

OXYTOCIN APOTEX

1. OXYTOCIN APOTEX (5 IU/mL & 10 IU/mL Injection)

OXYTOCIN APOTEX Oxytocin Injection 5 IU/ml
 OXYTOCIN APOTEX Oxytocin Injection 10 IU/ml

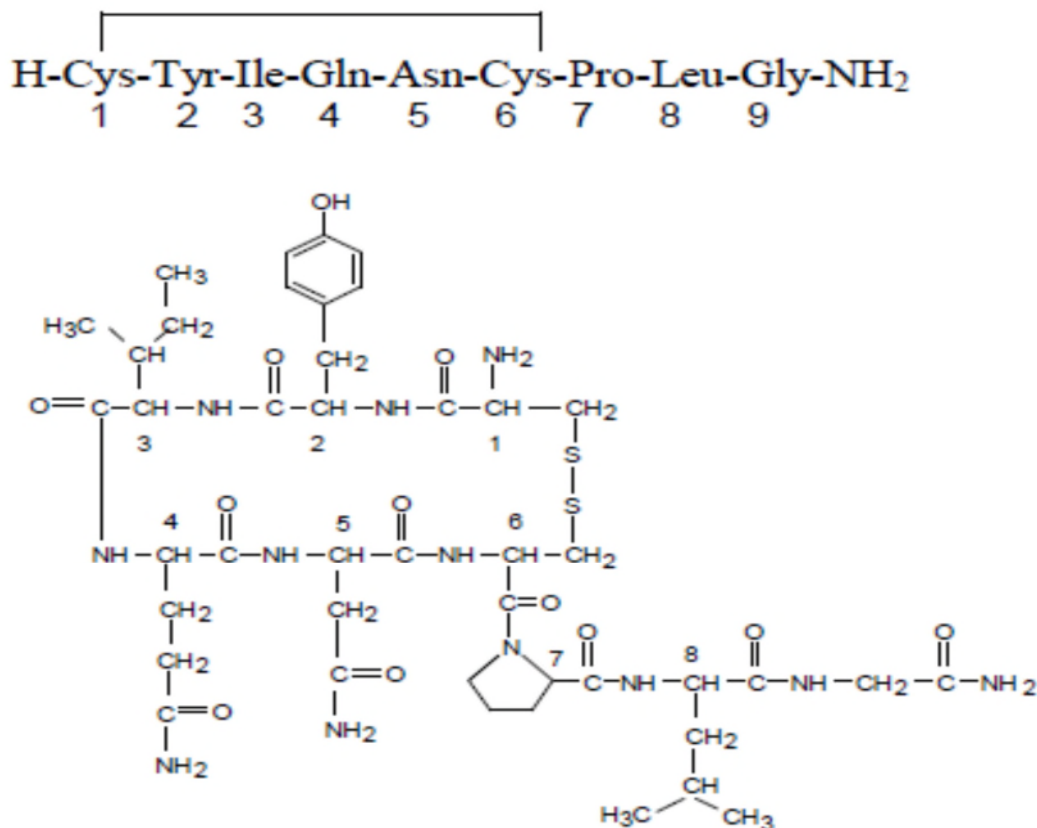
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin Injection 5 IU/ml and 10 IU/ml

Chemical Name: L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1 → 6) disulphide

Oxytocin is a white or almost white fluffy powder hygroscopic. Its molecular formula is $C_{43}H_{66}N_{12}O_{12}S_2$ which corresponds to a molecular weight of 1007.20.

Chemical Structure:





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Excipient(s) of known effect

Oxytocin APOTEX does not contain Glucose and lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for Injection. A colourless solution contained in transparent 1 mL glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antepartum:

- Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia).
- Enhancement of labour in selected cases of uterine inertia.
- Oxytocin 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

Induction or enhancement of labour

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 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 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 solution, e.g. 10 IU in 500 mL.



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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 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 APO-Oxytocin.
- Hypertonic uterine contractions, foetal distress when delivery is not imminent.
- Any condition in which, for foetal or maternal reasons, spontaneous labour is unadvisable 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 and in

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the presence of a uterine scar resulting from major surgery including classical caesarean section.

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

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

Cardiovascular disorders:

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.

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 4.5 *Interaction with other medicines and other forms of interaction*).

When Oxytocin 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 post-partum disseminated intravascular coagulation (DIC). The

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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 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 hemodynamic 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.

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 patients:

No studies have been performed in paediatric patients.

Geriatric patients:

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



4.5 Interaction with other medicines 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 (see 4.3 *Contraindications*).

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 4.4 *Special warnings and precautions for use*).

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.

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 Fertility, pregnancy and lactation

Use in Pregnancy:

Pre-clinical 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 4.4 *Special warnings and precautions for use*). 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.

Use in Lactation:

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.

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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 uterine contractions should not drive or use machines.

4.8 Undesirable effects

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 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 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 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 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 hemodynamic form of acute pulmonary oedema without hyponatraemia (see 4.4 *Special Warnings and precautions for use*).

The following adverse drug reactions have been reported 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 ($\geq 1/10$); common ($\geq 1/100$, < 1/10); uncommon ($\geq 1/1,000$, < 1/100); rare ($\geq 1/10,000$, < 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.

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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
Cardiac disorders	
Common:	Tachycardia, bradycardia
Uncommon:	Arrhythmia
Not known:	Myocardial ischaemia, QTc prolongation
Vascular disorders	
Not known:	Hypotension
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 administrative site conditions	
Not known:	Flushing
Blood and lymphatic system disorders	
Not known:	Disseminated intravascular coagulation
Skin and subcutaneous tissue disorders	
Not known:	Angioedema

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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 under 4.4 *Special warnings and precautions* and 4.8 *Undesirable effects*. 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, 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.

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group:

Posterior pituitary lobe hormones (ATC code H01B B02)

5.1 Pharmacodynamic Properties

Mechanism of action and Pharmacodynamics

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 Oxytocin does not



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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 desensitization of oxytocin receptors probably due to down-regulation of oxytocin-binding sites, destabilization of oxytocin receptors mRNA and internalization 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.

Intravenous injection and intramuscular injection. When administered by i.v. or i.m. injection for prevention or treatment of postpartum haemorrhage, Oxytocin 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.

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.

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 metabolizing 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 min. 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.



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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 metabolizing 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 (see 4.4 *Special warnings and precautions for use*).

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.

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 in early 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

Chlorobutanol Hemihydrate, Acetic Acid, Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life: 15 months from the date of manufacture.



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6.4 Special precautions for storage

Store below 25⁰ C. Protect from light. Do not freeze.

6.5 Nature and contents of container

Type I hydrolytic resistant class colourless borosilicate glass ampoules.

5 ampoules containing 1 mL of injection solution are packed in polyvinylchloride film liners.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
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9. DATE OF FIRST APPROVAL

11 April 2018

10. DATE OF REVISION OF THE TEXT

16 April 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
1, and 2	Name change from Apo-Oxytocin to Oxytocin APOTEX