FINAL PROPOSED CLEAN PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Oxytocin 10 IU/ml Cospharm

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule (Concentrate for solution for infusion, solution for injection).

Contains: Oxytocin 10 IU

Ethanol 96 % 0,48 % w/v

Sodium 0,10 % w/v

Preservative: Chlorobutanol 0,5 % w/v.

For a full list of excipients, see section 6.1.

Sugar free.

3 PHARMACEUTICAL FORM

A clear, colourless solution, free from visible particulate.

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 10 IU/ml Cospharm may also be indicated in 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

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 %). If a 5 IU ampoule is not available, it is recommended that 10 IU of Oxytocin be added to 1000 ml of physiological electrolyte solution (such as sodium chloride 0,9 %), to achieve the initial recommended dose of 5 IU/ml.

For patients in whom infusion of sodium chloride must be avoided; 5 % dextrose solution may be used as the diluent.

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 than10 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 Oxytocin 10 IU/ml Cospharm 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 Oxytocin 10 IU/ml Cospharm 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 Oxytocin 10 IU/ml Cospharm, 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 (0,1 to 0,4 ml/minute or 2 to 8 drops/ minute).

Note: Inadvertent paravenous infusion of Oxytocin 10 IU/ml Cospharm is not harmful.

Caesarian 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 hemorrhage:

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 Oxytocin 10 IU/ml Cospharm 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 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 10 IU/ml Cospharm 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 I U 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

Oxytocin 10 IU/ml Cospharm should be administered as an intravenous drip infusion or, preferably, by means of a variable-speed infusion pump.

4.3 Contraindications

- Patients with a known hypersensitivity to oxytocin or to any of the excipients listed in section 6.1.
- Hypertonic uterine contractions, 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 contra-indicated: 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 the presence of a uterine scar resulting from major surgery, including classical caesarean section.
- Oxytocin 10 IU/ml Cospharm should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.
- Oxytocin 10 IU/ml Cospharm must not be administered within 6 hours after vaginal prostaglandins have been given.

4.4 Special warnings and precautions for use

The induction of labour by means of Oxytocin 10 IU/ml Cospharm 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 10 IU/ml Cospharm should not be given as i.v. bolus injection as it may cause an acute short-

lasting hypotension accompanied with flushing and reflex tachycardia.

Oxytocin 10 IU/ml Cospharm 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 ischemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

Oxytocin 10 IU/ml Cospharm 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.

When Oxytocin 10 IU/ml Cospharm 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.
- Administration of Oxytocin 10 IU/ml Cospharm 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.
- The pharmacological induction of labour using Oxytocin 10 IU/ml Cospharm increases the risk of post-partum 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, Oxytocin 10 IU/ml Cospharm should be used with care, and the practitioner should be alerted by signs of DIC.

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 10 IU/ml Cospharm 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.

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 10 IU/ml Cospharm administration.

This medicine contains 0,0061 ml of alcohol (ethanol) per ampoule, which is equivalent to 0,48 % w/v. The amount of alcohol in this medicine is not likely to have an effect in adults. The alcohol in this medicine may alter the effects of other medicines.

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 10 IU/ml Cospharm can potentiate the uterine action of prostaglandins and analogues and vice versa.

Medicines prolonging the QT interval

Oxytocin 10 IU/ml Cospharm should be considered as potentially dysrhythmogenic, 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.

Interactions to be considered

Inhalation anaesthetics

Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) may enhance the hypotensive effects of Oxytocin 10 IU/ml Cospharm and reduce its oxytocic action. Inhalation, anaesthetics have a relaxing effect on the uterus and produce a notable inhibition of uterine tone and thereby, may diminish the uterotonic effect of Oxytocin 10 IU/ml Cospharm. Their concurrent use with Oxytocin 10 IU/ml Cospharm has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors / Sympathomimetics

Oxytocin 10 IU/ml Cospharm 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 10 IU/ml Cospharm may potentiate the pressor effect of sympathomimetic vasoconstrictor medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

Based on extensive experience with oxytocin's chemical structure and pharmacological properties, it is unlikely to present a risk of foetal abnormalities when used as indicated.

Breastfeeding

Oxytocin 10 IU/ml Cospharm may be found in small quantities in mothers 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 Oxytocin 10 IU/ml Cospharm because of the targeted indications.

4.7 Effects on ability to drive and use machines

Oxytocin 10 IU/ml Cospharm 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

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 10 IU/ml Cospharm 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 i.v. bolus injection of Oxytocin 10 IU/ml Cospharm 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 Oxytocin 10 IU/ml Cospharm at doses amounting to several IU may also lead to QTc prolongation.

In circumstances the pharmacological induction of labour using uterotonic medicines, including Oxytocin 10 IU/ml Cospharm, increases the risk of postpartum disseminated intravascular coagulation.

Water intoxication

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of Oxytocin 10 IU/ml.

Cospharm together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time.

The combined antidiuretic effect of Oxytocin 10 IU/ml Cospharm and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute ulmonary oedema without hyponatraemia

Symptoms of water intoxication include:

- Headache, anorexia, nausea, vomiting and abdominal pain.

- Lethargy, drowsiness, unconsciousness and grand-mal type seizures.
- Low blood electrolyte concentration.

The ADRs tabulated below are based on clinical trial results as well as postmarketing reports.

The adverse drug reactions derived from post-marketing experience with oxytocin as in Oxytocin 10 IU/ml Cospharm 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, ADRs are presented in order of decreasing seriousness.

Immune system disorders

Less frequent: Anaphylactoid reactions

Nervous system disorders

Frequent: Headache

Cardiac disorders

Frequent: Tachycardia, bradycardia

Less frequent: Dysrhythmia

Not known: Myocardial ischaemia, electrocardiogram QTc prolongation

Vascular disorders

Hypotension, shock, flushing

Gastrointestinal disorders

Frequent: Nausea, vomiting

Skin and subcutaneous tissue disorders:

Less frequent: Rash

Not known: Angioedema

Pregnancy, puerperium and perinatal conditions

Not known: Hypertonicity, tetanic contractions or rupture of the uterus, foetal distress syndrome, asphyxia and death

Metabolism and nutrition disorders

Not known: Water intoxication, maternal hyponatraemia

Respiratory, thoracic and mediastinal disorders

Not known: Acute pulmonary oedema

General disorders and administration site conditions

Not known: Flushing

Blood and lymphatic system disorders

Not known: Disseminated intravascular coagulation

Adverse drug reactions in foetus/neonate

Not known: Foetal distress syndrome, asphyxia and death.

Pelvic haematomas, neonatal jaundice and retinal haemorrhage have been associated with the use of oxytocin as in Oxytocin 10 IU/ml Cospharm.

Maternal death from severe hypertension and subarachnoid haemorrhage has occurred.

Pospartum haemorrhage and fatal afibrinogenaemia have been reported 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 providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

Healthcare providers should also report adverse reactions to the Holder Of Certificate of Registration:

Cospharm Investments (Pty) Ltd.

The contact details for our national reporting system are:

Email: rp@cospharm.org

Tel: 078 774 5503

Emergency: 078 774 5503

4.9 Overdose

As a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism has 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 hypotension, 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 Oxytocin 10 IU/ml Cospharm, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A19 Oxytocics

Pharmacotherapeutic group: Posterior pituitary lobe hormones

ATC code: H01B B02

Being synthetic, oxytocin does not contain vasopressin, but even in its pure form oxytocin possesses some real intrinsic vasopressin-like anti-diuretic activity.

Mechanism of action

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

Oxytocin exerts a stimulatory effect on the uterine smooth muscle, particularly towards the end of pregnancy, during labour, after delivery and in the puerperium, i.e. at times when the number of specific oxytocin receptors in the myometrium is increased.

When given by low-dose intravenous infusion, oxytocin elicits rhythmic uterine contractions that are

indistinguishable in frequency, force and duration from those observed during spontaneous labour.

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

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

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 oxytocin 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, oxytocin 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 for30 to 60 minutes after intramuscular administration; possibly less after intravenous injection.

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:

A g!ycoprotein aminopeptidase, oxytocinase, is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin.

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.

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. 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 per minute 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

Preclinical studies have not been conducted for Oxytocin 10 IU/ml Cospharm.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol

Ethanol (96 %)

Glacial acetic acid

Sodium acetate trihydrate

Sodium chloride

Water for injection

6.2 Incompatibilities

Oxytocin 10 IU/ml Cospharm should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin -inactivating enzymes. Oxytocin 10 IU/ml Cospharm is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store the ampoules refrigerated (2°C to 8 °C) in the original carton protected from light.

Protect from direct light

6.5 Nature and contents of container

A clear colourless solution free from visible particulate filled in 1 ml clear glass ampoules (USP Type I).

5 or 10 Ampoules are packed in a plastic ampoule tray.

6.6 Special precautions for disposal and other handling

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Cospharm Investments (Pty) Ltd.

24 Parrot Avenue

Extension 1, 1827

Johannesburg

8 REGISTRATION NUMBER(S)

55/19/0705

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 May 2023

10 DATE OF REVISION OF THE TEXT

To be allocated