SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lydagriks 10 mg/ml solution for injection
Lydagriks 20 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains lidocaine hydrochloride monohydrate corresponding to 10 mg lidocaine hydrochloride.

One ampoule of 5 ml contains 50 mg lidocaine hydrochloride.
One ampoule of 10 ml contains 100 mg lidocaine hydrochloride.
One vial of 20 ml contains 200 mg lidocaine hydrochloride.
One vial of 50 ml contains 500 mg lidocaine hydrochloride.

Excipient(s) with known effect:
This medicine contains less than 1 mmol sodium (23 mg) per ampoule of 5 ml.
This medicine contains 27.8 mg sodium per ampoule of 10 ml.
This medicine contains 55.6 mg sodium per vial of 20 ml.
This medicine contains 139 mg sodium per vial of 50 ml.

1 ml of solution for injection contains lidocaine hydrochloride monohydrate corresponding to 20 mg lidocaine hydrochloride.

One ampoule of 2 ml contains 40 mg lidocaine hydrochloride.
One ampoule of 5 ml contains 100 mg lidocaine hydrochloride.
One ampoule of 10 ml contains 200 mg lidocaine hydrochloride.
One vial of 20 ml contains 400 mg lidocaine hydrochloride.
One vial of 50 ml contains 1000 mg lidocaine hydrochloride.

Excipient(s) with known effect:
This medicine contains less than 1 mmol sodium (23 mg) per ampoule of 2 ml.
This medicine contains less than 1 mmol sodium (23 mg) per ampoule of 5 ml.
This medicine contains 23.8 mg sodium per ampoule of 10 ml.
This medicine contains 47.6 mg sodium per vial of 20 ml.
This medicine contains 119 mg sodium per vial of 50 ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
A clear, colourless or slightly yellowish solution free from visible particles.
pH of solution 5.0-6.5
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.

[Invented name] 10 mg/ml is intended for adults and children over 1 year of age.
[Invented name] 20 mg/ml is intended for adults.

4.2 Posology and method of administration

Posology

[Invented name] should only be used by, or under the supervision of, doctors with experience of regional anaesthesia. The lowest possible dose for adequate anaesthesia should be sought. The dose to be used depends on the age, body weight and clinical condition of the patient.

The table may serve as a guide for adults having a body weight of about 70 kilograms.

Route or method of administration	Recommended doses of lidocaine hydrochloride		
	Concentration (mg/ml)	Volume (ml)	Total dose (mg)
Infiltration anaesthesia:			
Small procedures	10 mg/ml	2-10 ml	20-100 mg
Large procedures	10 mg/ml 20 mg/ml	10-20 ml 5-10 ml	100-200 mg 100-200 mg
Intravenous regional anesthesia:			
Arm	10 mg/ml 20 mg/ml	10–20 ml 5–10 ml	100–200 mg 100–200 mg
Leg	10 mg/ml 20 mg/ml	20 ml 10 ml	200 mg 200 mg
Nerve blocks	10 mg/ml 20 mg/ml	2–20 ml 1–10 ml	20–200 mg 20–200 mg
Epidural anesthesia:			
Lumbar analgesia	10 mg/ml 20 mg/ml	25–40 ml 12.5–20 ml	250–400 mg 250–400 mg
Thoracic anaesthesia	10 mg/ml 20 mg/ml	20–30 ml 10–15 ml	200–300 mg 200–300 mg
Sacral surgical analgesia	10 mg/ml 20 mg/ml	40 ml 20 ml	400 mg 400 mg
Sacral obstetric analgesia	10 mg/ml 20 mg/ml	20–30 ml 10–15 ml	200–300 mg 200–300 mg

Highest recommended doses:
[Invented name] 10 mg/ml, 40 ml (400 mg of lidocaine hydrochloride).
[Invented name] 20 mg/ml, 20 ml (400 mg of lidocaine hydrochloride).

Paediatric population
[Invented name] should not be used in children younger than 1 year of age. Only the strength 10 mg/ml should be used. Special care has to be exercised when treating children under 4 years of age. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique must be selected carefully. Painful anaesthesia technique should be avoided. The behaviour of the child during treatment has to be monitored carefully.
The doses are calculated individually according to the patients' age, body weight and the nature of the procedure. The usual dosage for children above 2 years of age is 3-4 mg/kg body weight of a 10 mg/ml solution. For calculation, the average age weight is to be considered for overweight children.

The dose of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child's weight (in kilograms) x 1.33.
Do not exceed the equivalent of 5 mg lidocaine hydrochloride per kilogram of body weight.

Special populations
The dose should be reduced in patients with impaired renal or liver function, in the elderly and in patients in reduced general condition, according to age and physical condition (see section 4.4).

Method of administration
The method of administration of lidocaine varies according to the procedure (infiltration anaesthesia, intravenous regional anaesthesia, nerve block or epidural anaesthesia).
[Invented name] may be administered by intravenous, subcutaneous or epidural injection.
[Invented name] is not indicated for use in spinal anaesthesia.

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.
[Invented name] 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

With the exception of the most trivial procedures, regional and local anaesthetic procedures should always be performed with equipment for resuscitation available. In any large blockade an intravenous cannula should be inserted before the local anaesthetic is injected. Like all local anaesthetics, 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 severe hepatic or renal impairment.
- 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).

Some regional anaesthesia techniques may be associated with serious side effects, for example:
- Epidural anaesthesia may cause cardiovascular depression, especially in cases of concomitant hypovolaemia. Caution should always be exercised in patients with reduced cardiovascular function.
- Retrobulbar injections can, in rare cases, reach the cranial subarachnoid and cause, for example, temporary blindness, cardiovascular collapse, apnoea and convulsions. These symptoms must be treated immediately.
- Retro- and peribulbar injections with local anaesthetics carry a certain risk of persistent ocular muscle dysfunction.
- There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of the reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding the mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for lidocaine.

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.

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

Epidural anaesthetic may lead to a fall in blood pressure and bradycardia. The risk of such effects can be reduced, for example, by injection of a vasopressor. Decrease in blood pressure should be treated immediately intravenously with a sympathomimetic, which is repeated as needed.

[Invented name] solution for 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.

This medicinal product contains sodium.

10 mg/ml solution for injection

This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml ampoule, that is to say essentially 'sodium-free'.

This medicinal product contains 27.8 mg sodium per 10 ml ampoule, equivalent to 1.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 55.6 mg sodium per 20 ml vial, equivalent to 2.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 139 mg sodium per 50 ml vial, equivalent to 7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

20 mg/ml solution for injection

This medicinal product contains less than 1 mmol sodium (23 mg) per 2 ml ampoule, that is to say essentially 'sodium-free'.

This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml ampoule, that is to say essentially 'sodium-free'.

This medicinal product contains 23.8 mg sodium per 10 ml ampoule, equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 47.6 mg sodium per 20 ml vial, equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 119 mg sodium per 50 ml vial, equivalent to 6% 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

Medicines that 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 after short-term treatment with lidocaine in recommended doses.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of lidocaine 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 childbearing potential. 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 [Invented name].

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, influencing the ability to drive and use machines. Patients should be advised to avoid these activities until normal function is fully restored.

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).

Table 1 Tabulated list of adverse reactions

Very common (≥1/10)	*Gastrointestinal disorders*	Nausea
	Vascular disorders	Hypotension
Common (>1/100,<1/10)	*Cardiac disorders*	Bradycardia
	Vascular disorders	Hypertension
	Nervous system disorders	Paraesthesia, dizziness
	Gastrointestinal disorders	Vomiting
Uncommon (>1/1000 to <1/100)	*Nervous system disorders*	Symptoms of CNS toxicity (convulsions, circumoral paresthesia, numbness of tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, feeling of intoxication, tinnitus, dysarthria)
Rare (>1/10 000 to <1/1000)	*Immune system disorders*	Hypersensitivity reactions, including 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 the national reporting system listed in Appendix V.

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.

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

Treatment
Activated charcoal in case of oral overdose. (Provoked vomiting may be dangerous due to mucosal anaesthesia and risk for seizures 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 intravenous fluids and, if necessary vasopressoric, chronotropic and/or inotropic drugs with hemodynamic monitoring in more severe cases.

Convulsions may be controlled by the intravenous administration of anticonvulsive drugs, 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. For a successful outcome prolonged resuscitative effort may be required.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The use of intravenous lipid emulsion as an antidote to the local anaesthetic systemic toxicity (LAST) should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics, amides, ATC code: N01BB02
Lidocaine 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
Lidocaine is mainly eliminated through metabolism. Dealkylation to monoethylglycine xylidide (MEGX) is mediated by both CYP1A2 and CYP3A4. MEGX is metabolised to 2,6-dimethylaniline and glycine xylidide (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 parent compound. The elimination rate 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. The half-life may be more than doubled in patients with hepatic impairment. Renal impairment does not affect the kinetics but may increase the accumulation of metabolites.

Lidocaine crosses the placental barrier and concentration of unbound lidocaine remains the same in both mother and foetus. However, total plasma concentration is lower in the foetus, due to a lower degree of protein binding.

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 observed in rabbits at a maternally toxic dose. The offspring of rats treated with a maternally toxic dose 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 nasal cavity, subcutaneous tissue and liver. The clinical relevance of tumour 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

2 years

6.4 Special precautions for storage

Do not freeze.
Do not store above 25 °C.

6.5 Nature and contents of container

10 mg/ml solution for injection
Ampoules
5 ml or 10 ml clear Type I hydrolytic resistant class colourless borosilicate glass ampoules with one point cut are used for packaging. Ampoules are marked with a colour ring code. 5 or 10 ampoules are packed in a cardboard box.
Vials
20 ml and 50 ml Type I clear borosilicate moulded glass with crimp neck and in injection vials. The vials are closed with 20 mm bromobutyl rubber stoppers and with 20 mm aluminium flip-off seals. 10 vials are packed in a cardboard box.

20 mg/ml solution for injection
Ampoules
2 ml, 5 ml or 10 ml clear Type I hydrolytic resistant class colourless borosilicate glass ampoules with one point cut are used for packaging. Ampoules are marked with a colour ring code. 5 or 10 ampoules are packed in a cardboard box.
Vials
20 ml and 50 ml Type I clear borosilicate moulded glass with crimp neck and in injection vials. The vials are closed with 20 mm bromobutyl rubber stoppers and with 20 mm aluminium flip-off seals. 10 vials are packed in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use immediately after opening.
The medicinal product 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.
Only clear colourless solution free from particles or precipitates should be used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

2024-05-16