytocin, which mainly occurs in the liver and kidneys.

The metabolic clearance rate is approx. 20 ml/kg/minute in pregnant women.

##### Elimination

The plasma half-life of oxytocin ranges from 3-20 minutes. Oxytocin is excreted primarily in the form of metabolites in urine; less than 1% is excreted unchanged.

#### Pharmacokinetics in special patient populations

##### Renal impairment

The pharmacokinetics of oxytocin have not been studied in patients with renal impairment. However, it is known that oxytocin is excreted renally. Owing to the antidiuretic properties of oxytocin, accumulation of oxytocin may thus occur and its action may be potentiated or prolonged accordingly.

##### Hepatic impairment

The pharmacokinetics of oxytocin have not been studied in patients with hepatic impairment. However, as the enzyme responsible for metabolism is ubiquitous (including relevant activity in the placenta), no significant effect on oxytocin pharmacokinetics is expected in mild and moderate hepatic impairment. For severe hepatic impairment, see **'Warnings and precautions'**.

#### Preclinical data

Preclinical data for oxytocin reveal no special risk for humans based on conventional studies of single-dose acute toxicity, genotoxicity and mutagenicity.

#### Mutagenicity / carcinogenicity

An *in vitro* study was carried out to determine the genotoxicity and mutagenicity of oxytocin. Tests were negative for chromosomal aberration and sister chromatid exchange in human peripheral lymphocyte cultures. No significant changes in the mitotic index were noted. Oxytocin had no genotoxic properties.

The genotoxic potential of oxytocin has not been determined *in vivo*.

No carcinogenicity studies are available.

#### Reproductive toxicity

Treatment of rats with oxytocin in early pregnancy at doses in excess of the maximum recommended human dose caused embryonic loss in one study.

No standard teratogenicity or fertility studies with oxytocin are available.

#### Other information

##### Shelf life

Do not use after the expiry date (= EXP) printed on the pack. Nasal spray: After opening, the bottle must not be used for longer than 1 month. It is therefore recommended to write the date of opening on the label of the bottle.

##### Special precautions for storage

Keep out of the reach of children.

**Concentrate for solution for infusion / solution for injection:** Store in a refrigerator (2-8°C).

**Nasal spray:** Store in a refrigerator (2-8°C).

After opening, the bottle should be stored at room temperature (15-25°C).

##### Instructions for use and handling

**Nasal spray:** The patient should preferably use the nasal spray when seated.

The flip-off cap must be removed. Before the spray is used for the first time, the pump must be primed by depressing the actuator around three times until the spray solution is released. Holding the bottle upright, the nozzle must be inserted into one nostril, and the actuator depressed while inhaling gently through the nose.

#### Preparation of the continuous infusion

For continuous infusion, dilute 5 IU Syntocinon with 500 ml of a physiological electrolyte solution (such as 0.9% saline). This solution contains 10 mIU/ml. For patients in whom saline may not be used, 5% glucose solution may be used instead (see **'Warnings and precautions'**). To ensure even mixing of the solution for infusion, the bottle or bag must be inverted several times before use.

#### Preparation of the short infusion

For short infusion, dilute 5 IU Syntocinon with 50 ml (up to a maximum of 100 ml) of a physiological electrolyte solution (such as 0.9% saline). This solution contains 100 (or 50) mIU/ml. For patients in whom saline may not be used, 5% glucose solution may be used instead (see **'Warnings and precautions'**). To ensure even mixing of the solution for infusion, the bottle or bag must be inverted several times before use.

#### Pack sizes

Country specific pack sizes.

#### Manufacturer

See folding box.

#### Information last revised

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® = registered trademark

Novartis Pharma AG, Basle, Switzerland

#### This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children