SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ebovulon 10 IU (Oxytocin Injection BP 10IU/mL,)Sterile solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:
Oxytocin Injection BP.....10 IU.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL form

Sterile Solution for Injection

4. Clinical particulars 4.1

Therapeutic indications

Induction of labour.

Routine prevention and treatment of postpartum and post abortion haemorrhage.

4.2 Posology and method of administration

Posology

Paediatric population

There are no indications for use of Oxytocin in children or adolescents.
Older people (65 years and over)
There are no indications for the use of Oxytocin in elderly.

Method of administration

For Intramuscular (IM) or slow Intravenous (IV) use
Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins.

Oxytocin should be administered as an intravenous (i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump.

Incomplete, inevitable, or missed abortion: 5 IU (8.3 micrograms) 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), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute. Caesarean section: 5 IU (8.3 micrograms) 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 (8.3 micrograms) 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) 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 (8.3 micrograms) 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), followed in severe cases by i.v. infusion of a solution containing 5 to 20 IU (8.3 to 33.4 micrograms) of oxytocin in 500 ml of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

- Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress.

Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable 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
- In the presence of a uterine scar resulting from major surgery including classical caesarean section.

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

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

4.3 Special warnings and precautions for use

Oxytocin must only be administered as an IV infusion and never by IV 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 oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Cardiovascular disorders

Oxytocin 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.

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 .When Oxytocin is given for induction and enhancement of labour:

- **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-uterinesegment 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 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 IV 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 IV 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.

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 administration.

4.5 Interaction with other medicinal products 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.

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

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 oxytocin. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

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 Pregnancy and lactation

Pregnancy

The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons.

Animal reproduction studies have not been conducted with oxytocin. 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.

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.

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

The following adverse reactions have been reported in the mother:

- Anaphylactic reaction
- Postpartum hemorrhage
- Cardiac arrhythmia
- Fatal afibrinogenemia
- Nausea
- Vomiting
- Premature ventricular contractions
- Pelvic hematoma

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.

The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.

Severe water intoxication with convulsions and coma has occurred, and is associated with a slow oxytocin infusion over a 24-hour period. Maternal death due to oxytocin-induced water intoxication has been reported.

The following adverse reactions have been reported in the fetus or infant: Due to induced uterine mobility:

- Bradycardia
- Premature ventricular contractions and other arrhythmias
- Permanent CNS or brain damage • Fetal death

Due to use of oxytocin in the mother:

- Neonatal retinal hemorrhage
- Low Apgar scores at five minutes
- Neonatal jaundice

4.9 Overdose

The fatal dose of oxytocin has not been established. Oxytocin 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 section 4.8. In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment:

Treatment: When signs or symptoms of overdosage occur during continuous i.v. administration of oxytocin, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance,

and control 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

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 this product does not 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 desensitisation of oxytocin receptors probably due to down-regulation of oxytocinbinding sites, destabilisation of oxytocin receptors mRNA and internalisation 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.

5.2 Pharmacokinetic properties

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

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.

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 metabolising 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 minutes. 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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol BP, Glacial acetic acid BP & Water for Injections BP

6.2 Incompatibilities

Oxytocin Injection BP should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes.

Syntocinon is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperatures between 2 - 8°C. Do not freeze. Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Each Carton contains 10 ampoules.

6.6 Special precautions for disposal <and other handling>

For parenteral administration. The solution should be withdrawn using aseptic techniques using a sterile needle and syringe. The solution should be used immediately after opening of the ampoule. Any remaining solution should be discarded.

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