HBM Pharma		Leaflet OXYTOCIN EVEXY 10 IU/mL nav PH (HPH/I/10/2)			
SAP No	505777	Quality	white paper, 40 g/m²	Colours ■ Black	Replaces SAP:
Artwork No	N505777.01-PH	Dimensions	150x540 mm		Approved
DMcode	505777	Prepared	A.Vozarova/25.08.2022	FIBRE DIRECTION ≤1	
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OXYTOCIN

EVEXY

10 I.U./mL Solution for Injection
(I.M. / I.V. Infusion)
POSTERIOR PITUITARY LOBE HORMONE

℞

FORMULATION
Each mL contains:
Oxytocin..... 10 IU

PRODUCT DESCRIPTION
Clear colourless liquid with characteristic odour. Solution is filled in 1 mL transparent glass ampoule.

PHARMACODYNAMICS
Pharmacotherapeutic group: Systemic hormonal preparations, excl. sex hormones and insulins, oxytocin and analogues.
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 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 IV 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.

PHARMACOKINETIC PROPERTIES
Absorption
Plasma levels of oxytocin following intravenous (IV) 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 IV 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 fetus. Liver and kidney play 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 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.
Renal impairment
No studies have been performed in renally impaired patients. However, considering the excretion of oxytocin and its reduced urinary excretion because of antidiuretic 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.

INDICATIONS
Antepartum
– Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of membranes, pregnancy-induced hypertension (pre-eclampsia).
– Stimulation of labour in hypotonic uterine inertia.
– Early stages of pregnancy as an adjunctive therapy for the management of incomplete, inevitable, or missed abortion.
Postpartum
– During caesarean section, following delivery of the child.
– Prevention and treatment of postpartum uterine atony and haemorrhage

DOSAGE AND ADMINISTRATION / ROUTE OF ADMINISTRATION
Induction or enhancement of labour:
Oxytocin (Evexy) should not be started for 6 hours following administration of vaginal prostaglandins.
Oxytocin (Evexy) 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 (international units) of Oxytocin (Evexy) 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. 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 2 to 8 drops/minute (1 to 4 milliunits/minute). It may be gradually increased 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 20 drops/minute (10 milliunits/minute), and the recommended maximum rate is 40 drops/minute (20 milliunits/minute). In the unusual event that higher rates are required, as may occur in the management of fetal 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.
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 as well as the fetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or fetal 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 be ceased; it may be repeated on the following day, starting again from a rate of 2 to 8 drops/minute (1 to 4 milliunits/ minute).

Incomplete, inevitable, or missed abortion:
5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), if necessary, followed by IV infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section:
5 IU by IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV 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 IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) or 5-10 IU IM 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 IV infusion (5 IU diluted in physiological electrolyte solution and administered as an IV drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) or 5-10 IU IM, followed in severe cases by IV 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 or as prescribed by the physician.

Special populations
Renal and hepatic impairment
No studies have been performed in renally impaired and/or hepatically impaired patients.
Pediatric population
There are no indications for use of Oxytocin (Evexy) in children or adolescents.
Elderly (65 years and over)
There are no indications for use of Oxytocin (Evexy) in elderly.

Mode of administration
Intravenous (IV), intramuscular (IM) injection and intravenous infusion.

Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Single Dose.
Use Only Once or Discard any remaining portion.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients listed in section "Formulation".
- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress.

Any condition in which, for fetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contraindicated: e.g.:
- significant cephalopelvic disproportion;
- fetal malpresentation;
- placenta praevia and vasa praevia;
- placental abruption;
- cord presentation or prolapse;
- over distension 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 (Evexy) should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.
Oxytocin (Evexy) must not be administered within 6 hours after vaginal prostaglandins have been given.

WARNINGS AND PRECAUTIONS
Oxytocin (Evexy) 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 (Evexy) 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 (Evexy) 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.

When Oxytocin (Evexy) is given for induction and enhancement of labour:
- Fetal distress and fetal death: Administration of oxytocin at excessive doses results in uterine overstimulation which may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus.

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Careful monitoring of fetal 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 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 fetal 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.
Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin.

Effects on the ability to drive and use machines
Oxytocin (Evexy) can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

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 fetal 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
Animal reproduction studies have not been conducted with oxytocin. The effects of oxytocin on fertility are unknown.

DRUG INTERACTIONS
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.

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.

ADVERSE DRUG REACTIONS
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 IV infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus. Rapid IV bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia. These rapid haemodynamic changes may result in myocardial ischemia, particularly in patients with pre-existing cardiovascular disease. Rapid IV bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labour using uterotonic agents, including oxytocin, 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 together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time.

The combined antidiuretic effect of oxytocin and the IV fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary edema without hyponatraemia.
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.

Undesirable effects (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥≥1/10); common (≥≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports; not known (cannot be estimated from the available data). The adverse reactions (ADRs) 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 categorized 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.

Table 1 Adverse drug reactions in mother

System organ class	Adverse drug reaction
Immune system disorders	Rare: 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, haemorrhage
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 administration site conditions	Not known: flushing
Blood and lymphatic system disorders	Not known: disseminated intravascular coagulation

Table 2 Adverse drug reactions in fetus/neonate

System organ class	Adverse drug reaction
Pregnancy, puerperium and perinatal conditions	Not known: fetal distress, asphyxia and death
Metabolism and nutrition	Not known: neonatal hyponatraemia

OVERDOSE AND TREATMENT
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 "Adverse drug reactions". In addition, as a result of uterine oversti-mulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous IV administration of oxytocin, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water into-xication, 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.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION
Store in a refrigerator (2°C to 8°C). Do not freeze.

Keep all medicines out of reach of children.

AVAILABILITY
Type I hydrolytic resistant glass colourless borosilicate glass ampoule x 1 mL (net content). Box of 10's.

DRP-8748
Date of First Authorization: February 21, 2020
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