SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bupivacaine Grindeks 5 mg/ml
Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 5 mg bupivacaine hydrochloride.
One ampoule (10 ml) contains 50 mg of bupivacaine hydrochloride.

Excipient(s) with known effect: each ampoule (10 ml) contains 31.48 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Long acting local anaesthetic.

4.2 Posology and method of administration

Bupivacaine Grindeks 5 mg/ml should only be used by physicians with experience of regional anaesthesia or under the supervision of such a physician. The lowest possible dose for adequate anaesthesia should be used.

In order to prevent inadvertent intravascular injections, it is important to observe particular caution. Thorough aspiration before and during the injection of the total dose is recommended. The total dose must be injected slowly, 25-50 mg/min or in divided doses with continuous verbal contact being maintained with the patient and monitoring of heart rate. In epidural injection of high doses, a test dose of 3-5 ml Bupivacaine Grindeks 5 mg/ml with adrenaline is recommended. An inadvertent intravascular injection can cause symptoms such as a transient increase in heart rate and inadvertent intrathecal injection can produce signs of spinal block. If toxic symptoms occur, the injection must be discontinued immediately.

The doses given below are guides, and the dosage should be adjusted according to the extent of the block and the patient's general condition.

For *infiltration anaesthesia*: Bupivacaine Grindeks 5 mg/ml, 5-30 ml (25-150 mg bupivacaine hydrochloride) should be given.

For *diagnostic and therapeutic blocks*: Bupivacaine Grindeks 5 mg/ml, 0.5-20 ml (2.5-100 mg bupivacaine hydrochloride), for example, for trigeminal block 0.5-2.5 ml, (2.5-12.5 mg) and for stellatum block 5-10 ml, (25-50 mg) should be given.

For *intercostal block*: Bupivacaine Grindeks 5 mg/ml 2-3 ml (10-15 mg bupivacaine hydrochloride) per nerve up to a total of 10 nerves should be given.

For *larger blocks* (for example, epidural, sacral and brachial plexus anaesthesia): Bupivacaine Grindeks 5 mg/ml, 15-30 ml (75-150 mg bupivacaine hydrochloride).

For *obstetric anaesthesia* (for example, epidural anaesthesia and caudal anaesthesia for vaginal delivery and vacuum extraction): Bupivacaine Grindeks 5 mg/ml, 6-10 ml (30-50 mg bupivacaine hydrochloride). The doses are initial doses, which if necessary may be repeated every two to three hours.

For *epidural block* (for caesarean section): Bupivacaine Grindeks 5 mg/ml, 15-30 ml (75-150 mg bupivacaine hydrochloride).

For *continuous epidural anaesthesia* in the form of intermittent bolus doses, initially Bupivacaine Grindeks 5 mg/ml, 10 ml (50 mg bupivacaine hydrochloride) should be given, thereafter Bupivacaine Grindeks 5 mg/ml, 3-8 ml (15-40 mg bupivacaine hydrochloride) every 4-6 hours depending on the desired number of anaesthetised segments and the patient's age.

For con*tinuous epidural infusion* (for example, postoperative pain relief):

	Concentration	Volume	Dose
Lumbar epidural infusion: Bolus[1] Infusion	 5 mg/ml 5 mg/ml	 2.5-5 ml 2.5-3.75 ml/hour	 12.5-25 mg 12.5-18.75 mg[2]
Thoracic epidural infusion: Bolus[1] Infusion	 5 mg/ml 5 mg/ml	 2.5-5 ml 1.25-2.5 ml/hour	 12.5-25 mg 6.25-12.5 mg
Epidural infusion for vaginal delivery: Bolus[1] Infusion	 5 mg/ml 5 mg/ml	 3-5 ml 1-2.5 ml/hour	 15-25 mg 5-12.5 mg

1) If an adequate bolus dose was *not* given in the previous hour.
2) The maximum recommended dose per day should not be exceeded (see below).

Account must be taken of the dose given intra-operatively.

In cases of combination with an opioid the dose of bupivacaine may be reduced.
Throughout the time that the infusion is being given the patient must be monitored regularly with regard to blood pressure, heart rate and symptoms of toxicity. If any signs of a toxicity are observed the infusion must be stopped immediately.

For children under 12 years the following dose is recommended:

Caudal block: Bupivacaine Grindeks 5 mg/ml 0.25 ml/kg body weight up to 10 ml.

Maximum recommended doses

The maximum recommended dose for administration on one and the same occasion is calculated on the basis of 2 mg/kg body weight. For adults this is a maximum of 150 mg within a four-hour period.
Bupivacaine Grindeks 5 mg/ml: 30 ml (150 mg bupivacaine hydrochloride).
The maximum recommended dose per 24 hours is 400 mg. The total dose must be corrected on the basis of the patient's age, general health and other relevant circumstances.

4.3 Contraindications

Hypersensitivity to the active substance, amide-type local anaesthetic agents or to any of the excipients.

Bupivacaine should not be used for intravenous regional anaesthesia (IVRA or Bier's block). Bupivacaine should not be used for epidural anaesthesia in patients with pronounced hypotension such as in cardiogenic and hypovolaemic shock.

4.4 Special warnings and precautions for use

Procedures using regional or local anaesthetic procedures should always be performed in the vicinity of resuscitation equipment unless the procedure is very minor. An intravenous cannula should be inserted prior to large blocks, before the injection of local anaesthetic.

Reports have been received of cardiac arrest or death following the use of bupivacaine in epidural anaesthesia or peripheral nerve block. In some cases, resuscitation has been difficult or impossible despite appropriate treatment.

Extensive peripheral nerve blocks can involve the administration of large volumes of local anaesthetics to highly vascularised areas, often the vicinity of large blood vessels. In these cases, there is an increased risk of intravascular injection and/or systemic absorption, which can lead to high plasma concentrations.

Like all local anaesthetic agents, bupivacaine may cause acute toxic effects on the central nervous system and cardiovascular system if use results in high blood concentrations. This applies particularly after inadvertent intravascular administration or administration into highly vascularised areas.

Some regional anaesthesia techniques may be associated with severe adverse effects, as indicated below:

- Epidural anaesthesia can cause cardiovascular depression, particularly in cases of concomitant hypovolaemia. Therefore, caution should be exercised in patients with impaired cardiovascular function.
- In rare cases, retrobulbar injections may reach the cranial subarachnoid space and cause e.g. temporary blindness, cardiovascular collapse, apnoea and convulsions. These symptoms must be treated immediately.
- Retrobulbar and peribulbar injections of local anaesthetic are associated with a certain risk of persistent ocular muscle dysfunction. The primary causes are traumatic nerve injuries and/or local toxic effects on muscles and/or nerves due to injected local anaesthetic.
  The extent of this tissue damage depends on the degree of trauma, concentration of the local anaesthetic and the duration of exposure to the local anaesthetic. For this reason, the lowest possible effective dose should be used. Inadvertent intravascular injections in the head and neck area can cause cerebral symptoms even at low doses.
- Paracervical block can sometimes cause bradycardia or tachycardia in the foetus; and the foetal heart rhythm must be closely monitored.

Caution should be obsered in patients with AV block II or III, as local anaesthetic may decrease myocardium transmittance. Particular attention should also be paid to the elderly and patients with severe hepatic disease or severe renal impairement, patients in the late stage of pregnancy or with poor general health .

Patients being treated with class III antiarrhythmic agents (e.g. amiodarone) should be closely monitored and ECG monitoring should be considered since the cardiac effects of bupivacaine and class III antiarrhythmic agents may be additive.

Hepatic dysfunction, with reversible increases in aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), and bilirubin, have been observed in rare cases following repeated bupivacaine injections or bupivacaine infusions of long duration. Immediate discontinuation of bupivacaine has led to rapid clinical improvement. If signs of hepatic dysfunction are observed during administration of bupivacaine, the medicinal product must be discontinued immediately. (See section 4.8).

Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g., by injecting a vasopressor. Hypotension should be treated immediately with administration of an intravenous sympathomimetic and repeated if required.

There have been post-marketing reports of chondrolysis in patients receiving continuous postoperative intra-articular infusions of local anaesthetics. The majority of reported cases concerned chondrolysis in the shoulder joint. It has not been possible to establish a causal link due to several contributing factors as well inconsistencies in the scientific literature with regard to the mechanism of action. Intra-articular continuous infusion is not an approved indication for Bupivacaine Grindeks 5 mg/ml.

Paediatric population

The safety and efficacy of Bupivacaine Grindeks 5 mg/ml in children younger than 1 year have not been established. Only limited data are available.
The use of bupivacaine for intra-articular block in children aged 1 to 12 years has not been documented.
The use of bupivacaine for major nerve block in children aged 1 to 12 years has not been documented.

For epidural anaesthesia, children should be administered gradually increasing doses proportional to their age and weight,
Since epidural anaesthesia at the thoracic level in particular can result in severe hypotonia and impaired respiration.

This medicinal product contains 31.48 mg sodium per ampoule (10 ml), equivalent to 1.57 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with caution in combination with other local anaesthetic agents or class IB antiarrhythmics, as the systemic toxic effects are additive.
Specific interaction studies have not been performed with bupivacaine and class III antiarrhythmics (e.g. amiodarone), but caution is recommended (see also section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Pregnancy:

As Paracervical block increases the risk of reactions such as bradycardia and tachycardia in the foetus; close monitoring of the heart rate is required.
See also section 5.2 Pharmacokinetic properties.

Breast-feeding:

Bupivacaine is excreted into breast milk, but the risk of impact on the child is considered unlikely at therapeutic doses.

4.7 Effects on ability to drive and use machines

Depending on the dose and method of administration, bupivacaine may have a transient effect on mobility and coordination.

4.8 Undesirable effects

Undesirable effects caused by the medicinal product itself can be difficult to distinguish from the physiological effects of the nerve blockade (e.g. decrease in blood pressure, bradycardia), events caused directly by the needle puncture (e.g. nerve damage), or cases caused indirectly by the needle puncture (e.g. epidural abscess).
Neurological injury is a rare but well-known consequential adverse effect of regional anaesthesia, particularly in epidural and spinal anaesthesia.

For information on the symptoms and treatment of acute systemic toxicity, see section 4.9 Overdose.

Organ system	**Frequency**	**Symptom**
Immune system disorders	Rare (≥1/10,000, <1/1,000)	Allergic reactions, anaphylactic shock
Central and peripheral nervous system disorders	Common (≥ 1/100, < 1/10)	Paraesthesia, dizziness
	Uncommon (≥ 1/1,000, < 1/100)	Symptoms of CNS toxicity (convulsions, circumoral paraesthesia, numbness of the tongue, hyperacousis, visual disturbances, loss of consciousness, tremor, feeling of intoxication, tinnitus, dysarthria)
	Rare (≥ 10,000, <1/1,000)	Neuropathy, peripheral nerve damage, arachnoiditis, paresis, paraplegia
Eye disorders	Rare (≥1/10,000, < 1/1,000)	Double vision
Cardiac disorders	Common (≥1/100, < 1/10)	Bradycardia
	Rare (≥1/10,000, < 1/1,000)	Cardiac arrest, cardiac arrhythmias
Vascular disorders	Very common (≥1/10)	Hypotension
	Common (≥1/100, < 1/10)	Hypertension
Respiratory, thoracic and mediastinal disorders	Rare (≥1/10,000, < 1/1,000)	Respiratory depression
Gastrointestinal disorders	Very common (≥1/10)	Nausea
	Common (≥1/100, < 1/10)	Vomiting
Renal and urinary disorders	Common (≥1/100, < 1/10)	Urinary retention

Hepatobiliary disorders	Not known (cannot be estimated from the available data)	Impaired hepatic function/increase in ASAT and ALAT*.

*Hepatic impairment, with reversible increases in ASAT, ALAT, ALP, and bilirubin, have been observed following repeated bupivacaine injections or bupivacaine infusions of long duration. If signs of hepatic impairment are observed during treatment with bupivacaine, the medicinal product must be discontinued immediately. (See section 4.4).

Paediatric population

Adverse reactions in children are similar to those in adults, but it may be difficult to detect early signs of local anaesthetic toxicity in children where the blockade is given under sedation or general anaesthesia.

Reporting 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

Acute systemic toxicity*:*

Symptoms:

Systemic toxic reactions involve the central nervous system and the cardiovascular system. These reactions are caused by high blood concentrations of local anaesthetic, which can occur as a result of inadvertent intravascular injection, overdose or unusually rapid absorption from highly vascularised tissue (see also section 4.4 Special warnings and precautions for use).

CNS symptoms are similar for all amide-type local anaesthetics, while cardiac symptoms differ between different medicinal products, both quantitatively and qualitatively.

Inadvertent intravascular injections of local anaesthetics can cause immediate systemic toxic reactions (within seconds to a few minutes). Signs of systemic toxicity in the case of overdose occur later (15-60 minutes after injection) due to a slower increase in concentrations of local anaesthetic in the blood.

CNS toxicity occurs gradually, with symptoms and reactions of escalating severity. The initial symptoms are usually a feeling of intoxication, circumoral paraesthesia, numbness of the tongue, hyperacousis, tinnitus and visual disturbances. Difficulty in articulating, muscle spasms or tremor are more severe symptoms and precede generalised convulsions. These symptoms must not be interpreted as neurotic behaviour. Unconsciousness and grand mal convulsions may follow the symptoms listed above, and may last from a few seconds to several minutes. Hypoxia and hypercapnia develop rapidly, with subsequent convulsions due to increased muscular activity and insufficient ventilation. In severe cases, respiratory arrest may occur. Acidosis intensifies the toxic effects of local anaesthetics.

Recovery is dependent on the metabolism of the local anaesthetic agent and on distribution away from the central nervous system. The process is rapid unless very large amounts of the drug have been injected.

Cardiovascular effects usually indicate a more serious situation and are usually preceded by signs of CNS toxicity, however these can be masked by general anaesthesia or heavy sedation with drugs such as benzodiazepines or barbiturates. Blood pressure drops, bradycardia, arrhythmia and even cardiac arrest can occur as a result of high systemic concentrations of local anaesthetics. Cardiovascular toxic effects are often related to depression of the conduction system of the heart and myocardium, leading to decreased minute volume, hypotension, AV block, bradycardia and sometimes ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation and cardiac arrest. These conditions are often preceded by signs of severe CNS toxicity such as convulsions, but in rare cases cardiac arrest has occurred in the absence of prodromal CNS effects. Following a very rapid intravenous bolus injection, the blood concentrations of bupivacaine can be so high in the coronary vessels that circulatory effects arise, alone or preceding CNS effects. Myocardial depression can occur via this mechanism, potentially as the initial symptom of toxicity.

Extra attention must be paid to early signs of toxicity in pediatric patients, as children do not usually receive large blocks until after general anaesthesia has been initiated.

Treatment:

Adequate ventilation (free airways, oxygen, and intubation and controlled respiration if required) must be ensured in the case of total spinal blockade. In the event of a fall in blood pressure or bradycardia, administer a vasopressor, preferably with an inotropic effect.

If signs of acute systemic toxicity occur, the administration of local anaesthetic agents must be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate oxygen supply/ventilation support and the administration of anticonvulsant drugs.

If cardiovascular arrest occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, inotropic agents and/or lipid emulsion should be considered.
Children must be given doses proportional to their age and body weight when treating systemic toxicity.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation, ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Extended resuscitation may be warranted in the case of circulatory arrest.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics

ATC code: N01BB01

Bupivacaine Grindeks 5 mg/ml contains bupivacaine, which is a long-acting amide-type local anaesthetic . Bupivacaine reversibly blocks impulse transmission in the nerve fibres by inhibiting the transport of sodium ions through the nerve membrane. Similar effects can also be seen on excitatory membranes in the brain and cardiac muscle.

The most prominent characteristic of bupivacaine is the long duration of action; and the difference in duration of action between bupivacaine with and without adrenaline is relatively small.
Bupivacaine is well suited to continuous epidural blockage. Lower concentrations have less effect on motor nerve fibres and a shorter duration of action, and may be appropriate for prolonged analgesia such as in childbirth or postoperatively.

5.2 Pharmacokinetic properties

The rate of absorption is dependent on dose, route of administration and vascularisation of the injection site. Intercostal blocks lead to the highest plasma concentrations (4 mg/l following a dose of 400 mg) due to rapid absorption; subcutaneous abdominal injections lead to the lowest plasma concentrations. Rapid absorption and high plasma concentrations are seen in children following caudal block (approx. 1-1.5 mg/l after a dose of 3 mg/kg).

Bupivacaine has complete and biphasic absorption from the epidural space, with half-lives of approx. 7 minutes and 6 hours respectively. The slow absorption is rate- limited by the elimination of bupivacaine, which explains why the elimination half-life is longer following epidural administration than that intravenous administration.

The distribution volume of bupivacaine at steady state is 73 litres; the hepatic extraction ratio is 0.40; total plasma clearance is 0.58 l/min; the elimination half-life is 2.7 hours. The elimination half-life in newborns is up to 8 hours longer than in adults. The half-life in children over 3 months is equivalent to that in adults.

The pharmacokinetics in children are similar to those in adults.

Plasma protein binding is 96% and primarily involves alpha-1-glycoprotein. There may be an elevated level of this protein following major surgery, giving a higher total plasma concentration of bupivacaine. The unbound concentration of bupivacaine will however remain unchnaged. This explains why plasma concentrations above toxic levels can be well tolerated.
Bupivacaine is metabolised almost entirely in the liver, primarily through aromatic hydroxylation to 4-hydroxybupivacaine and N-dealkylation to pipecolylxylidine, both of which are mediated by cytochrome P450 3A4. Clearance is thus dependent on the hepatic blood flow and the activity of the metabolising enzyme.

Bupivacaine crosses the placenta and the concentration of unbound bupivacaine is the same in the mother and the foetus. However, the total plasma concentration is lower in the foetus, due to a lower degree of protein binding.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the safety evaluation other than what has already been included in the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide or hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

Alkalisation can cause precipitation as bupivacaine is poorly soluble at pH above 6.5.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25ºC. Do not freeze.

6.5 Nature and contents of container

10 ml of the solution for injection in Type I hydrolytic class colourless borosilicate glass ampoule with break line or one point cut.
5 ampoules are packed in a polyvinylchloride film liner.
1 liner is packed in a cardboard box.

6.6 Special precautions for disposal and other handling

For single use only. Solution for injections does not contain preservatives and should be used immediately after opening. Discard any unused solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The solution for injection must not be kept in such a way that it can act on metals, e.g. in needeles or syringes with metal parts. Metal ions can otherwise become dissolved in the solution, which may lead to cause swelling at the injection site.

7. MANUFACTURER

JSC GRINDEKS.
53 Krustpils St., Rīga, LV-1057, Latvia

8. MARKETING AUTHORISATION HOLDER

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

9. REGISTRATION NUMBER

168-99-36168-00

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