1.3

Labelling and Packaging

1.3.1 Package Insert/Summary of Product Characteristics:

Package insert:

Front

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CP-Oxytocin Injection

Oxytocin Injection BP 10 IU/m1 (For I.M./I.V use)

Composition :
Each ml of solution for injection contains:
Oxytocin Ph. Eur.....10 IU
Chlorobutanol BP..... 0.5% w/v
Water for injection BP..... q.s

INDICATIONS:
Oxytocin is not indicated for the elective induction of labor. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy, which is free of medical indications for the initiation of labor.
Oxytocin is indicated in the following: Antepartum; For induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, mild preeclampsia at or near term, when delivery is in the best interest of mother and fetus, or when membranes are prematurely ruptured and delivery indicated. For stimulation or reinforcement of labor as in selected cases of uterine inertia. As adjunctive therapy in the management of incomplete or inevitable abortion. Postpartum: To produce uterine contractions during the third stage of labor and to control postpartum bleeding and hemorrhage.

DOSAGE AND ADMINISTRATION:
Oxytocin 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).

Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Oxytocin Injection BP 10 IU/mL 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 Oxytocin Injection BP 10 IU/mL be added to 500 mL of a physiological electrolyte solution (such as sodium chloride 0.9%). For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent. To ensure even mixing, the infusion bottle must be turned upside down several times before use.

The initial infusion rate should be set at 1 to 4 milliunits/minute (2 to 8 drops/minute). It may be 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 labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event that higher rates are required, as may occur in the management of foetal death in utero or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated Oxytocin Injection BP 10 IU/mL solution, e.g., 10 IU in 500 mL.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump.
The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 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), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) immediately after delivery.

Route of administration: IM/IV

ACTION AND CLINICAL PHARMACOLOGY:
Oxytocin synthetic, acts on the smooth muscle of the uterus to stimulate contractions; response depends on the uterine threshold of excitability. It exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions and raises the tone of the uterine musculature. Synthetic oxytocin elicits only slight pressor and antidiuretic activity due to the absence of vasopressin. (Hypertension has been observed resulting from concomitant use of oxytocics and continuous caudal block anaesthesia).

DRUG INTERACTIONS:
Oxytocin should be used with special caution in conjunction with cyclopropane anaesthesia since the risk of arrhythmias may be increased. In instances where a vasoconstrictor drug is administered prophylactically in conjunction with continuous caudal block anaesthesia, severe hypertension may occur when oxytocin is given within3 to 6 hours of administration of the vasoconstrictor drug. Sudden, marked elevation of blood pressure occurring under these circumstances has been reported to respond to i.v. administration of chlorpromazine.

LH : 148 mm x 210 mm

Back

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

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

ADVERSE REACTIONS:
Water intoxication with headaches and nausea has been reported after prolonged or too rapid i.v. infusion of oxytocin (see Overdose: Symptoms and Treatment). Premature ventricular contractions, fetal bradycardia and cardiac arrhythmia have been noted. Hypotension, tachycardia and ECG changes have been observed following i.v. administration of concentrated solutions. Anxiety, dyspnea, precordial pain, edema, cyanosis or reddening of the skin and cardiovascular spasm and collapse has occurred on rare occasions. In very few cases, anaphylactic Reactions (dyspnea, hypotension shock) occurred. Overdosage may give rise to the following complications: slowing of fetal heart, meconium staining of the amniotic fluid and asphyxia; hypertonic contractions, uterine rupture, retention of the placenta, postpartum uterine inertia.

CONTRA-INDICATIONS:
Significant cephalopelvic disproportion.Severe toxemia.Malpresentation or malposition of the fetus or placenta previa. Prematurity or unripe cervix. Predisposition to uterine rupture (grand multiparity, overdistention of the uterus, previous caesarean section or other surgery involving the uterus). Hypertonic labor patterns. Prolonged use in uterine inertia. Factors predisposing to thromboplastin or amniotic fluid embolism (prolonged retention of dead fetus, abruptio placentae). Serious medical and obstetric conditions and any conditions in which fetal distress already occurs. Inability of physician to be in attendance. Hypersensitivity to oxytocin.

WARNINGS IN CLINICAL STATES:
Oxytocin, when given for induction or stimulation of labor, must be administered only by the i.v. route and with adequate medical supervision in a hospital.

PRECAUTIONS:
The following should be borne in mind when using oxytocin injection:
1. Use only under close medical/obstetrical supervision.
2. Never administer i.v. undiluted oxytocin, or use in high concentrations.
3. Oxytocin must not be used by more than one route simultaneously, e.g., parenteral and buccal, or parenteral and nasal.
When given for induction and stimulation of labor, Oxytocin Injection, USP must only be used as i.v. drip infusion, and not by i.m., nor by direct i.v. injection.
Careful monitoring (blood pressure, fetal heart rate, possible tocometry) is vital, in order to adjust dosage according to the individual response: if uterine activity interferes at any time with fetal heart rate, the infusion should be discontinued.
In patients with cardiovascular disorders, the infusion volume should be kept low by using a more concentrated solution.

SYMPTOMS AND TREATMENT OF OVERDOSE:
I.V. infusion of oxytocin in nonpregnant subjects given at a rate greater than 45milliunits/minute (4.5 mL/min=90 drops/min using 10 IU/L dilution) has been shown to have an antidiuretic effect comparable to that of vasopressin but of shorter duration. There are also a number of cases reported in the literature where high i.v. doses of oxytocin administered along with a large volume of electrolyte-free fluid have resulted in the development of water intoxication. However, high doses of oxytocin can be given without danger of water intoxication provided that the daily fluid intake is limited at this time. Acute overdose with oxytocin, therefore, is unlikely in any circumstances and adverse effects are to be expected only if the concomitant fluid intake is excessive.

SYMPTOMS:
Symptoms of Water Intoxication: Headache, anorexia, nausea, vomiting, abdominal pain, lethargy, drowsiness, unconsciousness, and grand mal type seizures have been reported. Owing to the excessive retention of water, the serum electrolyte concentration is low.

TREATMENT:
Discontinue Oxytocin and restrict all fluid intakes. Encourage diuresis by administration of a diuretic such as furosemide. The use of i.v. hypertonic sodiumchloride solution should be reserved for severe water intoxication with frank CNS disturbance. Careful supervision and, where necessary, correction of electrolyte imbalance should be undertaken, particularly in the diuretic phase. At the end of the diuretic phase, the hypertonic infusion, if used, should be stopped to avoid water retention due to excessive sodium.

STORAGE CONDITION:
Store between temperatures of 2°C to 8°C, Do not freeze. Protect from light.
Keep out of reach of children.

AVAILABILITY:
Oxytocin Injection BP 10 IU/ml is available as 1 mL clear glass ampoule USP type 1 Fiolax.

SHELF LIFE:
24 Months

Manufactured in India by :
Steril-Gene Life Sciences (P) ltd.
No.45, Main Road, Mangalam Village,
Villianur Commune, Puducherry - 605 110.

LH : 148 mm x 210 mm

Summary of Product Characteristics:

1.3.1.1 Name of the Medicinal Product

a) Name Of The Product : Oxytocin Injection BP

b) Strength : 10 IU/mL

c) Pharmaceutical Dosage Form : Solution for injection

1.3.1.2 Quantitative and Qualitative Composition:

Composition

Each ml of solution for injection contains

Oxytocin	Ph. Eur	10IU
Chlorobutanol	BP	0.5% w/w
Water for Injection	BP	q.s

Batch Size: 50.0 Litres (45,454 Ampoules)

S.No	Ingredients	Specification[1]	Label Claim	Qty/ml	Qty / 50L	Function of the Ingredients
1.	Oxytocin #*	Ph Eur.	10IU	16.667 mcg	833.35 mg	Active
2.	Ethanol 96%	Ph Eur./BP	-	0.0061ml	305.00 ml (246.00g)	Solubilizer
3.	Chlorobutanol **	BP	-	5.0 mg	250.0 g	Anti microbial Preservative
4.	Sodium Acetate trihydrate	Ph Eur./BP	-	1.0 mg	50.0	Buffer & Stabilizer
5.	Sodium Chloride	Ph Eur./BP	-	0.017 mg	850 mg	Tonicity Agent
6.	Glacial Acetic Acid	Ph Eur./BP	-	q.s	q.s	Acidifying Agent
7.	Water for injection	BP	-	q.s to 1.0 mL	q.s to 50.0 L	Vehicle

Abbreviation:

Ph Eur. – *European Pharmacopoeia,*

BP – British Pharmacopoeia

q.s -- Quantity Sufficient

[1] Current pharmacopoeial monographs are implied

In accordance with Ph.Eur 2016 "by convention, for the purpose of labeling Oxytocin preparation, 1mg of Oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600IU of biological activity"

* Denotes that the API has been taken as 100% assay and 0% water and acetic acid content. The quantity of Oxytocin shall vary based on the assay, water and acetic acid content

** Denotes that the Chlorobutanol has been taken as 100% assay and 0% water content. The quantity of Chlorobutanol shall vary based on the assay and water content.

Model Calculation

The actual quantity of **Oxytocin** to be taken is calculated using the below given formula,

$$OP = \text{Standard Quantity} \times \frac{100}{\text{Assay (anhydrous, acetic acid free basis)}} \times \frac{100}{(100 - \text{Water} + \text{Acetic acid Content})}$$

The actual quantity of **Chlorobutanol** to be taken is calculated using the below given formula,

$$= \text{Standard Quantity} \times \frac{100}{\text{Assay (anhydrous basis)}} \times \frac{100}{(100 - \text{Water Content})}$$

Overages: No overages of active pharmaceutical ingredient has been used in the formulation

Container Closure System:

Oxytocin Injection BP 10 IU/mL is packed in 1mL clear glass ampoules USP type I. 5 such ampoules are packed in a plastic ampoule tray, pre – folded literature will be placed in plastic ampoule tray and one ampoule tray in one printed carton along with leaflet.

1.3.1.3 Pharmaceutical Forms:

Liquid Injection

1.3.1.4 Clinical Particulars:

4.1 Therapeutic indication:

Oxytocin is not indicated for the elective induction of labor. Elective induction of labour is defined as the inititation of labour for convenience in an individual with a term pregnancy, which is free of medical indications for the initiation of labour.

Oxytocin is indicated in the following:

Antepartum

– Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of 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, following delivery of the child.

– Prevention and treatment of postpartum uterine atony and haemorrhage.

4.2 Posology And Method Of Administration:

Posology

Oxytocin 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).

Induction or enhancement of Labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins.

Oxytocin 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 (8.3 micrograms) 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% dextrose solution may be used as the diluent. 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 2 to 8 drops/minute (1 to 4 milliunits/minute). It may be gradually increased at intervals not shorter than 20 minutes and increments of not more than 1 to 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 of less than 20 drops/minute (10 milliunits/minute), and the recommended maximum rate is 40 drops/minute (20 milliunits/minute). In the unusual event that higher rates are required, as may occur in the management of foetal death *in utero* or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated oxytocin solution, e.g., 10 IU (16.7 micrograms) 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, aiming for 3 to 4 contractions every 10 minutes, 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 (8.3 micrograms), it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 2 to 8 drops/minute (1 to 4 milliunits/minute).

Incomplete, inevitable, or missed abortion: 5 IU (8.3 micrograms) 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), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 5 IU (8.3 micrograms) by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) immediately after delivery.

Prevention of postpartum uterine haemorrhage: The usual dose is 5 IU (8.3 micrograms) 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) 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 thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU (8.3 micrograms) 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), followed in severe cases by i.v. infusion of a solution containing 5 to 20 IU (8.3 to 33.4 micrograms) 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.

Paediatric population

There are no indications for use of Oxytocin in children or adolescents.

Older people (65 years and over)

There are no indications for use of Oxytocin in elderly.

Method of administration

For IM/IV use

4.3 Contraindication:

Hypersensitivity to the active substance or to any of the excipients.

Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress.

Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contraindicated: e.g.:

- Significant cephalopelvic disproportion
- Foetal malpresentation
- Placenta praevia and vasa praevia
- Placental abruption
- Cord presentation or prolapse
- Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy
- Polyhydramnios
- Grand multiparity
- In the presence of a uterine scar resulting from major surgery including classical caesarean section.

Oxytocin Injection BP 10 IU/mL should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

Oxytocin Injection BP 10 IU/mL must not be administered within 6 hours after vaginal prostaglandins have been given.

4.4 Special Warning And Special Precaution For Use:

Oxytocin must only be administered as an i.v. infusion and never by i.v. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

Induction of labour

The induction of labour 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.

Cardiovascular disorders

Oxytocin should be used with caution in patients who have a pre-disposition to myocardial ischaemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease and/or 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 known 'long QT syndrome' or related symptoms and to patients taking drugs that are known to prolong the QTC interval.

When Oxytocin is given for induction and enhancement of labour:

Foetal distress and foetal death: Administration of Oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.

Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.

Disseminated intravascular coagulation: In rare circumstances, 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 increased in particular if the woman has additional risk factors for DIC such as being 35 years of age or over, complications during 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 foetal death in utero, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism.

Water intoxication

Because Oxytocin possesses slight antidiuretic activity, its prolonged i.v. administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water intoxication associated with hyponatraemia. The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic 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.

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of Oxytocin.

4.5 Interaction With Other Medicaments And Other Forms Of Interaction:

Interactions resulting in a concomitant use not recommended

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.

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 history of long QT syndrome.

Interactions to be considered

Inhalation anaesthetics

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. Their concurrent use with Oxytocin has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors/Sympathomimetics

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those contained 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 Pregnancy and Lactation:

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

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines:

Oxytocin can induce labour, therefore caution should be exercised when driving or operating machines. Women with 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 what are normally considered to be low doses. When Oxytocin is used by i.v. infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal 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 with flushing and reflex tachycardia. These rapid haemodynamic changes may result in myocardial ischaemia, 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 the pharmacological induction of labour using uterotonic agents, including Oxytocin, increases the risk of postpartum disseminated intravascular coagulation.

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.

The combined antidiuretic effect of Oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia. Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.
2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.
3. Low blood electrolyte concentration.

Undesirable effects 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), including isolated reports; not known (cannot be estimated from the available data).

Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in mother

System organ class	Adverse drug reaction
Immune system disorders	Rare: 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
Gastrointestinal disorders	Common: Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Rash
Pregnancy, puerperium and perinatal conditions	Not known: Uterine hypertonicity, tetanic contractions, rupture of the uterus
Metabolism and nutrition disorders	Not known: Water intoxication, maternal 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 foetus/neonate

System organ class	Adverse drug reaction
Pregnancy, puerperium and perinatal conditions	Not known: Foetal distress, asphyxia and death
Metabolism and nutrition disorders	Not known: Neonatal hyponatraemia

4.9 Overdose:

The fatal dose of Oxytocin has not been established. Oxytocin 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.

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 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 eventually occur, by judicious use of diazepam. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

1.3.1.5 Pharmacological Properties:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones, Oxytocin and analogues,

ATC code: H01BB02

Mechanism of action

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 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 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 labour.

Being synthetic, Oxytocin in this product 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 desensitisation of Oxytocin receptors probably due to down-regulation of Oxytocin-binding sites, destabilisation of Oxytocin receptors mRNA and internalisation of Oxytocin receptors.

Plasma levels and onset/duration of effect

Intravenous infusion. When Oxytocin is given by continuous i.v. infusion at doses appropriate for induction or enhancement of labour, the uterine response sets in gradually and usually reaches a steady state within 20 to 40 minutes.

The corresponding plasma levels of Oxytocin are comparable to those measured during spontaneous first-stage labour. For example, Oxytocin plasma levels in 10 pregnant women at term receiving a 4 milliunits per minute intravenous infusion were 2 to 5 microunits/mL. Upon discontinuation of the infusion, or following a substantial reduction in the infusion rate, e.g. in the event of overstimulation, uterine activity declines rapidly but may continue at an adequate lower level.

5.2 Pharmacokinetics 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 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. Liver and kidney plays a major role in metabolising 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 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/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 metabolising 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:

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

1.3.1.6 Pharmaceutical Particulars:

6.1 List of Excipients

Ethanol 96%, Chlorobutanol, Sodium Acetate trihydrate, Sodium Chloride, Glacial Acetic Acid, Water for injections

6.2 Incompatibilities:

Oxytocin Injection BP 10 IU/mL should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Oxytocin Injection BP 10 IU/mL is incompatible with solutions containing sodium metabisulphite as a stabilizer.

6.3 Shelf Life:

24 months.

6.4 Special Precaution for Storage:

Store the ampoule refrigerated (2-8°C) in the original cartons protected from light. Do not freeze. Single use only. Keep out of reach of Children

6.5 Nature and contents of container

A Clear colorless solution free from visible particulate filled in USP Type I 1 mL clear glass Ampoule. Such 5 labeled Ampoules are packed in Plastic Ampoule Tray. Such Plastic Ampoule Tray placed in Printed Carton along with Literature.

6.6 Special precautions for disposal

Oxytocin Injection BP 10 IU/mL 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 for 48 hours at 25˚C.

Discard unused portion in accordance with local requirements.

1.3.1.7 Marketing Authorization Holder/Manufacturer:

Registered Office:

Steril-Gene Life Sciences (P) Ltd
No: 15, Gopalakrishnan Road,
T.Nagar, Chennai-600017,
India. Ph. No: 91-44-23452030/34

Factory Address:

Steril-Gene Life Sciences (P) Ltd
No. 45, Mangalam Main Road,
Mangalam Village, Villianur Commune,
Puducherry – 605 110. Ph. No: 91-413-2661103

1.3.1.8 Marketing Authorization Number:

Form No: 28 Licence No: 08 22 2288

1.3.1.9 Date of first Registration/Renewal of Registration:

19.02.2009

1.3.1.10 Date of last Revision Of Text

10.08.2017

1.3.1.11 Legal Category

POM