



SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT

SYNPITAN FORTE 5 I.U./ml solution for I.M./I.V. injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule (1 mL):

Active ingredient:

Oxytocin (synthetic).....5 IU

Excipients:

Sodium chloride.....9 mg

See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Ampoule containing solution for injection/infusion
Colorless, clear solution with a characteristic odor

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prenatal

- For the medical induction of labor, e.g., in cases of post-term pregnancy, premature rupture of membranes, pregnancy-induced hypertension (preeclampsia)
- Induction of labor in cases of hypotonic uterine inertia
- Treatment of incomplete, threatened, or delayed miscarriage in the early stages of pregnancy As an adjunctive treatment for postpartum hemorrhage.

Postpartum

- During cesarean section, but following the delivery of the infant.
- For the prevention and treatment of postpartum uterine atony and bleeding.

4.2 Dosage and administration

Dosage/frequency and duration of administration:

For induction or stimulation of labor:

Oxytocin should not be initiated for 6 hours following the administration of vaginal prostaglandins. SYNPITAN FORTE should be administered as an intravenous (I.V.) drip infusion or, preferably, via a variable-rate infusion pump. For drip infusion, it is recommended to add 5 IU of SYNPITAN FORTE to 500 mL of physiological electrolyte solution (such as 0.9% sodium chloride). For patients in whom sodium chloride infusion should be avoided, a 5% dextrose solution may be used as a diluent (see Section 4.4). To ensure thorough mixing, the bottle or bag should be shaken several times before use.

The initial infusion rate should be set at 1 to 4 milliunits per minute (2 to 8 drops per minute). It may be gradually increased in intervals of no less than 20 minutes and by no more than 1–2 milliunits per minute until a contraction pattern similar to normal labor contractions is achieved. In late pregnancy, this is usually achievable with an infusion rate of less than 10 milliunits per minute (20 drops per



minute), and the recommended maximum rate is 20 milliunits per minute (40 drops per minute).

When using a motor-driven infusion pump that delivers smaller volumes than those provided by a drip infusion, the appropriate concentration for infusion within the recommended dosage range must be calculated based on the pump's specifications.

The frequency, strength, and duration of contractions, as well as the fetal heart rate, must be closely monitored throughout the infusion. Once an adequate level of uterine activity is achieved—with the goal of 3 to 4 contractions every 10 minutes—the infusion rate can generally be reduced. In cases of uterine hyperactivity and/or fetal distress, the infusion must be stopped immediately.

In women at or near term, if regular contractions do not occur after a total infusion of 5 IU, it is recommended to discontinue the attempt to induce labor; the procedure may be repeated the following day starting at a rate of 1 to 4 milliunits per minute (see Section 4.3).

Cesarean section:

5 IU is administered as an IV infusion (diluted in a physiological electrolyte solution and administered as an IV drip infusion or, preferably, via a variable-rate infusion pump over a period of more than 5 minutes) immediately after delivery.

Prevention of postpartum uterine hemorrhage:

The standard dose is 5 IU via I.V. infusion (5 IU diluted in physiological electrolyte solution and administered as an I.V. drip infusion or, preferably, via a variable-rate infusion pump over 5 minutes) or 5–10 IU intramuscularly (I.M.) following placental delivery. In women receiving SYNPITAN FORTE to induce or accelerate labor, the infusion should be continued at an increasing rate during the third stage of labor and for several hours thereafter.

Treatment of postpartum uterine hemorrhage:

5 IU by IV infusion (diluted in a physiological electrolyte solution and administered as an IV drip infusion or, preferably, via a variable-rate infusion pump over 5 minutes) or 5–10 IU IM, 5–10 IU, followed by, in severe cases, an infusion of a solution containing 5 to 20 IU of oxytocin in 500 mL of electrolyte diluent administered intravenously, in the amount necessary to control uterine atony.

Treatment of incomplete, threatened, or delayed miscarriage:

Due to low receptor expression, the use of oxytocin is recommended starting from the 14th week of pregnancy.

Administered as an IV infusion of 5 IU (diluted in a physiological electrolyte solution and administered via IV drip infusion or, preferably, via a variable-rate infusion pump over 5 minutes); following this administration, the IV infusion rate may be increased to 20 to 40 units per minute as needed. If painful uterine contractions occur, the infusion rate should be reduced or the infusion temporarily stopped.

Administration:

SYNPITAN FORTE is administered via intramuscular injection and intravenous infusion.

Additional information for specific populations:

Renal impairment:

No studies have been conducted in patients with renal insufficiency.



Hepatic impairment:

No studies have been conducted in patients with hepatic insufficiency.

Pediatric population:

No studies have been conducted in pediatric patients.

Geriatric population:

No studies have been conducted in elderly patients (65 years of age and older).

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in Section 6.1
- Mechanical obstruction during childbirth
- Fetal distress
- Hypertonic uterine contractions

In cases where spontaneous delivery is not recommended and/or vaginal delivery is contraindicated due to fetal or maternal causes:

- Marked cephalopelvic disproportion
- Fetal malpresentation
- Placenta previa and vasa previa
- Placental abruption
- Cord presentation or prolapse
- Impaired uterine resistance to rupture or distension, as seen in multiple pregnancies
- Polyhydramnios
- Grand multiparity
- In the presence of a uterine scar resulting from major surgical procedures, including classical cesarean section

SYNPITAN FORTE should not be used for prolonged periods in cases of oxytocin-resistant uterine inertia, severe pre-eclampsia, and severe cardiovascular disorders.

SYNPITAN FORTE should not be administered within 6 hours of the administration of vaginal prostaglandins (see Section 4.5).

4.4 Special warnings and precautions for use

Caution is advised in patients with a history of cesarean section or other surgical uterine interventions.

Induction of labor with oxytocin should be performed only when medically absolutely indicated. Administration should take place only in a hospital setting and under qualified medical supervision.

When administered to initiate or augment labor, oxytocin should be administered only as an intravenous drip infusion.

Since it may cause acute, short-term hypotension accompanied by flushing and reflex tachycardia, IV bolus injection should not be administered.



Cardiovascular Diseases

SYNPITAN FORTE should be used with caution in patients prone to myocardial ischemia due to pre-existing cardiovascular disease (such as ischemic heart disease including hypertrophic cardiomyopathy, valvular heart disease, and/or coronary artery vasospasm) to avoid significant changes in blood pressure and heart rate.

QT syndrome

SYNPITAN FORTE should be used with caution in patients with known ‘long QT syndrome’ or associated symptoms, and in patients taking medications known to prolong the QT interval.

When SYNPITAN FORTE is administered to induce or facilitate labor:

- Administration of oxytocin in excessive doses can be dangerous for both the mother and the fetus, leading to fetal distress (fetal bradycardia, meconium-stained amniotic fluid, fetal asphyxia, and death) and uterine hyperstimulation, which may result in hypertonicity, tetanic contractions, or uterine rupture. Careful monitoring of fetal heart rate (ideally via cardiotocography (CTG)) and uterine activity is essential, allowing the dose to be adjusted based on the individual response. In patients with cardiovascular disease, oxytocin should be infused at a higher concentration while keeping the volume of infused fluid low.
- Particular caution is warranted in cases of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate pregnancy-induced hypertension, or heart disease, as well as in patients over 35 years of age or those with a history of lower uterine segment cesarean section.
- In rare cases, pharmacological labor induction using uterotonic agents increases the risk of postpartum disseminated intravascular coagulation (DIC). This risk is associated not with a specific drug but with the pharmacological induction itself. This risk increases, particularly when the woman is 35 years of age or older, has experienced complications during pregnancy (such as gestational diabetes, hypertension, or hypothyroidism), or has a gestational age exceeding 40 weeks—all of which are additional risk factors for DIC. In these women, oxytocin or any other alternative medication should be used with caution, and physicians should be vigilant for signs of DIC. Women with the risk factors mentioned above should be screened for fibrinolysis immediately after delivery.
- If the cervix is not dilated or is hard (risk of cervical rupture or fetal hypoxia), oxytocin should not be used to accelerate labor during the first and second stages of labor.

Water intoxication

Since oxytocin has mild antidiuretic activity, high-dose I.V. administration combined with prolonged high-volume fluid administration—such as in unavoidable or missed abortion treatment or postpartum hemorrhage management—can lead to water intoxication due to hyponatremia. The combined antidiuretic effect of oxytocin and IV fluid administration may lead to excessive fluid overload, resulting in the hemodynamic form of acute pulmonary edema without hyponatremia. To avoid these rare complications, the following precautions must be followed when administering high doses of oxytocin over an extended period:

- An electrolyte-containing diluent should be used (excluding dextrose)
- The volume of the infused fluid should be kept low (with oxytocin administered at a higher concentration than recommended for labor induction or stimulation)
- Oral intake should be restricted



- A fluid balance chart should be maintained, and serum electrolytes should be measured if electrolyte imbalance is suspected.

Parenteral oxytocin should not be administered simultaneously with an oxytocin-containing nasal spray.

Intrauterine death:

In cases of fetal death in utero and/or the presence of meconium-stained amniotic fluid, difficult labor should be avoided as it may lead to amniotic fluid embolism.

Renal impairment

Caution is advised in patients with severe renal impairment due to potential fluid retention and potential oxytocin accumulation (see Section 5.2).

Anaphylaxis in women with latex allergy

Anaphylaxis has been reported following oxytocin administration in women with a known latex allergy. Due to the structural homology between oxytocin and latex, a latex allergy/intolerance may be a significant predisposing risk factor for anaphylaxis following oxytocin administration.

This medicinal product contains less than 1 mmol (23 mg) of sodium per ampoule; therefore, it is essentially “sodium-free.”

4.5 Interactions with other medicinal products and other forms of interaction

Contraindicated other medical products

Prostaglandins and analogs

Prostaglandins and their analogs increase uterine contractions; therefore, oxytocin may potentiate the uterine effects of prostaglandins and their analogs, and vice versa. Therefore, their concurrent use is not recommended (see Section 4.3).

Medicinal products not recommended for concurrent use

Drugs that prolong the QT interval

Oxytocin should be considered potentially arrhythmogenic in patients with other risk factors for Torsades de Pointes, such as those taking drugs that prolong the QT interval or patients with a history of long QT syndrome (see Section 4.4).

Interactions to be considered

Inhalation anesthetics

Inhalation anesthetics (e.g., cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and produce a marked inhibition of uterine tone, thereby potentially reducing the uterotonic effect of oxytocin. Concomitant use with oxytocin has also been reported to cause cardiac arrhythmias.

Vasoconstrictors/Sympathomimetics

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, including those found in local anesthetics.

Caudal anesthetics

When administered during or after caudal block anesthesia, oxytocin may enhance the vasoconstrictive effects of sympathomimetic agents.



Additional information on special populations

No data available.

Pediatric population:

Not applicable.

4.6 Fertility, pregnancy and lactation

General recommendation:

Pregnancy category: C

Women of childbearing potential/Contraception:

Not applicable for SYNPITAN FORTE due to the intended indications.

Pregnancy:

Animal reproduction studies have not been conducted with oxytocin. Based on extensive experience with this drug and its chemical structure and pharmacological properties, it is not expected to pose a risk of fetal abnormalities when used as directed. Oxytocin is contraindicated during pregnancy except for strictly medical reasons, such as the initiation or augmentation of labor or spontaneous or induced abortion.

Lactation:

Oxytocin may pass into breast milk in small amounts. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the gastrointestinal tract and is rapidly inactivated.

Fertility

Not applicable to SYNPITAN FORTE due to its intended indications.

4.7 Effects on the ability to drive and use machinery

No studies have been conducted on the effects on the ability to drive and use machinery. Women experiencing uterine contractions should not operate machinery or vehicles.

4.8 Undesirable effects

Since uterine sensitivity varies widely, uterine spasms may occur even at doses normally considered low. Excessive doses may cause excessive uterine stimulation, leading to fetal distress, asphyxia, and death, or result in uterine overstimulation that can cause hypertonicity, tetanic contractions, soft tissue damage, or uterine rupture.

Following a rapid IV bolus injection, it may cause acute, short-term hypotension accompanied by facial flushing and reflex tachycardia. (See Section 4.4) These rapid hemodynamic changes may cause myocardial ischemia, particularly in patients with pre-existing cardiovascular disease. Rapid IV bolus injection of oxytocin in doses up to several IU may also cause QT prolongation.

Pharmacological induction of labor using uterotonic agents rarely increases the risk of postpartum disseminated intravascular coagulation (see Section 4.4).

Water intoxication

Cases of water intoxication associated with maternal and neonatal hyponatremia have been reported when high doses of oxytocin were administered over a prolonged period along with large volumes of



electrolyte-free fluids (see Section 4.4). The combined antidiuretic effect of oxytocin and the administration of intravenous (I.V.) fluids may lead to excessive fluid overload, resulting in a hemodynamic form of acute pulmonary edema without hyponatremia (see Section 4.4).

Symptoms of water intoxication include:

1. Headache, loss of appetite, nausea, vomiting, and abdominal pain.
2. Drowsiness, lethargy, loss of consciousness, and grand mal seizures
3. Low blood electrolyte concentrations

Adverse reactions are presented according to the MedDRA system organ classes and the MedDRA frequency convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); unknown (cannot be estimated from available data).

Adverse reactions reported in the mother

Blood and lymphatic system disorders:

Unknown: Disseminated intravascular coagulation

Immune system disorders:

Rare: Anaphylactoid reaction associated with dyspnea, hypotension, or shock

Metabolic and nutritional disorders:

Unknown: Water intoxication, maternal hyponatremia

Nervous system disorders:

Common: Headache

Cardiac disorders:

Common: Tachycardia, bradycardia

Uncommon: Arrhythmia

Unknown: Myocardial ischemia, QTc prolongation on electrocardiogram, reflex tachycardia

Vascular diseases:

Unknown: Hypotension, bleeding

Respiratory, chest, and mediastinal disorders:

Unknown: Acute pulmonary edema

Gastrointestinal disorders:

Common: Nausea, vomiting

Skin and subcutaneous tissue disorders:

Rare: Itching, hives

Unknown: Angioedema

Pregnancy, postpartum conditions, and perinatal disorders:

Unknown: Uterine hypertonus, tetanic uterine contractions, uterine rupture

General disorders and conditions related to the application site:



Unknown: Redness

Adverse reactions reported in fetuses/newborns

Metabolic and nutritional disorders:

Unknown: Neonatal hyponatremia

Pregnancy, puerperium, and perinatal conditions:

Unknown: Fetal distress syndrome, asphyxia, and death

Reporting of suspected adverse drug reactions

Reporting suspected adverse reactions after authorization 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 the national reporting system.

4.9 Overdose

Overdose may cause the following complications: fetal distress (fetal bradycardia, meconium-stained amniotic fluid, asphyxia), hypertonicity, tetanic contractions, uterine rupture, water intoxication.

Toxicity: No symptoms were observed when 2–3 and 10 IU were administered intramuscularly to newborns, respectively, and when 8 IU were administered nasally to children aged ½–1½ years. Serious toxicity has been observed in adults following an infusion of 80 IU in an isotonic glucose solution over 35 hours, 488 IU over 40 hours, and 800 IU over 60 hours (1 IU corresponds to 1.67 micrograms).

Symptoms: Antidiuretic effect—risk of water intoxication (hyponatremia, hypoosmolality, cerebral edema). Vascular spasm, hypertension.

Treatment: If signs or symptoms of overdose occur during continuous intravenous administration of oxytocin, the infusion must be stopped immediately and the mother given oxygen. Observation is required in cases of fluid retention. In cases of water intoxication, diuretics (mannitol or furosemide), sodium infusion, and treatment for cerebral edema should be administered. Other symptomatic treatments may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Systemic hormonal preparations (excluding sex hormones and insulins), pituitary and hypothalamic hormones and analogs, posterior pituitary hormones, oxytocin and analogs

ATC code: H01BB02

Oxytocin stimulates uterine contractions (frequency and strength) during labor, accelerates uterine involution, and aggregates myoepithelial cells in the mammary gland, thereby facilitating the ejection process. Since synthetic oxytocin does not contain vasopressin, it does not raise blood pressure at recommended doses and is therefore suitable for use in preeclampsia.

Oxytocin stimulates the smooth muscles of the uterus more strongly toward the end of pregnancy, during labor, and immediately after delivery. During these periods, the number of oxytocin receptors in the myometrium increases.



Oxytocin receptors are G-protein-coupled receptors. Activation of the receptor by oxytocin triggers the release of calcium from intracellular stores, thereby leading to myometrial contraction.

Oxytocin induces rhythmic contractions in the upper segment of the uterus with a frequency, intensity, and duration similar to those observed during labor.

Synthetic oxytocin does not contain vasopressin; however, even in its pure form, oxytocin possesses weak intrinsic vasopressin-like antidiuretic activity.

Based on *in vitro* studies, it has been reported that prolonged exposure to oxytocin causes desensitization of oxytocin receptors, likely due to downregulation of oxytocin binding sites, destabilization of oxytocin receptor mRNA, and internalization of oxytocin receptors.

Plasma levels and onset/duration of action

Intravenous infusion. When oxytocin is administered via continuous intravenous infusion at appropriate doses to induce or augment labor, the uterine response begins gradually and typically reaches a steady state within 20 to 40 minutes. The corresponding oxytocin plasma levels are similar to those measured during spontaneous first-stage labor. For example, in 10 pregnant women receiving an intravenous infusion of 4 microunits per minute, oxytocin plasma levels ranged from 2 to 5 microunits/mL. Following discontinuation of the infusion or a significant reduction in infusion rate, such as in cases of overstimulation, uterine activity decreases rapidly but may continue at a sufficiently low level.

5.2 Pharmacokinetic properties

General characteristics

Absorption:

In pregnant women, plasma levels of oxytocin have been observed to range from 2 to 5 microunits/mL following an intravenous infusion of 4 milliunits/minute.

When administered via intravenous infusion, the effect occurs gradually and typically reaches a steady state after 20–40 minutes.

Oxytocin acts rapidly following intravenous or intramuscular (I.M.) injection; approximately 1 minute after I.V. injection and 2–4 minutes after I.M. injection.

The effect lasts for 30–60 minutes after an I.M. injection and likely for a slightly shorter duration after an I.V. injection.

Distribution:

The volume of distribution at steady state is approximately 12.2 L or 170 mL/kg in men. Plasma protein binding is low. It crosses the placenta in both directions. Oxytocin may be present in small amounts in breast milk.

Biotransformation:

Oxytocinase is a glycoprotein aminopeptidase produced during pregnancy. The enzyme is present in plasma and can break down oxytocin. Enzymatic activity increases gradually until labor begins, then rises rapidly and decreases again after delivery. Enzyme activity is also high in placental and uterine tissues during this period. The liver and kidneys play a significant role in the metabolism and clearance of oxytocin from plasma. Therefore, the liver, kidneys, and systemic circulation contribute to the biotransformation of oxytocin.



Elimination:

The plasma half-life of oxytocin ranges from 3 to 20 minutes. While metabolites are excreted in the urine, less than 1% of oxytocin is excreted unchanged in the urine. In pregnant women, the metabolic clearance is ~17 mL/kg/min. Metabolic clearance is approximately 20 mL/kg/min in both men and non-pregnant women.

Linearity/Non-linearity:

No data available.

Characteristic features in patients

Renal impairment:

No studies have been conducted in patients with renal impairment. However, given the reduced urine output due to oxytocin excretion and its antidiuretic properties, prolonged administration may lead to potential accumulation of oxytocin.

Hepatic impairment:

No studies have been conducted in patients with hepatic impairment. Pharmacokinetic changes are unlikely in patients with hepatic dysfunction, as oxytocinase—the enzyme responsible for the metabolism of oxytocin—is not limited to the liver, and oxytocinase levels in the placenta are significantly elevated during this period. Therefore, the biotransformation of oxytocin in patients with hepatic dysfunction may not result in significant changes in the metabolic clearance of oxytocin.

5.3 Preclinical safety data

Non-clinical data, based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, and mutagenicity, do not indicate any special hazard to humans. Standard teratogenicity, reproductive performance, and carcinogenicity studies with oxytocin are not available.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Chlorobutanol
Sodium chloride
Acetic acid
Distilled water

6.2 Incompatibilities

Except in certain very specific cases, oxytocin preparations should only be infused in physiological electrolyte (infusion) solutions.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store the product at 2°C to 8°C.

Do not use this product and/or its packaging if it shows any signs of damage.

6.5 Nature and contents of container

A 1 mL amber-colored, labeled, ring-shaped ampoule made of Type I glass.
Available in packages containing 3, 6, and 50 1 mL ampoules.

6.6 Special precautions for disposal and other handling

All patients receiving an IV oxytocin infusion must be under the supervision of healthcare personnel who are fully informed about this medication and capable of recognizing complications. Oxytocin should not be administered if a physician capable of intervening in the event of any complications is not present.

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

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

78/71

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 13.12.1965

Date of last renewal: 05.02.2013

DATE OF REVISION OF THE TEXT