AUSTRALIAN PRODUCT INFORMATION

VIATOCINON

oxytocin injection

1 NAME OF THE MEDICINE

Oxytocin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VIATOCINON ampoule contains either 5 IU (approximately 8.33 micrograms) or 10 IU (approximately 16.66 micrograms) of oxytocin as the active ingredient.

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

3 PHARMACEUTICAL FORM

VIATOCINON is a solution for injection which is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VIATOCINON is indicated for:

- the induction of labour
- inadequate uterine effort
- management of third stage of labour
- post-partum haemorrhage

4.2 DOSE AND METHOD OF ADMINISTRATION

This product is for single use in one patient only. Any residue must be discarded.

Dosage Regimens

Induction or Augmentation of Labour

VIATOCINON should only be administered as an intravenous infusion, preferably by means of a variable speed infusion pump, or by drip infusion. It should not be administered by subcutaneous, intramuscular or intravenous bolus injection.

The initial infusion rate should be set at 1 to 4 milliunits/min. This rate may be gradually increased at intervals of not shorter than 20 min, 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/min. The recommended maximum rate is 20 milliunits/min. The increments in infusion rate should not be as high once contractions have been established as those used to initiate contractions. Once an adequate level of uterine activity is attained, the infusion rate can often be reduced.

The frequency and duration of contractions and fetal heart rate must be carefully monitored during oxytocin administration, the latter preferably by electronic means, and the infusion must be discontinued immediately in the event of uterine hyperactivity, fetal distress or fetal heart abnormalities.

If regular contractions are not established after the infusion of 5 IU oxytocin, the attempt to induce labour should be terminated. It can generally be repeated on the following day, starting again from a rate of 1 to 4 milliunits/min.

In general, the dose of VIATOCINON required for the augmentation of labour is less than that required for induction. Therefore, the initial infusion rate should be at the lower end of the recommended range.

Third Stage of Labour and Puerperium (haemorrhage, subinvolution of the uterus)

5 to 10 IU by intramuscular injection or 5 IU by slow bolus intravenous injection. In patients given VIATOCINON by drip to induce or stimulate labour, the infusion should be continued during the third stage.

Caesarean Section

5 IU by intravenous infusion or slow bolus intravenous injection after delivery of the fetus.

Instructions for Use and Handling

Infusion Fluids

Compatibility of VIATOCINON has been demonstrated with 0.9% saline and 5% dextrose solutions. VIATOCINON is not compatible with solutions containing bisulphites and metabisulphites as preservatives.

Due attention should be paid to the choice of infusion fluid in individual patients. Generally, VIATOCINON should be administered in a combination of dextrose and an electrolyte solution (such as 4% dextrose in N/5 saline), or in an isotonic electrolyte solution. The use of 5% dextrose in water is not recommended.

Due to the absence of compatibility studies, VIATOCINON must not be mixed with other medicinal products.

Preparation of Infusion Solution

For drip infusion, the preparation of a solution containing 10 IU oxytocin per 1 litre infusion fluid is recommended. To ensure even mixing of the drip solution, the bottle or bag must be turned upside down several times before use. Using this concentration, the recommended initial infusion rate of 1 to 4 mU/min corresponds to 0.1 to 0.4 mL/min, and the recommended maximum rate of 20 mU/min is reached at a rate of 2 mL/min.

When using a mechanical infusion pump which delivers smaller volumes than those given by drip infusion, a more concentrated oxytocin solution will be required. The concentration suitable for infusions within the recommended dosage range (1 to 20 mU/min) must be calculated according to the specification of the pump used.

4.3 CONTRAINDICATIONS

VIATOCINON is contraindicated in any of the following conditions:

- fetal distress
- any condition in which, for fetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contraindicated: e.g. cephalo-pelvic disproportion, abnormal presentation, cord presentation or prolapse, excessive distension or impaired resistance of the uterus to rupture (e.g. multiple pregnancy, polyhydramnios), parity greater than 4, elderly multiparae, grand multiparity and in the presence of uterine scar resulting from major surgery including previous Caesarean section or other surgery involving the uterus
- severe toxaemia, predisposition to amniotic fluid embolism (fetal death-in-utero, abruptio placentae), hypertonic contractions, placenta praevia and vasa praevia, placental abruption
- hypersensitivity to oxytocin or to any of the excipients in the formulation
- VIATOCINON must not be administered within 6 hours after vaginal prostaglandins have been given

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Induction or Augmentation of Labour

The induction of labour by means of oxytocic agents should be attempted only when strictly indicated for medical reasons rather than for convenience. Administration should only be under hospital conditions, and all patients receiving intravenous oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications must be immediately available.

When oxytocin is given for the induction and augmentation of labour, it must only be administered as an intravenous infusion, preferably by means of a motor-driven variable speed infusion pump, and not by subcutaneous, intramuscular or intravenous bolus injection as it may cause an acute short-lasting hypotension accompanied by flushing and reflex tachycardia

Administration of oxytocin at excessive doses results in uterine overstimulation which may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring is essential (fetal heart rate, uterine response - by tocometry if possible, blood pressure), so that dosage may be titrated to individual response.

When oxytocin is used for the induction of labour, there is a chance that infants with unanticipated prematurity may be delivered. To reduce this risk, it is recommended that, in women with uncertain obstetric dating, the maturity of the fetus be assessed by ultrasonic measurement of fetal biparietal diameter.

Third Stage of Labour and Puerperium

When oxytocin is used for prevention or treatment of uterine haemorrhage, rapid intravenous bolus injection of oxytocin at high doses should be avoided, as it may cause acute short-lasting hypotension accompanied by flushing and reflex tachycardia.

These rapid haemodynamic changes may result in myocardial ischemia, particularly in patients with pre-existing cardiovascular disease. Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

When oxytocin is used for the management of the third stage of labour, multiple pregnancy must be excluded before the drug is injected.

Use with Caution in the Following Circumstances

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 (note: use is contraindicated in elderly multiparae), or with a history of lower-uterine-segment caesarean section

In the case of fetal 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 (see section 4.3 Contraindications).

Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia or severe cardiovascular disorders. In patients with cardiovascular disorders, the infusion volume should be kept low by using a more concentrated solution.

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

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.

In situations where more prolonged periods of administration may be required, such as in the treatment of inevitable or missed abortion, in the management of postpartum haemorrhage, or earlier in gestation when the uterus is less sensitive to oxytocin, special precautions must be taken to avoid water intoxication.

Water Intoxication

Water intoxication associated with maternal and neonatal hyponatraemia, which is potentially fatal, has been reported in cases where high doses of oxytocin have been administered together with large amounts of electrolyte-free fluid over a prolonged period of time. The weak anti-diuretic activity of oxytocin, acting to increase water reabsorption from the glomerular filtrate, may be a contributing factor, but the major cause is the use of large amounts of electrolyte-free fluids. The combined antidiuretic effect of oxytocin and the intravenous fluid administration may also cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia.

Renal impairment: caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin.

The symptoms and signs of water intoxication are:

1. Headache, anorexia, nausea, vomiting and abdominal pain
2. Lethargy, drowsiness, unconsciousness and grand mal type seizures
3. Low blood electrolyte concentration including maternal and neonatal hyponatraemia
4. Possible acute pulmonary oedema without hyponatraemia

Therefore, if high doses or a more prolonged period of administration is expected, the following precautions must be observed:

1. A strict fluid balance chart must be kept
2. Low-sodium infusion fluids should be avoided
3. Oxytocin should be infused in small volumes of isotonic fluid (not dextrose), using higher concentrations than recommended for the induction and augmentation of labour at term in non-complicated cases
4. Fluid intake by mouth must be restricted
5. Maternal serum electrolytes should be measured at regular intervals e.g. 8 to 12 hourly

<u>Treatment of Water Intoxication</u>

1. Discontinue oxytocin
2. Restrict fluid intake
3. Promote diuresis
4. Correct electrolyte imbalance
5. Control convulsions, e.g. with judicious use of diazepam
6. If coma is present: maintain a free airway and carry out the routine measures for care of an unconscious patient

Disseminated Intravascular Coagulation

In rare circumstances (i.e. incidence rate < 0.0006), the pharmacological induction of labour using uterotonic agents, including dinoprostone or oxytocin, increases the risk of post-partum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is increased in particular if the woman has other risk factors for DIC such as 35 years of age or over, complications during the pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC (fibrinolysis).

Anaphylaxis in Women with Latex Allergy

There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

Use in the Elderly

Safety and effectiveness in elderly patients have not been established

Special Populations

No studies have been performed in renally-impaired patients and hepatically-impaired patients.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Prostaglandins and their analogues facilitate contraction of the myometrium hence may potentiate the uterotonic effect of oxytocin and vice versa. Very careful monitoring is, therefore, recommended in cases of concomitant administration.

Some inhalation anaesthetics, e.g. cyclopropane, enflurane, halothane, sevoflurane, desflurane or isoflurane, have a relaxing effect on the uterus and produce a notable inhibition of uterine tone and thereby may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

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).

Oxytocin should be given with caution in patients taking drugs that are known to prolong the QTc interval.

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those contained in local 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

Effects on Fertility

There are no studies on the potential effect of oxytocin on fertility

Use in Pregnancy

Pregnancy category: A

Use of oxytocin has contributed significantly to the safety of parturition. However, there have been instances of idiosyncratic sensitivity of the uterus resulting in fetal anoxia.

Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of fetal abnormalities when used as indicated.

Treatment of rats with oxytocin early in pregnancy, in doses approximately three thousand times the dose used to induce labour in humans, caused embryonic fetal loss in one study. No standard embryofetal development studies with oxytocin are available.

Use in Lactation

Endogenous 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

VIATOCINON can induce uterine contractions and, therefore, caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions are ranked 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.

Immune System Disorders

Rare: anaphylactoid reaction associated with dyspnoea, hypotension or shock.

Nervous System Disorders

Common: headache*

Cardiac Disorders

Common: tachycardia, bradycardia

Uncommon: arrhythmia

Gastrointestinal Disorders

Common: nausea, vomiting

Skin and Subcutaneous Tissue Disorders

Rare: rash

* Headaches can be associated with fluid overload (see section 4.4 Special Warnings and Precautions for Use – Water Intoxication).

Post-marketing Experience

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 categorised as 'not

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

Table 1: Adverse Drug Reactions in the Mother

Immune System Disorders
anaphylactic reaction and shock
Cardiac Disorders
myocardial ischaemia, QTc prolongation
Vascular Disorders
hypotension
Pregnancy, Puerperium and Perinatal Disorders
uterine hypertonicity, tetanic contractions, rupture of the uterus
Metabolism and Nutrition Disorders
water intoxication, maternal hyponatraemia
Respiratory, Thoracic and Mediastinal Disorders
acute pulmonary oedema
General Disorders and Administration Site Conditions
flushing
Blood and Lymphatic System Disorders
disseminated intravascular coagulation
Skin and Subcutaneous Tissue Disorders
angioedema

Table 2: Adverse Drug Reactions in the Fetus/Neonate

Pregnancy, Puerperium and Perinatal Disorders
fetal distress, asphyxia and death
Metabolism and Nutrition Disorders
neonatal hyponatraemia

Other adverse events that have been reported include ECG changes following intravenous administration of concentrated solutions, hypertension, neonatal jaundice, neonatal convulsions, oedema, cardiovascular spasm and collapse.

Water intoxication associated with maternal and neonatal hyponatraemia, which is potentially fatal, can result from high doses or prolonged periods of infusion of oxytocin in electrolyte-free fluids. The combined ant diuretic effect of oxytocin and the intravenous fluid administration may also cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia (see section 4.4 Special Warnings and Precautions for Use).

When oxytocin is used by intravenous infusion for the induction or augmentation of labour, its administration at excessive doses results in uterine overstimulation which may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus.

Rapid intravenous bolus injection of oxytocin at doses as little as 2 IU may result in acute short-lasting hypotension accompanied by flushing and reflex tachycardia (see section 4.4 Special Warnings and Precautions for Use). These rapid haemodynamic changes may result in myocardial ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid intravenous bolus injection of oxytocin at these doses may also lead to QTc prolongation.

Amniotic fluid embolism (in association with pre-disposing factors, e.g. tumultuous labour, fetal death-in-utero, meconium-stained amniotic fluid) has been reported.

Increases in post-partum bleeding have been observed rarely in conjunction with oxytocin. This effect probably relates more to abnormality of uterine action rather than to side effects of the drug.

There are rare reports of post-partum disseminated intravascular coagulation following the induction of labour using oxytocin (see section 4.4 Special Warnings and Precautions for Use).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdosage may give rise to the following complications:

- fetal distress (fetal bradycardia, meconium staining of the amniotic fluid, fetal asphyxia)
- uterine hypertonicity, tetanic contraction or rupture
- placental abruption
- amniotic fluid embolism
- water intoxication (see section 4.4 Special Warnings and Precautions for Use)

Treatment

When signs or symptoms of overdosage occur during continuous intravenous administration of VIATOCINON, the infusion must be discontinued at once and oxygen should be given to the mother. In the event of water intoxication, it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance and control possible convulsions by judicious use of diazepam (see section 4.4 Special Warnings and Precautions for Use – Water Intoxication).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

The active substance in VIATOCINON is a synthetic nonapeptide identical to oxytocin, a hormone released by the posterior lobe of the pituitary gland of mammals.

The hormone is prepared synthetically to avoid possible contamination with vasopressin (ADH) and other small polypeptides with biologic activity.

Oxytocin stimulates the smooth muscle of the uterus, producing rhythmic contractions, particularly towards the end of pregnancy, during labour, after delivery and in the puerperium, that is, at times when the number of specific oxytocins receptors in the myometrium is increased. When given by low-dose intravenous infusion, oxytocin injection elicits rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour. At higher infusion doses, or when given by a single injection, the drug is capable of causing sustained tetanic uterine contractions. Upon discontinuation of the infusion or following a substantial reduction in the infusion rate (e.g. in the event of over stimulation), uterine activity declines rapidly but may continue at an adequate lower level.

Oxytocin also causes contraction of the myo-epithelial cells surrounding the mammary alveoli. It therefore facilitates lactation in women experiencing difficulty in breast feeding. Synthetic oxytocin has only very slight pressor and anti-diuretic activity due to the absence of vasopressin.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid intravenous bolus injection, has a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia (see section 4.4 Special Warnings and Precautions for Use).

Oxytocin, being a polypeptide, is largely inactivated in the alimentary tract and is therefore virtually ineffective when ingested.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Intravenous Infusion

When oxytocin is given by continuous intravenous infusion at doses appropriate for induction or augmentation 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 an intravenous infusion at a rate of 4 milliunits/min, were 2 to 5 microunits/mL.

Intravenous Injection and Intramuscular Injection

When administered by intravenous or intramuscular injection for prevention or treatment of post-partum haemorrhage, oxytocin acts rapidly, with a latency period of less than 1 minute by intravenous injection and of 2 to 4 minutes by intramuscular injection. The oxytocic response lasts for 30 to 60 minutes after intramuscular administration and possibly less after intravenous injection.

Distribution

Oxytocin distributes throughout the extracellular fluid, with minimal amounts reaching the fetus. The steady-state distribution volume determined in 6 healthy men after intravenous injection was 12.2 L or 0.17 L/kg. Plasma protein binding is very low. Oxytocin may be found in small quantities in mother's breast milk.

Metabolism

A glycoprotein aminopeptidase, oxytocinase, is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. Enzyme activity increases gradually until term approaches, at which time it rises steeply to high levels. Enzyme activity then declines after delivery. Enzyme activity in the placenta and in the uterine tissue is also high during this period. There is little or no degradation of oxytocin by plasma in men, non-pregnant women or cord blood.

Excretion

The relative ease with which the rate and force of uterine contractions can be regulated by the intravenous infusion of oxytocin is due to the short half-life of oxytocin. Values reported by various investigators range from 3 to 20 minutes. Removal of oxytocin from plasma is accomplished mainly by the liver and the kidneys. The metabolic clearance rate amounts to about 20 mL/kg/min in men as well as in pregnant women. Less than 1% of a given dose is excreted unchanged in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Oxytocin has no genotoxic properties.

Carcinogenicity

No carcinogenicity studies with oxytocin are available. Oxytocin did not induce chromosomal aberration and sister chromatid exchange in human peripheral lymphocytes *in vitro.*

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The ampoules also contain the following inactive ingredients: sodium acetate trihydrate, glacial acetic acid, sodium hydroxide and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C. Refrigerate. Protect from Light.

Once removed from fridge the ampoules may be stored below 25°C for up to **4 weeks only**, provided that the product is used **BEFORE PRINTED EXPIRY DATE**. Thereafter discard ampoules.

Keep out of the reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: ampoule (1 mL clear glass)

Pack size: 5, 10

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

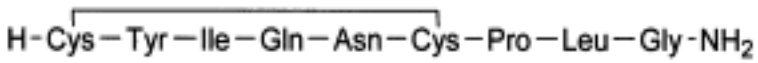
AUST R 164608– VIATOCINON oxytocin 5 IU/1 mL injection ampoule
AUST R 164131– VIATOCINON oxytocin 10 IU/1 mL injection ampoule

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



CAS Number

50-56-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11/03/2011

10 DATE OF REVISION

24/11/2021

Summary Table of Changes

Section Changed	Summary of New Information
2 & 7	Minor editorial changes.
6.1	Update excipients to include sodium hydroxide.
6.5	Updated to include ARTG information.
8	Update sponsor details.

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