SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lidocaine Grindeks 20 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 20 mg lidocaine hydrochloride.
Each 5 ml ampoule contains 100 mg lidocaine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
A clear, colourless or slightly yellowish liquid, free from visible particles.
pH of solution 5.0-7.0
Osmolality of solution 0.310-0.340 Osmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous regional anaesthesia, infiltration anaesthesia, nerve blocks and epidural anaesthesia.
Lidocaine Grindeks is indicated in adults.

4.2 Posology and method of administration

Posology

Lidocaine Grindeks should only be used by, or under the supervision of, doctors with experience of regional anaesthesia. The lowest possible dose producing the required effect should be given.
Aspiration to control for accidental intravenous injection is recommended before injection of the full dose. Inject slow and keep contact with the patient during injection. For epidural injection, a small test dose of 3-5 ml is recommended.
Injection of a cold solution below the body temperature should be avoided, as this could be painful.

Intravenous regional anaesthesia
Arm: 5-10 ml of solution (100-200 mg of lidocaine hydrochloride).
Leg: 10 ml of solution (200 mg of lidocaine hydrochloride).

Nerve blocks
1-2 ml of solution (20-40 mg of lidocaine hydrochloride).

Epidural anaesthesia
Lumbar analgesia: 12.5-20 ml of solution (250-400 mg of lidocaine hydrochloride).

Thoracic anaesthesia: 10-15 ml of solution (200-300 mg of lidocaine hydrochloride).
Sacral surgery analgesia: 20 ml of solution (400 mg of lidocaine hydrochloride).
Sacral obstetric analgesia:10-15 ml of solution (200-300 mg of lidocaine hydrochloride).

The recommended maximum single dose of lidocaine hydrochloride should not exceed 400 mg.

The dose should be reduced for patients in poor general condition.

Paediatric population

Other pharmaceutical forms/strengths are more appropriate for administration to this population.

Method of administration

The method of administration of lidocaine varies according to the procedure (intravenous regional anaesthesia, infiltration anaesthesia, nerve blocks or epidural anaesthesia).

Lidocaine Grindeks may be administered by intravenous, intramuscular, subcutaneous or epidural injection.

4.3 Contraindications

Hypersensitivity to the active substance, to local anaesthetics of the amide type or to any of the excipients listed in section 6.1.
Lidocaine Grindeks should not be used for epidural anaesthesia in patients with pronounced hypotension or with cardiogenic or hypovolemic shock.

4.4 Special warnings and precautions for use

Lidocaine should be administered by persons with resuscitative skills and equipment. Facilities for resuscitation should be available when administering local anaesthetics.
In any large blockade an intravenous cannula should be inserted before the local anaesthetic is injected. As with all local anaesthetic agents, lidocaine can cause acute central nervous and cardiovascular toxic effects when its use causes high concentrations in the blood, particularly after extensive intravascular administration.

Caution should be exercised in the treatment of the following patient categories:
- The elderly and generally debilitated patients.
- Patients with AV block II or III, as local anaesthetic can decrease myocardial conductivity.
- Patients with congestive heart failure, bradycardia or impaired respiratory function.
- Patients with severe hepatic disease or renal impairment.
- Patients with epilepsy.
- Patients treated with class III antiarrhythmics (e.g. amiodarone) should be kept under careful supervision and ECG monitoring should be considered, as the cardiac effects of lidocaine and class III antiarrhythmics may be additive (see section 4.5).

Epidural anaesthesia may cause severe side effects such as cardiovascular depression, especially in cases of concomitant hypovolaemia. Caution should always be exercised in patients with reduced cardiovascular function.

The main reasons are traumatic nerve injuries and/or local toxic effects on muscles and nerves caused by the injected local anaesthetic. The extent of these tissue injuries depends on the size of the trauma, the concentration of the local anaesthetic and the duration of tissue exposure to the local anaesthetic. For this reason, the lowest effective dose should be used.

Extensive intravascular injections in the head and neck areas may cause cerebral symptoms even at low doses.

The effect of local anaesthetics may be reduced if the injection is made into an inflamed or infected area.

Epidural anaesthetic may lead to a fall in blood pressure and bradycardia. The risk can be reduced by intravenous administration of crystalloidal or colloidal fluid. Hypotension should be treated immediately, with, for example, ephedrine 5-10 mg intravenously, repeated as needed.
Intramuscularly injected lidocaine may increase creatinine phosphokinase concentration which can interfere with the diagnosis of acute myocardial infarction.

Lidocaine injection is probably porphyrinogenic and should not be administered to patients with acute porphyria, unless absolutely unavoidable. Strict caution should be exercised in all patients with porphyria.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which inhibit the metabolism of lidocaine (e.g. cimetidine) may cause potentially toxic plasma concentrations when lidocaine is given repeatedly in high doses over long periods of time. Such interactions have no clinical relevance during short-term treatment with lidocaine in recommended doses.

Lidocaine Grindeks should be used with caution with other local anaesthetics or class Ib antiarrhythmic drugs, as the toxic effects are additive.
Specific interaction studies with local anaesthetics and class III antiarrhythmics (e.g. amiodarone) have not been carried out, but caution is recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on treatment in pregnant women.

Lidocaine crosses the placenta. It is reasonable to assume that lidocaine has been used in a great number of pregnant women and women of fertile age. There is no evidence that lidocaine causes disturbances in the reproductive process such as increased incidence of malformations or has any direct or indirect effect on the foetus. The risk to humans has, however, not been completely investigated.
Animal studies are incomplete regarding the effects of lidocaine on pregnancy, embryonic/foetal development, delivery and development after birth (see section 5.3).

In short-term use during pregnancy and at delivery the benefits should be weighed against the risks. Paracervical blockade or pudendal blockade with lidocaine increases the risk of reactions such as bradycardia/tachycardia in the foetus. The heart rate of the foetus must therefore be carefully monitored (see section 5.2).

Breastfeeding
Lidocaine is excreted in breast milk in small quantities. An effect on the child is unlikely when used at recommended doses. Breastfeeding can therefore be continued during treatment with Lidocaine Grindeks.

4.7 Effects on ability to drive and use machines

Depending on dose and method of administration, lidocaine can have a temporary effect on movement and coordination.

4.8 Undesirable effects

Summary of the safety profile
Undesirable effects caused by the medicine itself can be difficult to distinguish from the physiological effects of the nerve blockade (e.g. hypotension, bradycardia), and conditions caused by the needle directly (e.g. nerve injury) or indirectly (e.g. epidural abscess).

Undesirable effects are listed in Table 1 using 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 form the available data).

Table 1 Tabulated list of adverse reactions

Very common	*Vascular disorders*	Hypotension
	Gastrointestinal disorders	Nausea
Common	*Nervous system disorders*	Paraesthesia, dizziness
	Cardiac disorders	Bradycardia
	Vascular disorders	Hypertension
	Gastrointestinal disorders	Vomiting
Uncommon	*Nervous system disorders*	Symptoms of CNS toxicity (convulsions, circumoral paresthesia, numbness of tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, drowsiness, light-headedness, tinnitus, feeling of intoxication, dysarthria)
Rare	*Immune system disorders*	Hypersensitivity reactions, urticaria, rash, angioedema, in severe cases anaphylactic shock
	Nervous system disorders	Neuropathy, peripheral nerve injuries, arachnoiditis
	Eye disorders	Double vision
	Cardiac disorders	Cardiac arrest, arrhythmias
	Respiratory, thoracic and mediastinal disorders	Respiratory depression

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
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4.9 Overdose

Accidental intravascular injections of local anaesthetics can cause immediate systemic toxicity (within seconds to a few minutes). Signs of systemic toxicity due to overdose appear later (15-60 minutes after injection) as a result of a slower increase in the concentration of the local anaesthetic in the blood (see section 4.8). If signs of systemic toxicity appear, injection should be stopped immediately.

Toxicity:
Peroral administration: less than 50 mg seems to be of no risk for young children. 75 mg to a 2-year old child reduced the pain, 100 mg to 5 months child gave severe, 300 + 300 mg within 4 hours to 3½-year old child gave severe to very severe, 400-500 mg to 2-year old child and 1 g for 12 hours to a 1-year old child gave very severe intoxication. 600 mg to an adult reduced the pain, 2 g to an adult gave moderate intoxication.
Parenteral administration: 50 mg i.v. to a child of 1 month gave very severe intoxication. 200-400 mg infiltration to an adult gave severe, 500 mg to an elderly of 80-years old and 1 g i.v. to adults gave very severe intoxication.

Topical administration: 8.6-17.2 mg/kg to young children when application on burn wounds of the skin gave severe intoxication.

Symptoms
First CNS excitation, subsequently CNS depression. In large doses, rapid onset of convulsions can be the first symptom. Restlessness, dizziness, visual disturbances, perioral paraesthesia, nausea. Subsequently ataxia, auditory changes, euphoria, confusion, speech difficulty, paleness, sweating, tremor, convulsions, coma, respiratory arrest. Arrhythmias, mainly bradyarrhythmias, but with large doses, also ventricular tachycardia, ventricular fibrillation, QRS widening, AV block. Heart failure, hypotension (methemoglobinaemia described in isolated cases).

Treatment
Activated charcoal at peroral overdosage. (Provoked vomiting may be dangerous due to mucosal anaesthesia and risk for convulsions in an early stage. If a gastric lavage is necessary, it should be performed via a tube and after endotracheal intubation).

In the event of an overdose, immediate steps should be taken to maintain the circulation and respiration and to control convulsions.
A patent airway should be established and oxygen should be administered, together with assisted ventilation if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids, dobutamine and, if necessary, noradrenaline (initially 0.05 µg/kg/min, increasing as needed by 0.05 µg/kg/min every 10 minutes), with hemodynamic monitoring in more severe cases. Ephedrine can also be used.

Convulsions may be controlled by the intravenous administration of diazepam or thiopental sodium, bearing in mind that anticonvulsant drugs may also depress respiration and the circulation.
Atropine may be given for bradycardia. If cardiac arrest should occur, standard resuscitation procedures should be instituted.
Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics, amides, ATC code: N01BB02

Lidocaine Grindeks 20 mg/ml solution for injection contains lidocaine, which is a local anaesthetic of the amide type. Lidocaine reversibly blocks the impulses in the nerve fibres by inhibiting transport of sodium ions through the nerve membrane. Similar effects can also be seen on excitatory membranes in the brain and cardiac muscle. Lidocaine has a rapid onset of action, high anaesthetic potency and low toxicity. Lower concentrations of lidocaine have less effect on motor nerve fibres.

5.2 Pharmacokinetic properties

Absorption and distribution
The rate of absorption will depend on dose, route of administration and perfusion at the injection site. Intercostal blockades lead to the highest plasma concentrations (approx. 1.5 µg/ml per 100 mg injected), whereas subcutaneous injections in the abdominal area lead to lowest plasma concentrations (approx. 0.5 µg/ml per 100 mg injected). The volume of distribution at steady state is 91 litres and binding to plasma proteins, mainly to alpha-1-acid glycoprotein, is 65 %.

Absorption is total and biphasic from the epidural space with half-lives of approximately 9.3 minutes and 82 minutes respectively. The slow absorption is the time-limiting factor in elimination of lidocaine, which explains the slower elimination after epidural injection than after intravenous injection.

Biotransformation and elimination
Elimination of lidocaine is chiefly through metabolism, mainly by dealkylation to monoethylglycine xylidide (MEGX), which is mediated by both CYP1A2 and CYP3A4. MEGX is metabolised to 2,6-dimethylaniline and glycinexylidide (GX). 2,6-dimethylaniline is further converted by CYP2A6 to 4-hydroxy-2,6-dimethylaniline which is the major urinary metabolite (80 %) and is excreted as a conjugate. MEGX has a convulsant activity similar to that of lidocaine whereas GX lacks convulsant activity. MEGX appears to occur in plasma concentrations similar to the mother substance. The speed of elimination of lidocaine and MEGX after an intravenous bolus dose is approx. 1.5-2 hours and 2.5 hours respectively.
Due to rapid metabolism in the liver, the kinetics are sensitive to all hepatic conditions.
Lidocaine crosses the placental barrier and concentration of unbound lidocaine will be the same in both mother and foetus. However, total plasma concentration will be lower in the foetus, due to a lower degree of protein binding.

Hepatic impairment
The half-life can be more than doubled in patients with hepatic impairment.

Renal impairment
Renal impairment does not affect the kinetics but can increase the accumulation of metabolites.

5.3 Preclinical safety data

Reproductive toxicity
In studies of embryo/foetal development in rats and rabbits with lidocaine given during organogenesis, no teratogenic effects were observed. Embryotoxicity was seen in rabbits at doses toxic to the mother. The young rats treated with doses toxic to the mother during late pregnancy and lactation showed reduced postnatal survival.

Genotoxicity and carcinogenicity
Genotoxicity studies of lidocaine were negative. Carcinogenicity of lidocaine has not been studied. Lidocaine's metabolite, 2,6-dimethylaniline, has a genotoxic potential in vitro. In a carcinogenicity study of rats with exposure to 2,6-dimethylaniline in utero, postnatally and throughout their lifetime, tumours were seen in the nostrils, subdermally and in the liver. The clinical relevance of these findings for short-term/intermittent lidocaine use is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Lidocaine hydrochloride has been reported to be incompatible in solutions with amphotericin B, sulfadiazine sodium, methohexital sodium, cefazolin sodium, or phenytoin sodium.
Acid stable drugs such as adrenaline hydrochloride, noradrenaline acid tartrate, or isoprenaline may begin to deteriorate within several hours of mixture with lidocaine hydrochloride as lidocaine solutions may raise the pH of the final solution above the maximum pH for their stability.
Alkalisation can result in precipitation since lidocaine is only slightly soluble in pH over 6.5.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

5 ml clear colourless glass ampoules. Pack size: 10 ampoules.

6.6 Special precautions for disposal and other handling

Use immediately after opening.
The solution for injection must not be stored in contact with metals, e.g needles or metal parts of syringes as dissolved metal ions may cause swelling at the site of injection.

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)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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