## 1. NAME OF THE MEDICINAL PRODUCT

**Oxytocin - Grindeks**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 10 IU (16.7 micrograms) oxytocin.
Each 1 ml ampoule also contains 2.99 mg (0.13 mmol) sodium.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for Injection/ Infusion.
For I.M., I.V Injection and I.V. Infusion.
Clear colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Oxytocin - Grindeks may be used for:

- Induction of labour for medical reasons;
- Stimulation of labour in hypotonic uterine inertia;
- During Caesarean section following the delivery of the child;
- Prevention and treatment of postpartum uterine atony and haemorrhage.
- Oxytocin- Grindeks may also be indicated in early stages of pregnancy as an adjunctive therapy for the management of incomplete, inevitable or missed abortion.

### 4.2. Posology and method of administration

Oxytocin should be used only in a clinical setting and only under medical supervision. For the individual dosage, careful monitoring of the birth is required (CTG, blood pressure and pulse of the mother).

*Induction or enhancement of labour:*

For labour induction or to increase contractions, Oxytocin - Grindeks may only be administered as an intravenous continuous infusion and never as subcutaneous, intramuscular or intravenous bolus injection.

Oxytocin -Grindeks should be administered as an intravenous drip infusion or, preferably, using a variable-speed infusion pump. For drip infusion, it is recommended that 10 IU of Oxytocin -Grindeks should be added to 1000 mL of an isotonic sodium chloride solution 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 1-4 mU/min (2-8 drops/min). It may be gradually increased at intervals not shorter than 20 min, 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 mU/min (20 drops/min), and the recommended maximum rate is 20 mU/min (40 drops/min). In the unusual event

that higher rates are 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 - Grindeks 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.
If regular contractions are still absent after the infusion of 500 mL (5 IU), the attempt at labour induction should be ceased. A fresh attempt can generally be made on the following day.
Throughout the entire duration of infusion, the frequency, intensity and duration of contractions, as well as the foetal heart rate, must be carefully monitored. As soon as appropriate uterine activity has been achieved, the infusion rate can often be reduced. The infusion must be discontinued immediately in the event of excessive uterine activity and/or signs of placental malnutrition (foetal distress).
*Caesarean section:*
Immediately after extraction of the infant, 5 IU can be injected slowly I.V.
*Prevention of postpartum uterine haemorrhage:*
The usual dose is 5 IU slowly I.V. 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 uterine haemorrhage:*
5-10 IU I.M. or 5 IU slowly I.V., followed in severe cases by intravenous infusion of a solution containing 5-20 IU of oxytocin in 500 ml of a non-hydrating diluent, run at the rate necessary to control uterine atony.
Due to the antidiuretic effect of Oxytocin -Grindeks which suppresses urine excretion (see section 4.8 Undesirable effects), the following measures should be observed when administering Oxytocin - Grindeks at high doses:
An isotonic sodium chloride solution (not glucose) should be used and the infused volume of fluid must be kept low. At the same time, oral fluid intake should be restricted and the fluid balance monitored. If an electrolyte imbalance is suspected, serum electrolytes must be monitored.
*Incomplete, inevitable, or missed abortion:*
5 IU I.M. or slowly I.V., if necessary followed by intravenous infusion at a rate of 20-40 mU/min or higher.

**4.3. Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section **6.1.**
- 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 contraindicated: 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**

Oxytocin - Grindeks must only be administered as an I.V. infusion and never by 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 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 - Grindeks 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 -Grindeks 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 (see section 4.5 Interaction with other medicinal products and other forms of interaction).

When Oxytocin -Grindeks 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- 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 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 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 Pharmacokinetic properties).

**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 important predisposing risk factor of anaphylaxis following oxytocin administration.

## 4.5. Interactions with other medicinal products and other forms of interaction

Interaction resulting from concomitant use is 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 (see section 4.3 Contraindications).

*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 Special warnings and precautions for use).

**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

Animal reproduction studies have not been conducted with oxytocin. The effects of oxytocin on fertility are unknown. 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. One study has shown that treatment of rats with oxytocin in early pregnancy at doses considered sufficiently in excess of the maximum recommended human dose caused embryonic loss. No standard reproductive performance studies with oxytocin are available.

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 -Grindeks 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 is used by IV. 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 Special warnings and precautions for use). 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 (see section 4.4. Special warnings and precautions for use).

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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports; not known (cannot be estimated from the available data). The 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 dyspnea, hypotension or shock |
| Nervous system disorders | Common: Headache |
| Cardiac disorders | Common: Tachycardia, bradycardia<br>Uncommon: Arrhythmia<br>Not known: Myocardial ischemia, electrocardiogram QTc prolongation |
| Vascular disorders | Not known: Hypotension, haemorrhage |
| Gastrointestinal disorders | Common: Nausea, vomiting |
| Skin and subcutaneous tissue disorders | Rare: Rash,<br>Not known: angioedema |
| Pregnancy, puerperium and perinatal conditions | Not known: Uterine hypertonicity, tetanic contractions of uterus, 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: Foetal distress, 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

### 4.9. Overdose

The fatal dose of Oxytocin -Grindeks has not been established. Oxytocin- Grindeks 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 (Undesirable effects). In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

*Treatment:* When signs or symptoms of overdosage occur during continuous I.V. administration of Oxytocin -Grindeks, 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

Pharmacotherapeutic group: Systemic hormonal preparation, excl. sex hormone and insulin, oxytocin and analogues, ATCcode: H01BB02

*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-protein-coupled receptors. Activation of receptors 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 Oxytocin -Grindeks 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-Grindeks 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. 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.

**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.
*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 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 significantly increase. Therefore, biotransformation of oxytocin in impaired hepatic function may not result in substantial changes in metabolic clearance of oxytocin.

### 5.3. Pre-clinical 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

Sodium chloride
Acetic acid, glacial
Sodium acetate trihydrate
Sodium hydroxide
Water for injections

### 6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

### 6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after opening the ampoule and after dilution:

For single use only. For immediate use after opening.

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C when diluted with the solutions stated in section 6.6. From a microbiological point of view, 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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.4. Special precautions for storage

Store between 2°C and 8°C. Do not freeze.

See section 6.3 for storage of diluted product.

### 6.5. Nature and contents of container

Transparent 1 ml PhEur type I glass ampoules.

Pack sizes:

5 ampoules
10 ampoules

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Oxytocin is compatible with the following infusion fluids: 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. MANUFACTURER**

JSC Grindeks, 53 Krustpils St., Riga, LV-1057, Latvia

**8. IMPORTER AND LICENSE HOLDER:**

A.L. Medi Market, 3 Hakatif St., Emek Hefer Industrial Park, 3877701

**9. MARKETING AUTHORISATION NUMBER**

165-47-35690-00

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