New Zealand Data Sheet

1 PRODUCT NAME

OXYTOCIN INJECTION BP 5 IU/mL solution for injection
OXYTOCIN INJECTION BP 10 IU/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin Injection BP 5 IU/mL solution for injection
1 mL ampoule contains 5 IU oxytocin (equivalent to 8.3 mcg/mL)

Oxytocin Injection BP 10 IU/mL solution for injection
1 mL ampoule contains 10 IU oxytocin (equivalent to 16.6 mcg/mL)

Excipient(s) with known effect:
Oxytocin Injection BP contains sodium but less than 1 mmol (23 mg) sodium per ampoule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oxytocin Injection BP is a clear and colourless solution for injection containing oxytocin and is packaged in a clear colourless glass ampoule.

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).
- Enhancement of labour in selected cases of uterine inertia.
- Oxytocin Injection BP may also be indicated in early stage of pregnancy, as adjunctive therapy for management of incomplete, inevitable or missed abortion.

Postpartum

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

4.2 Dose and method of administration

Oxytocin Injection BP is administered via intramuscular (i.m.) or intravenous (i.v.) injection, or as an i.v. infusion, in accordance with the instructions below.

Dose

Induction or enhancement of labour
Oxytocin Injection BP should be administered as an 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 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 (see section 4.4 Special warnings and precautions for use). 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 1 to 4 milliunits/minute (2 to 8 drops/minute). It may be increased gradually 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 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event of higher rates being 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 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 and also the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, 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 should be terminated; 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) or 5 to 10 IU i.m., 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.

Prevention of postpartum uterine haemorrhage
The usual dose is 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) or 5 to 10 IU i.m. after delivery of the placenta.

In women given Oxytocin Injection BP 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 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), or 5 to 10 IU i.m., followed in severe cases by intravenous infusion of a solution containing 5 to 20 IU of oxytocin in 500 mL of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

4.3 Contraindications

Known hypersensitivity to oxytocin or to any of the excipients of Oxytocin Injection BP.

Hypertonic uterine contractions, foetal distress when delivery is not imminent.

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 (e.g. breech presentation); placenta praevia and vasa praevia, placental abruption, umbilical cord entanglement or prolapse; overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy, polyhydramnios, grand multiparity and in the presence of a uterine scar resulting from major surgery including classical Caesarean section.

Any of the following conditions:
- Tendency of the uterus to pass into tetanic contractions (sustained uterine contractions);
- Immature cervix;
- Imminent foetal asphyxia (acute, severe oxygen deficiency in the newborn following inadequate oxygen intake);
- Uterine hyperactivity (increased) should be avoided in the event of foetal death *in utero* and in the presence of meconium-stained amniotic fluid given the risk of amniotic fluid embolism.

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

4.4 Special warnings and precautions for use

Induction of labour:
The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons, rather than for convenience. Administration should only be under hospital conditions and qualified medical supervision.

Oxytocin Injection BP 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 should not be given as i.v. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

When Oxytocin Injection BP is given for induction and enhancement of labour:

- It must only be administered as an i.v. infusion, and never by s.c., i.m. or i.v. bolus injection.

- **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 the pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative medicine should be used with care, and the practitioner should be alerted by signs of DIC.

Cardiovascular disorders:
Oxytocin Injection BP 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.

QT syndrome:
Oxytocin Injection BP should be given with caution to patients with known 'long QT syndrome' or related symptoms, and to patients taking medicines that are known to prolong the QTc interval. See section 4.5 Interaction with other medicines and other forms of interaction.

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.

The limit of 16 milliunits/minute should only be briefly exceeded as the possibility of hyperbilirubinaemia (excess serum levels of bilirubin) in the child cannot be ruled out with any certainty following long-term administration of high dose levels. Furthermore, retinal haemorrhage has been reported in newborn infants following hyperactive uterine activity.

Renal impairment:
No studies have been performed in renally impaired patients. Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin. See section 5.2 Pharmacokinetic properties: renal impairment.

Hepatic impairment:
No studies have been performed in hepatically impaired patients. See section 5.2 Pharmacokinetic properties: hepatic impairment.

Geriatric patients:
No studies have been performed in elderly patients (65 years old and over).

Paediatric population:
No studies have been performed in paediatric patients. See section 4.3 Contraindications and section 4.4: Special warnings and precautions for use: water intoxication.

4.5 Interaction with other medicines and other forms of interaction

Interactions resulting in a concomitant use is not recommended

Prostaglandins and their analogues:
Prostaglandins and their analogues facilitate contraction of the myometrium (layer of muscle in uterine wall), hence, oxytocin can potentiate the uterine action of prostaglandins, their analogues and vice versa (see section 4.3 Contraindications).. Since this synergistic effect is unpredictable and cannot be controlled, the concomitant administration of oxytocin and prostaglandins should be avoided. It is recommended that an interval of at least six hours be allowed between prostaglandin administration and subsequent oxytocin administration.

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 (see section 4.4 Special warnings and precautions for use). Oxytocin should be given with caution in patients taking medicines that are known to prolong the QTc interval.

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 uteronic effect of oxytocin. They 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.

Vasoconstrictors/sympathomimetrics:
Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetrics, even those contained in local anaesthetics. When taken simultaneously, sympathomimetic medicines that increase blood pressure and oxytocin can cause prolonged arterial hypertension (extended rise of blood pressure). Patients receiving antihypertensive medication should be closely monitored as the effect of this substance can be enhanced during oxytocin administration.

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

Other:
The uterus-contracting effect of oxytocin is potentiated by methylergometrin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Preclinical data for oxytocin reveal no special hazard based on conventional studies of single dose acute toxicity, genotoxicity and mutagenicity. No standard teratogenicity and reproductive performance studies with oxytocin are available (see section 5.3 Preclinical safety data). Based on the wide experience with this medicine and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

Breastfeeding

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.

Fertility

No standard reproductive performance studies with oxytocin are available. See section 5.3 Preclinical safety data: Carcinogenicity, teratogenicity and reproduction toxicity section.

4.7 Effects on ability to drive and use machines

Oxytocin Injection BP can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

When oxytocin is used by i.v. infusion for the induction or enhancement of labour, its administration 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.

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 (see section 4.4 Special warnings and precautions for use). 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.

In rare circumstances (i.e. incidence rate < 0.0006), the pharmacological induction of labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and precautions for use).

Water intoxication
Water intoxication associated with maternal and neonatal hyponatraemia 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 (see section 4.4 Special warnings and precautions for use).

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 (see section 4.4 Special warnings and precautions for use).

b. Tabulated summary of adverse reactions

The following adverse drug reactions have been reported with oxytocin regardless of the mode of administration:

Adverse reactions (*Table 1* and *2*) 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. The adverse drug 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 categorised as unknown. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in mother

Immune system disorders	
Rare:	Anaphylactic/Anaphylactoid reaction associated with dyspnoea, hypotension or shock
Nervous system disorders	
Common:	Headache (especially at high doses)
Cardiac disorders	
Common:	Tachycardia, bradycardia
Uncommon:	Arrhythmia (at high doses)
Not known:	Myocardial ischaemia, QTc prolongation
Vascular disorders	
Not known	Hypotension following rapid intravenous injection (during the postpartum period)
Gastrointestinal disorders	
Common:	Nausea, vomiting (especially at high doses)
Skin and subcutaneous tissue disorders	
Rare:	Rash
Not known:	Angioedema
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 administrative site conditions	
Not known:	Flushing
Blood and lymphatic system disorders	
Not known:	Disseminated intravascular coagulation
Renal and urinary disorders	
Very rare:	Decreased urination, water intoxication with reduced blood serum sodium levels (hyponatraemia) in the mother and the child (especially with i.v. infusion). These can lead to cerebral oedema, seizures and coma. These symptoms occur mainly when oxytocin is administered intravenously at very high dose levels with a large fluid intake for a prolonged period. Hyponatraemia can be avoided if an electrolyte solution is used for infusion.

Table 2 Adverse drug reactions in foetus/neonate

Pregnancy, puerperium and perinatal conditions	
Not known:	Foetal distress, asphyxia and death
Metabolism and nutrition disorders	
Not known	Neonatal hyponatraemia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

The **symptoms and consequences of overdose** are those mentioned in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects above. In addition, placental abruption and/or amniotic fluid embolism as a result of uterine overstimulation have been reported.

Treatment
When signs or symptoms of overdose occur during continuous i.v. administration of Oxytocin Injection BP, 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 dieresis, correct electrolyte imbalance; and control possible convulsions.

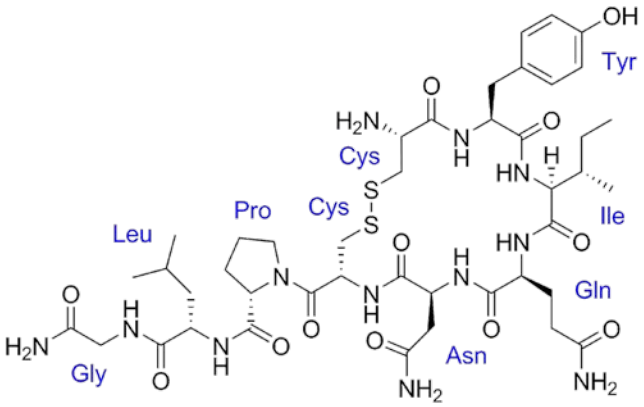
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones
ATC code: H01B B02 Oxytocin

Chemical structure:



Molecular formula: $C_{43}H_{66}N_{12}O_{12}S_2$
Relative molecular mass: 1007.19
CAS number: 50-56-6

Oxytocin is L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide. It occurs as white or almost white hygroscopic powder. It is very soluble in water. It dissolves in dilute solutions of acetic acid and of ethanol (96%).

Mechanism of action

The active substance of Oxytocin Injection BP 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-protein coupled receptors. Activation of receptor by oxytocin triggers release of calcium from intracellular stores and thus leads to myometrial contraction. See below pharmacodynamic effects section.

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.

Pharmacodynamic effects

When given by low-dose i.v. infusion, Oxytocin Injection BP elicits rhythmic uterine contractions in the upper segment of uterus, similar in frequency, force and duration to those observed during labour. At higher infusion dosages, or when given by single injection, the medicine is capable of causing sustained tetanic uterine contractions.

In addition to its effects on the uterus, oxytocin contracts the myoepithelial cells surrounding the mammary alveoli, thereby causing milk ejection and facilitating breast-feeding.

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

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid i.v. bolus injection, is 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).

5.2 Pharmacokinetic properties

Absorption

Oxytocin is rapidly absorbed from the i.m. site. Plasma levels of oxytocin following intravenous infusion at 4 milliunits per minute in pregnant women at term were 2 to 5 microunits/mL.

Plasma levels and onset/duration of effect:

Intravenous infusion. When Oxytocin Injection BP 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.

Intravenous injection and intramuscular injection. When administered by i.v. or i.m. injection for prevention or treatment of postpartum haemorrhage, Oxytocin Injection BP acts rapidly with a latency period of less than 1 minute by i.v. injection, and of 2 to 4 minutes by i.m. injection. The oxytocic response lasts for 30 to 60 minutes after i.m. administration, possibly less after i.v. injection.

Oxytocin is not active orally.

Distribution

Oxytocin distributes throughout the extracellular fluid, with minimal amounts reaching the foetus. 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.

Biotransformation/Metabolism

Oxytocinase is a glycoprotein aminopeptidase produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. It is produced from both the mother and the foetus. 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.

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. There is little or no degradation of oxytocin by plasma from men, non-pregnant women, or cord blood.

Elimination

The relative ease with which the rate and force of uterine contractions can be regulated by the i.v. infusion of Oxytocin Injection BP is due to the short half-life of oxytocin. The plasma half life of oxytocin ranges from 3 to 20 minutes. Removal of oxytocin from plasma is accomplished mainly by the liver and the kidneys. The metabolites are excreted in urine whereas less than 1% of the oxytocin is excreted unchanged in urine. 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.

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 the metabolising enzyme, oxytocinase, is not confined to the liver alone. The oxytocinase levels in the placenta during the term is 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

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

Effects (foetal loss in rats) in one pre-clinical study were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Acute toxicity:
Single dose toxicity studies with oxytocin in rats and mice have been conducted by the oral, intravenous and subcutaneous application routes. Acute oral (and subcutaneous) toxicity was 20.5 mg/kg bodyweight in rats and exceeded 514 mg/kg bodyweight in mice. By the intravenous route, the lethal oxytocin dose amounted to 2.3 mg/kg bodyweight in rats and to 5.8 mg/kg bodyweight in mice. Thus, the intravenous lethal oxytocin dose in mice exceeds the usual intravenous dose in humans by a factor of greater than one thousand.

Mutagenicity:
An *in vitro* genotoxicity and mutagenicity study with oxytocin has been reported. Tests were negative for chromosomal aberration and sister chromatid exchange in human peripheral lymphocyte cultures. No significant changes in the mitotic index were noticed. Oxytocin had no genotoxic properties. The genotoxic potential of oxytocin has not been determined *in vivo*.

Carcinogenicity, teratogenicity and reproduction toxicity:
Treatment of rats with oxytocin early in pregnancy at doses considered sufficiently in excess of the maximum recommended human dose caused embryonic loss in one study. No standard teratogenicity, reproductive performance and carcinogenicity studies with oxytocin are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Acetic acid, glacial
Sodium acetate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Oxytocin Injection BP must not be mixed with other medicinal products.

6.3 Shelf life

The shelf life of Oxytocin Injection BP is 36 months from date of manufacture.

From a microbiological point of view, the ready-to-use preparation should be used immediately or stored at 2 to 8°C for not more than 24 hours. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store Oxytocin Injection BP between 2°C and 8°C.

Oxytocin Injection BP can be stored temporarily at 25°C (e.g. in the delivery room) for 6 months. After this time Oxytocin Injection BP must be discarded and not returned to the refrigerator.

6.5 Nature and contents of container

Oxytocin Injection BP 5 IU/mL solution for injection is available in 5 x 1 mL clear glass ampoules per pack.

Oxytocin Injection BP 10 IU/mL solution for injection is available in 5 x 1 mL clear glass ampoules per pack.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

06 June 2013

10 DATE OF REVISION OF TEXT

28 January 2019

Summary table of changes

Section changed	Summary of new information
All	Reformatting of text to new Data Sheet SPC format. Relocation or addition of text under new headings and subheadings in line with the new Data Sheet format. Minor editorial changes.
4.2	Addition of dosage instruction. Relocation of text.
4.3, 4.6, 5.1, 5.3	Addition of new safety information.
4.4, 4.5, 4.8, 5.2	Addition of subheadings and new safety information. Relocation of text under new subheading where relevant.