# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Syntocinon Ampoules 5 IU/ml Concentrate for solution for infusion or Solution for intramuscular injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: synthetic oxytocin.

Each 1 ml ampoule contains 5 IU oxytocin as a concentrate for solution for infusion or solution for intramuscular injection.

Excipients with known effect: each 1 mL ampoule contains 0.2 mg sodium and 5 mg ethanol 94% w/w.

For a full list of excipients, see section 6.1 List of Excipients.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion or solution for intramuscular injection.
Clear colourless, sterile solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Induction of labor for medical reasons; stimulation of labour in hypotonic uterine inertia; during cesarean section, following the delivery of the child; prevention and treatment of postpartum uterine atony and hemorrhage.
Syntocinon may also be indicated in early stages of pregnancy as an adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

### 4.2 Posology and method of administration

Posology
*Induction or enhancement of labor:* Syntocinon should be administered as an intravenous (i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of Syntocinon be added to 500 ml of a physiologic 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 4.4, special warnings and special 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 1-4 milliunits/minute (2-8 drops/minute). It may be gradually increased 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 that higher rates are required, as may occur in the management of fetal death in utero or for induction of labor at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated Syntocinon solution, eg 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 as well as 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 be ceased; it may be repeated on the following day, starting again from a rate of 1-4 milliunits/minute.

*Incomplete, inevitable, or missed abortion:* 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) or 5 to 10 IU i.m., if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute

*Cesarean section:* 5 IU by intravenous 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 (5IU 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 to 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 hemorrhage:* 5 IU by iv infusion (5IU 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 i.v. infusion of a solution containing 5-20 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 population**
No studies have been performed in pediatric patients.
**Elderly population**
No studies have been performed in elderly patients (65 years old and over).

**4.3 Contraindications**

- Hypersensitivity to oxytocin or to any of the excipients listed in section 6.1.
- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress when delivery is not imminent. Any condition in which for fetal or maternal reasons spontaneous labor is unadvisable and/or vaginal delivery is contra-indicated: eg:

- fetal 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.

Syntocinon must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5, Interactions with other medicinal products and other forms of Interaction).

**4.4 Special warnings and precautions for use**

**Induction of labor**
The induction of labor by means of oxytocin should be attempted only when strictly indicated for medical reasons. 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 preeclamptic toxemia 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.

**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 (see section 4.5, Interactions with other medicinal products and other forms of Interaction).

When Syntocinon is given for induction and enhancement of labor:

- It must only be administered as an intravenous infusion and never by intravenous bolus injection.
- Fetal distress and foetal death:administration of oxytocin at excessive doses results in uterine overstimulation which may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring of fetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.
- Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension 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 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.

**Intrauterine death**
In the case of fetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labor must be avoided, as it may cause amniotic fluid embolism.

**Water intoxication**
Because oxytocin possesses slight antidiuretic activity, its prolonged intravenous administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion, or in the management of postpartum hemorrhage, may cause water intoxication associated with hyponatremia. The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary 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.

**Renal Impairment**
Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin. (see section 5.2, Pharmacokinetic properties).

**Anaphylaxis in women with latex allergy**
There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Due to the existing structural homology between oxytocin and latex, latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

**Excipients informations**
Syntocinon contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially "sodium- free".
This medicine contains 5 mg of alcohol (ethanol) in each dosage unit. The amount in dose of this medicine is equivalent to less than 0.12 ml beer or 0.05 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

**4.5 Interaction with other medicinal products and other forms of interactions**

**<u>Interaction resulting in a concomitant use not recommended.</u>**

**Prostaglandins and their analogues**
Prostaglandins and their analogues facilitate contraction of the myometrium. Hence oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see section 4.3, 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 4.4, Special warnings and precautions for use).

**Interactions to be considered**

**Inhalation anesthetics**
Inhalation anaesthetics (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 anaesthetics.

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

**4.6 Fertility, pregnancy and lactation**

The induction of labor by means of oxytocin should be attempted only when strictly indicated for medical reasons.
**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 the 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 Syntocinon because of the targeted indications.

**4.7 Effects on ability to drive and use machines**

Not relevant.

**4.8 Undesirable effects**

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses.

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 fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage 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 4.4, 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 DIC (see section 4.4, Special warnings and precautions for use).

**Water intoxication**
Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see section 4.4 Special warnings and special precautions for use).

Symptoms of water intoxication include: Headache, anorexia, nausea, vomiting, abdominal pain, lethargy, drowsiness, unconsciousness and grand-mal type seizures and low blood electrolyte concentration.
The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary edema without hyponatremia (see section 4.4. Special warnings and special precautions for use).

The following adverse drug reactions (ADRs) have been reported regardless of the mode of administration:
ADRs (Table 1 and 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), Not known (cannot be estimated from the available data) including isolated reports. The ADRs tabulated below are based on clinical trial results as well as postmarketing reports.
The ADRs 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 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 1Adverse drug reactions in mother**

| **System organ class** | **Adverse drug reaction** |
|---|---|
| **Blood and lymphatic system disorders** | |
| Not known | Disseminated intravascular coagulation |
| **Immune system disorders** | |
| Rare: | Anaphylactic/Anaphylactoid reaction associated with dyspnea and hypotension; Anaphylactic/Anaphylactoid or shock |
| **Metabolism and nutrition disorders** | |
| *Not known* | Water intoxication, Hyponatremia |
| **Nervous system disorders** | |
| Common: | Headache |
| **Cardiac disorders** | |
| Common:<br>Uncommon:<br>Not known: | Tachycardia, bradycardia<br>Arrhythmia<br>Myocardial ischemia, Electrocardiogram QTc prolongation |
| **Vascular disorders** | |
| Not known: | Hypotension |
| **Respiratory, thoracic and mediastinal disorders** | |
| Not known | Acute pulmonary oedema |
| **Gastrointestinal disorders** | |
| Common: | Nausea, vomiting |
| **Skin and subcutaneous tissue disorders** | |
| Rare:<br>Not Known | Rash<br>Angioedema |
| **Pregnancy, puerperium and perinatal conditions** | |
| Not known: | Uterine hypertonus, tetanic contractions of uterus,, uterine rupture. |
| | |
| | |
| **General disorders and administration site conditions** | |
| Not known: | Flushing |
| | |

**Table 2 Adverse drug reactions in fetus/neonate**

| **System organ class** | **Adverse drug reaction** |
|---|---|
| **Metabolism and nutrition disorders** | |
| Not known | Neonatal hyponatremia |
| **Pregnancy, puerperium and perinatal conditions** | |
| Not known: | Fetal distress syndrome, asphyxia and death |
| | |

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;
Fax: +353 1 6762517. Website: www.hpra.ie ; E-mail: medsafety@hpra.ie .

**4.9 Overdose**

The fatal dose of Syntocinon has not been established. Syntocinon is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under sections 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

*Treatment*
When signs or symptoms of overdosage occur during continuous i.v. administration of Syntocinon, the infusion must be discontinued at once and oxygen should be given to the mother.

In cases of water intoxication, it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur. In the case of coma, a free airway should be maintained with either routine measures normally employed in the nursing of the unconscious patient.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

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

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 Syntocinon 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.

**5.2 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 labor, the uterine response sets in gradually and reaches a steady state usually 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 on an adequate lower level.

**Intravenous injection and intramuscular injection.**
When administered by i.v. or i.m. injection for prevention or treatment of postpartum hemorrhage, 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 last for 30 to 60 minutes after i.m. administration, possibly less after i.v. injection.

**Absorption**

Oxytocin is rapidly absorbed from the i.m. site. Plasma levels of oxytocin following intravenous 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 i.v. 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. The liver and kidneys play a major role in metabolizing and clearing oxytocin from the plasma. Thus, liver, kidney and systemic circulation contribute to the biotransformation of oxytocin.

**Elimination**
Plasma half life of oxytocin ranges from 3 to 20 min. The metabolites are excreted in urine whereas less than 1% of the oxytocin is excreted unchanged in urine. The metabolic clearance rate amounts to 20 mL/kg/ min in the pregnant woman.

**Renal impairment**
No studies have been performed in renally impaired patients. However, considering the excretion of oxytocin and its reduced urinary excretion because of anti-diuretic properties, the possible accumulation of oxytocin can result in prolonged action.

**Hepatic impairment**
No studies have been performed in hepatically impaired patients. Pharmacokinetic alteration in patients with impaired hepatic function is unlikely since metabolizing enzyme, oxytocinase, is not confined to liver alone and the oxytocinase levels in placenta during the term has significantly increased. Therefore, biotransformation of oxytocin in impaired hepatic function may not result in substantial changes in metabolic clearance of oxytocin .

**5.3 Preclinical safety data**

**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.

**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.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium Acetate trihydrate
Glacial acetic acid
Chlorobutanol hemihydrate
Sodium chloride
Ethanol 94% w/w
Water for injection.

**6.2 Incompatibilities**

SYNTOCINON should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. SYNTOCINON is incompatible with solutions containing sodium metabisulphite as a stabiliser.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

**6.3 Shelf life**

3 years.

In-use shelf-life when kept in the outer carton and not stored above 30 °C: 3 months.

**6.4 Special precautions for storage**

Store in a refrigerator (2-8°C).

In use storage conditions: Do not store above 30°C. Keep the ampoules in the outer carton in order to protect from light.

**6.5 Nature and contents of container**

Cardboard boxes of 5 and 10 glass ampoules, type 1, Ph. Eur.

The ampoules are made of colourless glass.

**6.6 Special precautions for disposal and other handling**

Syntocinon is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: Sodium/potassium chloride (103 mmol Na+ and 51 mmol K+), Sodium bicarbonate 1.39%, Sodium chloride 0.9%, Sodium lactate 1.72%, Dextrose 5%, Laevulose 20%, Macrodex 6%, Rheomacrodex 10%, Ringer's solution.

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

**7 MARKETING AUTHORISATION HOLDER**

Alfasigma S.p.A
Via Ragazzi del '99, n. 5
40133 Bologna (BO)
Italy

**8 MARKETING AUTHORISATION NUMBER**

PA2206/003/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 1st April 1979

Date of last renewal: 1st April 2009

**10 DATE OF REVISION OF THE TEXT**

July 2020