Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

SANTOCYN® Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10 units of oxytocin.
This medicine contains small amounts of ethanol (alcohol), less than 100 mg per dose (4.81 mg). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.
A clear, colorless, sterile solution in 1 ml clear glass ampoules.

4. CLINICAL PARTICULARS

4.1 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).
- Stimulation of labour in hypotonic uterine inertia.
- Early stages of pregnancy as adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

Postpartum

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

Consideration should be given to official guidelines, e.g. those from WHO, listed in the Reference section at the end of this SmPC.

4.2 Posology and method of administration

SANTOCYN® should be administered as an intravenous infusion or preferably, by means of a variable-speed infusion pump. It can also be given by intramuscular injection (but intravenous use can produce more rapid onset of action and allow better control of dosing).
Attention should be paid to the oxytocin cold chain (i.e. the requirements of a temperature-controlled supply chain, see Section 6.4).

Induction or enhancement of labour

If vaginal prostaglandins have been used, oxytocin should be started at least 6 hours after use of vaginal prostaglandins. Oxytocin should be administered as an intravenous drip infusion or preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 units of oxytocin 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% glucose solution may be used as the infusion fluid (see section 4.4 Special warnings and precautions for use).
To ensure even mixing, the infusion 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).
The infusion rate may be gradually increased at intervals of at least 20 minutes and increments of not more than 1-2 milliunits/minute, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion rate 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 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 oxytocin solution, e.g. 10 units in 500 ml.
When using a motor-driven infusion pump which delivers smaller volumes than with drip infusion, the concentration suitable for infusion must be calculated according to the specifications of the pump.
With either method of infusion, the frequency, strength, and duration of contractions as well as the fetal heart rate must be carefully monitored throughout the infusion. Once the level of uterine activity adequate, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity or fetal distress, the infusion must be discontinued immediately.
If, in women who are at term or near term, regular contractions are not established after a total dose of 5 units, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again at an infusion rate of 1 to 4 milliunits/minute.

Incomplete, inevitable, or missed abortion
The usual dose is 5 units by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or preferably, by means of a variable-speed infusion pump) over 5 minutes, if necessary followed by intravenous infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section
The usual dose is 5 units by intravenous infusion (diluted in physiological electrolyte solution and administered as a 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 10 units by intramuscular or intravenous injection. Alternatively, 5 units can be given by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or preferably, by means of a variable-speed infusion pump) over 5 minutes after delivery of the placenta. In women given oxytocin 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.

Treatment of postpartum uterine haemorrhage
The usual dose is 10 units by intramuscular or intravenous injection. Alternatively, 5 units can be given by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes), followed in severe cases by infusion of a solution containing 5 to 20 units of oxytocin in 500 ml of an electrolyte-containing diluent, run at a rate necessary to control uterine atony.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress.

Any condition in which, for fetal or maternal reasons, spontaneous labour is inadvisable or vaginal delivery is contra-indicated: e.g:

- Significant cephalopelvic disproportion
- Fetal malpresentation

- Placenta praevia and vasa praevia
- Placental abruption
- Cord presentation or prolapse
- Over-distension or impaired resistance of the uterus to rupture as in multiple pregnancy.
- Polyhydramnios
- Grand multiparity
- Presence of a uterine scar from major surgery including classical caesarean section.

Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.
Oxytocin must be administered at least 6 hours after vaginal prostaglandins have been given (see section 4.5).

4.4 Special warnings and precautions for use

Attention should be paid to the oxytocin cold chain (i.e. the requirements of a temperature-controlled supply chain, see section 6.4).
Oxytocin via intravenous infusion is preferred, as intravenous bolus injection may cause short-lasting hypotension accompanied by flushing and reflex tachycardia.

Induction of labour
The induction of labour by oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.
Oxytocin should not be infused via the same apparatus as blood or plasma, because it is rapidly inactivated by oxytocin-inactivating enzymes.

Cardiovascular disorders
Oxytocin should be used with caution in patients who have a predisposition to myocardial ischaemia due to cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease and ischaemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT Syndrome
Oxytocin should be given with caution to patients with 'long QT syndrome' or related symptoms and to patients taking drugs that prolong the QTc interval (see section 4.5).

Use for induction and enhancement of labour
Fetal distress and fetal death: Excessive doses of oxytocin can result 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 pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.
Disseminated intravascular coagulation: Rarely, the pharmacological induction of labour using uterotonic agents, including oxytocin increases the risk of postpartum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is particularly increased if the woman has additional risk factors for DIC such as being over 35 years of age, complications during pregnancy and

gestational age more than 40 weeks. In these women, oxytocin or another alternative drug should be used with care, and the practitioner should be alert for signs of DIC, such as bleeding from multiple sites, internal bleeding, purpura of extremities, severe malaise and fever.

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

Water intoxication
Because oxytocin has mild antidiuretic activity, water intoxication associated with hyponatremia may result from prolonged intravenous infusion at high doses with large volumes of fluid (e.g. in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage).
The combined antidiuretic effect of oxytocin and the intravenous fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatremia.
Features of water intoxication include:
- Headache, anorexia, nausea, vomiting and abdominal pain.
- Lethargy, drowsiness, unconsciousness and grand –mal type seizures.

To avoid this rare complication, 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 glucose);
- 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 and 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).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended
Prostaglandins and their analogues
Prostaglandins and its analogues facilitate contraction of the myometrium. They should not be used concomitantly with oxytocin because oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see section 4.3 Contraindications).

Drugs prolonging the QT interval
Oxytocin is potentially arrhtyhmogenic and concomitant drugs which prolong the QT interval should be used with caution (see section 4.4).

Other interactions
Inhalation anaesthetics
Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) relax the uterus and inhibit uterine tone and thereby, may diminish the uterotonic effect of oxytocin. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors and sympathomimetics
Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those in local anaesthetics.

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

4.6 Fertility, pregnancy and lactation
Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its pharmacological properties, it is not expected to cause fetal abnormalities when used as indicated.
Oxytocin may be present in small quantities in breast milk. However, it is not expected to cause harmful effects in the newborn because it is rapidly inactivated in the alimentary.
The effects of oxytocin on fertility are not known.

4.7 Effects on ability to drive and use machines
Oxytocin can induce labour. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects
As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by low doses. When oxytocin is used for the induction or enhancement of labour, excessive doses can result 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.
Undesirable effects (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000), including isolated reports; not known (cannot be estimated from the available data). The adverse reactions tabulated below are based on clinical trial results as well as post-marketing reports.
The adverse drug reactions derived from post-marketing experience with oxytocin 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. Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in mother

System Organ Class	Adverse reaction
Immune system disorders	Rare: anaphylactic or anaphylactoid reaction associated with dyspnoea, hypotension or shock
Nervous system disorders	Common: headache
Cardiac disorders	Common: tachycardia, bradycardia Uncommon: arrhythmia Not known: myocardial ischaemia, QTc prolongation
Vascular disorders	Not known: hypotension, haemorrhage, angioedema

Gastrointestinal disorders	Common: nausea, vomiting
Skin	Rare: rash
Pregnancy, puerperium and perinatal conditions	Not known: uterine hypertonus, tetanic contractions of uterus, rupture of the uterus
Metabolism and nutrition disorders	Not known: water intoxication, hyponatraemia
Respiratory, thoracic and mediastinal disorders	Not known: acute pulmonary oedema
General disorders and administration site conditions	Not known: flushing
Blood and lymphatic system disorders	Not known: disseminated intravascular coagulation

Table 2 Adverse drug reactions in fetus/neonate

Not known: fetal distress, asphyxia and death
Not known: neonatal hyponatraemia

4.9 Overdose

The fatal dose of oxytocin has not been established. Oxytocin is inactivated 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 and 4.8. In addition, as a result of uterine overstimulation, placental abruption and amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous intravenous administration of oxytocin, 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 occur. In the case of coma, a free airway should be maintained with 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: H01BB02

Mechanism of action

Oxytocin is a synthetic cyclic nonapeptide that is identical to the natural hormone that is released by the posterior pituitary into the systemic circulation in response to suckling and labour.

Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, 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 leading to myometrial contraction. Oxytocin elicits rhythmic contractions in upper segment of uterus, similar in frequency, force and duration to those in labour.

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

Plasma levels and onset and duration of effect
When oxytocin is given by continuous intravenous 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 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.

5.2 Pharmacokinetic properties

Absorption
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 intravenous 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 breast milk.

Biotransformation/metabolism
Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy by both the mother and the fetus. It appears in the plasma and is capable of degrading oxytocin. Liver and kidneys play a major role in metabolising and clearing oxytocin from the plasma.

Elimination
The plasma half-life of oxytocin ranges from 3 to 20 minutes. 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/minute in the pregnant woman.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Chlorobutanol hemihydrate
Glacial acetic acid
Sodium acetate, anhydrous
Ethanol
Sodium chloride
Water for injection

6.2 Incompatibilities

Oxytocin is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

18 months. Shelf life after first opening the container: the solution should be used immediately.

6.4 Special precautions for storage

Store between 2° and 8°C.

6.5 Nature and contents of container

Clear and colorless type I glass ampoule with a white color break. It has double orange rings and red vertical "SANBE" print containing 1 mL of solution for injections. The ampoules are inserted to plastic blister divider, each plastic blister contains 5 ampoules and each folding box (made of ivory paper 310 g) contains 2 plastic blisters.

6.6 Special precautions for disposal

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

7. SUPPLIER

PT SANBE FARMA
Jl. Taman Sari 10,
Bandung, Indonesia
Tel: + 62 22 4207725
Fax: + 62 22 4238476
medical@sanbe-farma.com

Manufactured by:
PT SANBE FARMA
Sterile Preparation Plant, Unit 3
Jl. Industri Cimareme No. 8, Desa Cimareme,
Kecamatan Ngamprah, Kabupaten Bandung Barat - Indonesia

8. FDA APPLICATION NUMBER

n/a (will be added after registered)

9. DATE OF REGISTRATION

n/a (will be added after registered)

10. DATE OF REVISION OF THE TEXT

February 09th, 2021

REFERENCE LIST