Oxytocin Injection I.P.

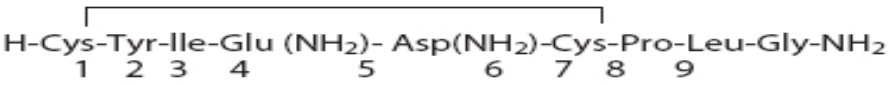
PITOCIN®

1. NAME OF THE MEDICINAL PRODUCT

PITOCIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin is a synthetically prepared hormone that stimulates contractions of uterine smooth muscle. The product is formulated as a sterile, aqueous solution of synthetic oxytocin for intravenous infusion or intramuscular injection. Oxytocin has the empirical formula $C_{43}H_{66}N_{12}O_{12}S_2$ and the following structural formula:



Molecular Weight = 1007.19

Each ml contains Oxytocin IP as Oxytocin Solution (Synthetic) equivalent to 10 Oxytocin units (5 Oxytocin units in 0.5 ml) in a 0.5 ml ampoule and Oxytocin IP as Oxytocin Solution (Synthetic) equivalent to 5 Oxytocin units in a 1 ml ampoule.

For a full list of excipients, see section 6.1.

All strengths/presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

IMPORTANT NOTE: Elective induction of labor is defined as the initiation of labor in a pregnant individual who has no medical indications for induction. Since the available data are inadequate to evaluate the benefit-to-risk considerations, oxytocin is not indicated for elective induction of labor.

Antepartum:

Oxytocin is indicated for the initiation or improvement of uterine contractions in order to achieve vaginal delivery in the following situations:

1. Induction of labor in patients with a medical indication for the initiation of labor (e.g., Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus, or when membranes are prematurely ruptured and delivery is indicated).

2. Stimulation or reinforcement of labor (e.g., selected cases of uterine inertia).

3. Adjunctive therapy in the management of incomplete or inevitable abortion.

Postpartum:

Oxytocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

4.2 Posology and Method of Administration

The dosage of oxytocin is determined by the uterine response, and therefore must be highly individualized and initiated at a very low level.

Induction or Stimulation of Labor

Parenteral:

Inspect parenteral drug product visually for particulate matter and discoloration prior to administration.

Intravenous infusion (drip method) is the only acceptable method of parenteral administration. Accurate control of the rate of infusion is essential and best accomplished by an infusion pump.

The standard solution for infusion of oxytocin is prepared by aseptically adding the contents of two 0.5 ml ampoules (each containing 5 units of oxytocin) to 1000 ml of 0.9% aqueous sodium chloride or Ringer's lactate, and rotating the combined solution in the infusion bottle for thorough mixing. The same concentration can be obtained by adding the contents of one 0.5-ml ampoule (containing 5 units of oxytocin) with 500 ml of electrolyte solution. Establish the infusion with a separate bottle of physiologic electrolyte solution not

containing oxytocin. Attach the oxytocin-containing bottle with the infusion pump to the infusion line as close to the infusion site as possible.

The initial dose should be 0.5-1 mU/min (equal to 3-6 mL of the dilute oxytocin solution per hour). At 30-60 minute intervals, the dose should be gradually increased in increments of 1-2 mU/min until the desired contraction pattern has been established. Once the desired frequency of contractions has been reached and labor has progressed to 5-6 cm dilation, the dose may be reduced by similar increments. Studies have shown that infusion rates up to 6 mU/min give the same oxytocin levels that are found in spontaneous labor. At term, higher infusion rates should be given with great care, and rates exceeding 9-10 mU/min are rarely required. Before term, when the sensitivity of the uterus is lower due to fewer oxytocin receptors, a higher infusion rate may be required.

Electronically monitor the uterine activity and fetal heart rate. If uterine contractions become too powerful, the infusion must be stopped immediately and oxytocin stimulation of the uterine musculature will soon wane (See section 4.4 **Special Warnings and Precautions for Use**). Discontinue oxytocin immediately in the event of uterine hyperactivity and/or fetal distress. Administer oxygen to the mother, and preferably place her in a lateral position. The condition of the mother and fetus should immediately be evaluated and appropriate actions taken.

Control of Postpartum Uterine Bleeding

Intravenous infusion (drip method)

If the patient has an intravenous infusion running, 10 to 40 units of oxytocin may be added to the bottle, depending on the amount of electrolyte or dextrose solution remaining (maximum 40 units to 1000 ml). Adjust the infusion rate to sustain uterine contraction and control uterine atony.

Intramuscular Administration

Ten (10) units (one ml) of oxytocin can be given after the delivery of the placenta.

Treatment of Incomplete, Inevitable, or Elective Abortion

Intravenous infusion of 10 units of oxytocin added to 500 ml of a physiologic saline solution or 5% dextrose-in-water solution may help the uterus contract after a suction or sharp curettage.

Subsequent to intra-amniotic injection of hypertonic saline, prostaglandins, urea, etc., for midtrimester elective abortion, the injection-to-abortion time may be shortened by infusion of oxytocin at the rate of 10 to 20 mU (20 to 40 drops) per minute. The total dose should not exceed 30 units in a 12-hour period due to the risk of water intoxication.

Use in the Elderly

Safety and effectiveness in the elderly have not been established.

Use in Children

Safety and effectiveness in patients below the age of 18 years have not been established.

4.3 Contraindications

Antepartum use of oxytocin is contraindicated in the following situations:

1. Significant cephalopelvic disproportion, as determined by the physician.
2. Unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery.
3. Obstetrical emergencies where the benefit-to-risk ratio for the fetus or mother favors surgical intervention.
4. Fetal distress where delivery is not imminent.
5. Adequate uterine activity fails to achieve satisfactory progress.
6. Hyperactive or hypertonic uterus.
7. Vaginal delivery is contraindicated (e.g. invasive cervical carcinoma, active herpes genitalis, total placenta previa, vasa previa, cord presentation, or prolapse of the cord).
8. Hypersensitivity to oxytocin or its ingredients.

4.4 Special Warnings and Special Precautions for Use

Oxytocin should not be used simultaneously by more than one route. The drug can, however, be administered successively by different routes.

Oxytocin, when given for induction of labor or augmentation of uterine activity, should be administered only by the intravenous route and with adequate medical supervision in a hospital.

General

All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available.

Cautious administration of oxytocin is required to avoid overstimulation of the uterus which can be hazardous to both the mother and the fetus. When properly administered, oxytocin should stimulate uterine contractions comparable to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are sensitive to oxytocin. This fact must be considered by the physician in exercising his judgement regarding patient selection. However, it must be borne in mind that only intrauterine pressure recording can accurately measure the intrauterine pressure during contractions. Electronic fetal monitoring provides the best means for early detection of overdosage (See section 4.9 **Overdose**). A fetal scalp electrode provides a more dependable recording of the fetal heart rate.

Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and any condition in which there is a predisposition for uterine rupture such as previous major surgery on the cervix or uterus including cesarean section, overdistension of the uterus, grand multiparity, past history of uterine sepsis, or of traumatic delivery. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgement of the physician. The decision can be made only by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

Oxytocin has been shown to have an intrinsic antidiuretic effect. Due to the possibility of water intoxication, restricted total fluid intake may be indicated.

When oxytocin is used for induction or reinforcement of already existing labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before use of the drug.

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 (See section 4.5 **Interaction with other medicinal products and other forms of interaction**).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Severe hypertension has been reported when oxytocin was given 3 to 4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia.

The concomitant use of cyclopropane anesthesia has been associated with hypotension and maternal sinus bradycardia with abnormal atrioventricular rhythms.

Oxytocin can enhance the neuromuscular blockade of succinylcholine.

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 (See Section 4.4 **Special warnings and precautions for use**).

4.6 Pregnancy and Lactation

There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on widespread experience, the chemical structure, and pharmacological properties of oxytocin, fetal abnormalities are not expected when used as indicated (See Section 4.8 **Undesirable side effects**).

4.7 Effects on Ability to Drive and Use Machines

The effect of oxytocin on the ability to drive or use machinery has not been studied.

4.8 Undesirable Effects

The following adverse events have been reported in the mother and fetus/infant:

Gastrointestinal: Nausea, vomiting in mother.

Cardiovascular: Cardiac arrhythmia in mother and fetus, fetal bradycardia, hypertensive episode in mother, ventricular premature contractions in mother and fetus.

Endocrine, metabolic: Water intoxication syndrome: Water intoxication has occurred, particularly with the following conditions: slow infusions 24 hours, continuous infusions in electrolyte-free solutions, and large doses (40 to 50 mU/min) infused for long periods.

Hematologic: Fatal afibrinogenemia in mother.

Hepatic: Neonatal jaundice.

Immunologic: Anaphylaxis in mother.

Neurologic: Maternal convulsions, coma, and death due to oxytocin-induced water intoxication have been reported. Subarachnoid hemorrhage in mother, permanent CNS or brain damage in fetus, fetal death, neonatal seizures.

Ophthalmic: Neonatal retinal hemorrhage.

Renal: Pelvic hematoma in mother.

Reproductive: Postpartum hemorrhage, rupture of uterus in mother. Excessive dosage or sensitivity to oxytocin may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.

Other: Low Apgar score at 5 minutes in neonate.

4.9 Overdose

Overdosage depends upon uterine hyperactivity whether or not due to uterine sensitivity to oxytocin. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a

resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, perinatal hepatic necrosis or death.

Water intoxication with convulsions may occur if large doses are used for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Oxytocin has specific receptors in the myometrium and the receptor concentration increases greatly during pregnancy, reaching a maximum in early labor at term. Response to a given dose is very individualized and depends on the sensitivity of the uterus, which is determined by the oxytocin receptor concentration. Oxytocin has inherent pressor and antidiuretic properties, which may manifest during administration of large doses.

Mechanism of action- Uterine motility depends on the formation of the contractile protein actomyosin under the influence of the Ca^{2+}-dependent phosphorylating enzyme myosin light-chain kinase. Oxytocin promotes uterine contractions by increasing intracellular Ca^{2+}.

5.2 Pharmacokinetic Properties

The plasma half-life of oxytocin is 1 to 6 minutes, which is decreased in late pregnancy and lactation. Following intravenous administration, uterine response occurs almost immediately and subsides within one hour. Following intramuscular administration, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours.

Oxytocin is distributed throughout the extracellular fluid. Small amounts of the drug probably reach fetal circulation. Oxytocin is rapidly metabolized in the kidney and liver. Small amounts are excreted in the urine unchanged.

5.3 Preclinical Safety Data

Animal reproduction studies have not been conducted with oxytocin. There are no animal studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Chlorbutol (0.5%w/v)
Glacial Acetic Acid IP
Water for Injection IP

6.2 Incompatibilities*

Solutions

Isotonic solution of balanced electrolytes (Sodium Chloride, Sodium Acetate, Sodium Gluconate, Potassium Chloride, and Magnesium Chloride) in Dextrose 5% (with oxytocin 10.4 U/L, approximately 80% oxytocin decomposition in 6 hours at room temperature due to the bisulfite content)

Drugs

A. Ascorbic Acid

Ascorbic acid with oxytocin, oxytocin will undergo a 20 percent loss of potency in 8 hours

B. Fibrinolysin

Fibrinolysin incompatible with oxytocin (Pitocin®)
Fibrinolysin 2 g/L with oxytocin 5 U/L, visually incompatible in Dextrose 5% in water.

C. Fibrinolysin, human

Fibrinolysin, human (2 g/L with oxytocin 5 U/L physically incompatible in Dextrose 5% in water)

D. Norepinephrine

Norepinephrine (incompatible with oxytocin)

E. Phytonadione

Phytonadione (50 mg/L with oxytocin 5 U/L, haze or precipitate formation reported within 1 hour only in Dextran 12%)

F. Sodium bisulfite

Sodium bisulfite (rapidly decomposes oxytocin)

G. Theophylline

Aminophylline
Aminophylline with oxytocin, 20% decomposition of oxytocin reported in 8 hours.

H. Warfarin

Warfarin (100 mg/L with oxytocin 5 U/L physically incompatible in Dextrose 5% in water)

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Store in a cold place. Do not freeze.

6.5 Nature and Contents of Container

Ampoules of 0.5 ml and 1 ml.

6.6 Instructions for Use/Handling

Discard the solution if the content is not clear.

*Reference: Oxytocin- Drugdex drug evaluations