PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OXYJECT solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 10 IU/ml oxytocin.

Excipients with known effect:

Each vial contains 1 mg of sodium acetate as buffering agent.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

OXYJECT is a clear colourless solution.

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 membrane, pregnancy-induced hypertension (pre-eclampsia).
- Enhancement of labour in selected cases of uterine inertia.
- Early stage of pregnancy, as adjunctive therapy for the management of incomplete, inevitable or missed abortion.

Postpartum:

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

4.2 Posology and method of administration

Posology

Induction or enhancement of labour:

OXYJECT should be administered as an intravenous (IV) drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of OXYJECT be added to 500 ml of a physiological electrolyte solution (such as sodium chloride 0,9 %). For patients in who infusion of sodium chloride must be avoided, 5 % dextrose solution may be used as the diluent (see section 4.4).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 (0,1 to 0,4 ml/min or 2 to 8 drops/minute). It may be gradually increased at intervals not shorter than 20 minutes 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 (1 ml/minute or 20 drops/minute), and the recommended maximum rate is 20 milliunits/min (2 ml/minute or 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 OXYJECT 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 OXYJECT infusion must be discontinued immediately.

If, in women who are at term or near term, regular contraction are not established after the infusion of a total amount of 5 IU OXYJECT, 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 milli units/minute (0,1 to 0,4 ml/minute or 2 to 8 drops/minute) (see section 4.3).

Note: Inadvertent paravenous infusion of OXYJECT is not harmful.

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 of the foetus.

Prevention of postpartum uterine haemorrhage:

The usual dose is 5 IU by intravenously 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 intramuscular after delivery of the placenta. In women given OXYJECT for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labourand for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage:

5 IU by 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 OXYJECT in 500 ml of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

Incomplete, inevitable, or missed abortion:

5 IU by intravenous infusion (5 IU diluted in physiological electrolyte solution and administered as an I.V. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes). If necessary followed by intravenous infusion at a rate of 20 to 40 milliunits/minute or higher.

Method of administration

OXYJECT is administered by intravenous infusion.

4.3 Contraindications

OXYJECT is contraindicated in patients with a known hypersensitivity to the active substance, oxytocin, or to any of the excipients listed in section 6.1.

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

Any conditions in which, for foetal or maternal reasons, spontaneous labour is unadvisable and/or vaginal delivery is contraindicated:

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

OXYJECT should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.
OXYJECT must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5).

4.4 Special warnings and precautions for use

OXYJECT should not be given as I.V. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

Induction of labour

The induction of labour by means of OXYJECT should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Cardiovascular disorders

OXYJECT 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.
Infusion volume should be low in patients with cardiovascular disorders.

QT syndrome

OXYJECT 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).

When OXYJECT is given for induction and enhancement of labour:

- It must only be administered as an intravenous infusion, and never by subcutaneous, intramuscular or intravenous bolus injection.
- Foetal distress and foetal death: Administration of OXYJECT 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: The pharmacological induction of labour using uterotonic medicines, including OXYJECT increases the risk of postpartum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular medicine 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, OXYJECT 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

OXYJECT possesses slight anti-diuretic activity, its prolonged intravenous 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 OXYJECT and the I.V. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia.

To avoid these complications, the following precautions must be observed whenever high doses of OXYJECT 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.

Renal impairment

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin (see section 5.2).

Anaphylaxis in women with latex allergy

There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Due to the existing structural homology between oxytocin and latex, latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

OXYJECT should not be given parenterally at the same time as other oxytocics.

4.5 Interaction with other medicines and other forms of interaction

Interaction resulting in a concomitant use not recommended.

Prostaglandins and their analogues

Prostaglandins and its analogues facilitate contraction of the myometrium hence oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see section 4.3). Therefore, concomitant administration requires careful monitoring.

Medicines prolonging the QT interval

Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for Torsades de Pointes such as medicines which prolong the QT interval or in patients with history of long QT syndrome (see section 4.4). OXYJECT should be givent 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 uterotonic effect of OXYJECT and enhance the hypotensive effect of OXYJECT. Their concurrent use with OXYJECT has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors/Sympathomimetics

OXYJECT 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

Pregnancy

Based on extensive experience with oxytocin, its chemical structure and pharmacological properties, it is unlikely 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, it is unlikely to cause harmful effects in the newborn because it is inactivated in the alimentary tract.

Fertility

Not applicable for OXYJECT because of the targeted indications.

4.7 Effects on ability to drive and use machines

OXYJECT 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

Summary of the safety profile

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by I.V. infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Rapid intravenous bolus injection of OXYJECT at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see section 4.4). These rapid haemodynamic changes may result in myocardial ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid I.V. bolus injection of OXYJECT at doses amounting to several IU may also lead to QTc prolongation.

The pharmacological induction of labour using uterotonic medicines, including OXYJECT increases the risk of postpartum disseminated intravascular coagulation (i.e. absolute risk attributable to induction is 6 in 10 000) (see section 4.4).

Water intoxication

Prolonged or too rapid infusion of OXYJECT has an antidiuretic effect, which may cause transient water intoxication.

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of OXYJECT have been administered together with large amounts of electrolyte -free fluid over a prolonged period of time (see section 4.4).

The combined antidiuretic effect of OXYJECT 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).

Symptoms of water intoxication include:

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

Tabulated list of adverse reactions

With either mode of administration OXYJECT may cause the following undesirable effects in mothers:

Blood and lymphatic system disorders:

Frequency unknown: Disseminated intravascular coagulation.

Immune system disorders:

Less frequent: Anaphylactic/ Anaphylactoid reaction associated with dyspnoea, hypotension or Anaphylactic/ Anaphylactoid shock.

Metabolism and nutrition disorders:

Frequency unknown: Water intoxication, maternal hyponatraemia.

Nervous system disorders:

Frequent: Headache.

Cardiac disorders:

Frequent: Tachycardia, bradycardia.

Less frequent: Dysrhythmia.

Frequency unknown: Myocardial ischaemia, Electrocardiogram QTc Prolongation.

Vascular disorders:

Frequent: Hypotension.

Frequency unknown: Haemorrhage.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Acute pulmonary oedema.

Gastrointestinal disorders:

Frequent: Nausea, vomiting.

Skin and subcutaneous tissue disorders:

Less frequent: Rash.

Frequency unknown: Angioedema.

Pregnancy, puerperium and perinatal conditions:

Frequency unknown: Uterine hypertonus, hypertonicity, tetanic contractions of uterus, rupture of the uterus.

General disorders and administration site conditions:

Frequent: Flushing.

Adverse reactions in the foetus / neonate:

Metabolism and nutrition disorders:

Frequency unknown: Neonatal hyponatraemia.

Pregnancy, puerperium and perinatal conditions:

Frequency unknown: Foetal distress syndrome, asphyxia and death.

Pelvic haematomas, neonatal jaundice and retinal haemorrhage may be associated with the use of OXYJECT

Maternal death from severe hypertension and subarachnoid haemorrhage may occur.

Pospartum haemorrhage and fatal afibrinogenaemia may occur and may be due to obstetric complications.

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 to SAHPRA via the "*6.04 Adverse Drug Reaction Reporting Form*", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The fatal dose of OXYJECT has not been established. OXYJECT is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under sections 4.4 and 4.8. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Overdosage following prolonged or too rapid infusion, may give rise to the following complications: foetal distress (bradycardia and dysrhythmias, meconium staining of amniotic fluid, foetal asphyxia).

Uterine hypertonicity, tetanic contraction, uterine rupture, extensive laceration of soft tissue, subarachnoid haemorrhage, severe hvootension. water retention and intoxication with convulsions, coma and even foetal and maternal death.

Treatment:

When signs or symptoms of overdosage occur during continuous I.V. administration of OXYJECT, 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 that may eventually occur by judicious use of diazepam. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 19 Oxytocics

Pharmacotherapeutic group: Posterior pituitary lobe hormones.

ATC Code: H01B B02.

Mechanism of action

Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis.

This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labour.

Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased.

The oxytocin receptors are G-proteins coupled receptors. Activation of receptor by oxytocin triggers release of calcium from intracellular stores and thus leads to myometrial contraction.

Oxytocin elicits rhythmic contractions in upper segment of uterus, similar in frequency, force and duration to those observed during labour.

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

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.

At higher infusion dosages, or when given by single injection, this medicine is capable of causing sustained tetanic contractions.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid intravenous bolus injection, is a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia.

5.2 Pharmacokinetic properties

Plasma levels and onset/duration of effect

Intravenous infusion:

When OXYJECT is given by continuous intravenous 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 60 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 intravenous or intramuscular injection
for prevention or treatment of postpartum haemorrhage, OXYJECT acts rapidly with a latency period of less than 1 minute by intravenous injection, and of 3 to 7 minutes by intramuscular injection. The oxytocic response lasts for 30 to 60 minutes after intramuscular administration; possibly less after intravenous injection.

Absorption

Plasma levels of oxytocin following intravenous infusion at 4 milliunits per minute in pregnant women at term were 2 to 5 microunits/ml.

Distribution

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 in healthy males. Plasma protein binding is very low. Oxytocin may be found in small quantities in mother's breastmilk.

Biotransformation

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. Enzyme activity increase 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 for men, non-pregnant women, or cord blood.

Liver and kidney play a major role in metabolising and clearing oxytocin from the plasma. Thus, liver, kidney and systemic circulation contribute to the biotransformation of oxytocin.

Elimination

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. 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.

Renal impairment

No studies have been performed in renally impaired patients. However, considering the excretion of oxytocin and its reduced urinary excretion because of anti-diuretic properties, the possible accumulation of oxytocin can result in prolonged action.

Hepatic impairment

No studies have been performed in hepatically impaired patients. Pharmacokinetic alteration in patients with impaired hepatic function is unlikely since metabolising enzyme, oxytocinase,

is not confined to liver alone and the oxytocinase levels in placenta during the term has significantly increased. Therefore, biotransformation of oxytocin in impaired hepatic function may not result in substantial changes in metabolic clearance of oxytocin.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid

Sodium acetate

Water for injection

6.2 Incompatibilities

OXYJECT should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin- inactivating enzymes. OXYJECT is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator between 2 ˚C – 8 ˚C, do not freeze.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

OXYJECT solution for injection is packed as 10 x 1 ml Type 1 borosilicate glass, clear ampoule packed in a clear PVC pocket ampoule. The pocket of 10 ampoules are packed in an outer carton.

6.6 Special precautions for disposal and other handling

Snap ampoules: no file required.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

52/19/0903.902

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT

To be allocated.