SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxytocin Grindeks 8.3 microgram/ml solution for injection/infusion
Oxytocin Grindeks 16.7 microgram/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 8.3 microgram oxytocin (5 IU).
1 ml of solution contains 16.7 microgram oxytocin (10 IU).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion (Injection/Infusion).
Colourless, clear liquid, free from visible particles.
pH of solutions 3.5-4.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antepartum

- Induction of labour for medical reasons, e.g. in case of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia);
- stimulation of labour in hypotonic uterine inertia;
- in 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.

4.2 Posology and method of administration

Posology

Induction or enhancement of labour:
Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Oxytocin Grindeks 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 Grindeks 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 section 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 gradually increased at intervals not shorter than 20 minutes and increments of not more than 1-2 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).

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 foetal 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 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 be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute (see section 4.3 Contraindications).

Oxytocin Grindeks is well tolerated by the tissue therefore inadvertent extravascular infusion is not harmful.

Caesarean section:
1 ml Oxytocin Grindeks 5 IU/ml as i.v. infusion (1.0 ml diluted in physiological sodium chloride solution and administered via i.v. drip infusion or preferably by means of a variable-speed infusion pump over 5 minutes) after delivery.

Prevention of postpartum 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 5-10 IU i.m. after delivery of the placenta. In women given Oxytocin Grindeks 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 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 5-10 IU i.m., followed in severe cases by i.v. 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.

Incomplete, inevitable, or missed abortion:
Due to lower receptor expression, the use of oxytocin is recommended *from 14th week of pregnancy.*
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), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute. If painful uterus contractions occur, the drop rate should be decreased or the infusion temporarily stopped.

<u>Route of administration</u>

Intramuscular (i.m.) injection and intravenous (i.v.) infusion.

Elderly
There are no indications for use of Oxytocin Grindeks in elderly patients.

Renal impairment
No studies have been performed in renally impaired patients.

Hepatic impairment
No studies have been performed in hepatically impaired patients.

Paediatric population
There are no indications for use of Oxytocin Grindeks in children or adolescents.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- mechanical obstruction to delivery;
- foetal distress;
- hypertonic uterine contractions.

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

Oxytocin Grindeks must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Precaution should be observed in patients with a history of ceasarean section or other surgical uterus interventions.

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.

When given for induction and enhancement of labour, oxytocin must only be administered as an intravenous drip infusion.

Oxytocin Grindeks should never be administered by intravenous bolus injection as it may cause a 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 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 QT interval.

When Oxytocin Grindeks is given for induction and enhancement of labour:
- Administration of oxytocin at excessive doses can be hazardous to both mother and foetus, resulting in uterine overstimulation which may cause foetal distress (foetal bradycardia, meconium-stained amniotic fluid, foetal asphyxia and death) and hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate (if possible cardiotocography (CTG)) and uterine motility is essential, so that the dosage may be adjusted to individual response. For patients with cardiovascular disease, the volume of infused fluid should be kept low by infusing oxytocin at a higher concentration.

- 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.

- In rare circumstances, the pharmacological induction of labour using uterotonic agents increases the risk of postpartum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent 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 (such as gestational diabetes, hypertension, hypothyroidism) during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative medicine should be used with caution, and the practitioner should be alerted by signs of DIC. Women with the above mentioned risk factors should be examined concerning fibrinolysis immediately after labour.

Water intoxication
Since 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 and the intravenous 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.

Parenteral oxytocin must not be given simultaneously with oxytocin-containing nasal spray.

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.

Renal impairment
Caution should be exercised in patients with severe renal impairment due to 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.

4.5 Interaction with other medicinal products and other forms of interaction

Other medicinal products contraindicated

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).

Concomitant use not recommended

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 section 4.4).

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 Fertility, pregnancy and lactation

Pregnancy
Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this medicine and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated. Oxytocin is contraindicated in pregnancy with exception of use for strictly medical reasons such as induction or enhancement of labour or at spontaneous or induced abortion.

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

No studies on the effects on the ability to drive and use machines have been performed. 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 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 at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see section 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 the pharmacological induction of labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section 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 together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see section 4.4).
The combined antidiuretic effect of oxytocin and the intravenous 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.

Adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency 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), not known (cannot be estimated from the available data).

Adverse drug reactions in mother

Blood and lymphatic system disorders
Not known: disseminated intravascular coagulation

Immune system disorders
Rare: Anaphylactoid reactions associated with dyspnoea, hypotension or shock

Metabolism and nutrition disorders
Not known: Water intoxication, maternal hyponatraemia

Nervous system disorders
Common: Headache

Cardiac disorders
Common: Tachycardia, bradycardia
Uncommon: Arrhythmia
Not known: Myocardial ischaemia, electrocardiogram QTc prolongation, reflex tachycardia.

Vascular disorders
Not known: Hypotension, haemorrhage

Respiratory, thoracic and mediastinal disorders
Not known: Acute pulmonary oedema

General disorders and administration site conditions
Not known: Flushing

Gastrointestinal disorders
Common: Nausea, vomiting

Skin and subcutaneous tissue disorders
Rare: Rash, urticaria
Not known: Angioedema

Pregnancy, puerperium and perinatal conditions
Not known: Uterine hypertonus, tetanic contractions of uterus, rupture of the uterus.

Adverse drug reactions in foetus/neonate

Pregnancy, puerperium and perinatal conditions
Not known: foetal distress syndrome, asphyxia and death

Metabolism and nutrition disorders
Not known: Neonatal hyponatraemia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

[To be completed nationally]

4.9 Overdose

Overdosage may cause the following complications: foetal distress (foetal bradycardia, meconium-stained amniotic fluid, asphyxia), hypertonicity, tetanic contractions, rupture of the uterus, water intoxication.

Toxicity: no symptoms were seen when 2-3 and 10 IU respectively was given i.m. to newborns and 8 IU was given by nasal administration to children of ½-1½ years of age.
Serious intoxication was seen in adults after infusion of 80 IU in a solution of isotonic glucose during 35 hours, infusion of 488 IU during 40 hours and infusion of 800 IU during 60 hours.
(1 IU corresponds to 1.67 microgram).

Symptoms: antidiurethic effect – risk for water intoxication (hyponatraemia, hypo-osmolality, cerebral oedema).Vascular spasm, hypertension.

Treatment: in the case of fluid retention observation is necessary. In the event of water intoxication, diuretics (mannitol or furosemide), infusion of sodium and cerebral oedema therapy should be administered. Other symptomatic treatment may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oxytocin and analogues, ATC code: H01BB02

Oxytocin stimulates contractions (frequency and strength) during labour, accelerates the involution of the uterus and pulls together the myoepithelial cells of the mammary gland, thereby making the emptying process easier.
Being synthetic, Oxytocin Grindeks does not contain vasopressin and is therefore not blood pressure-raising with the recommended doses, and may therefore be used at pre-eclampsia.

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.
When *intravenous infusion* is used the effect occurs gradually, with steady state usually after 20-40 min.
After *intravenous or intramuscular (i.m.) injection*, Oxytocin Grindeks acts rapidly; in approx. 1 min after i.v. injection and 2-4 min after i.m. injection. The effect remains for 30-60 min after i.m. injection and probably for a somewhat shorter period after i.v. injection.

Distribution
At steady state the distribution volume is approx. 12.2 L or 170 ml/kg in men. Plasma protein binding is low. Oxytocin crosses the placenta in both directions. Oxytocin may be found in small quantities in mother's breast milk.

Biotransformation/Metabolism
The enzyme oxytocinase, a glycoprotein aminopeptidase, is produced during pregnancy. The enzyme is found in plasma and it is capable of degrading oxytocin. The enzymatic activity increases gradually until labour begins it then increases rapidly, and decreases again after delivery. The enzyme activity is also high in the placental and uterine tissues during this period. Liver and kidneys play an important 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 min. The metabolites are excreted in urine whereas less than 1 % of the given dose is excreted unchanged in the urine. The metabolic clearance is ~17 mL/kg/min in pregnant women. Metabolic clearance is approx. 20 ml/kg/min in both men and non-pregnant women.

Renal impairment
No studies have been performed in renal 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and mutagenicity.
No standart teratogenicity, reproductive performance and carcinogenicity studies with oxytocin are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid glacial
Sodium chloride
Sodium hydroxide (for pH-adjustment)
Water for injection

6.2 Incompatibilities

Oxytocin should not be infused via the same apparatus as blood or plasma, because oxytocin can be inactivated.
Oxytocin is incompatible with solutions containing sodium metabisulphite as stabiliser.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

5 years
After first opening: the medical product should be used immediately.
After dilution for infusion: Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C. From a microbiological point of view, unless the method of opening/ reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze.

6.5 Nature and contents of container

1 ml transparent type I borosilicate glass ampoules with break ring or open point cut.
Pack sizes: 5, 10 or 100 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Oxytocin Grindeks is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium chloride 0.9 %, dextrose 5 %, Ringer's solution, acetated Ringer's solution.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Oxytocin Grindeks 8.3 microgram/ml solution for injection/infusion: Nr.: 140479
Oxytocin Grindeks 16.7 microgram/ml solution for injection/infusion: Nr.: 140480

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of authorisation: 8.1.2021

10. DATE OF REVISION OF THE TEXT

2021-10-07