SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lidocaine Accord 10 mg/ml solution for injection
Lidocaine Accord 20 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg/ml:
Each ml of solution for injection contains 10 mg lidocaine hydrochloride.
Each 2 ml ampoule of solution for injection contains 20 mg lidocaine hydrochloride.
Each 5 ml ampoule of solution for injection contains 50 mg lidocaine hydrochloride.
Each 10 ml ampoule of solution for injection contains 100 mg lidocaine hydrochloride.
Each 20 ml vial of solution for injection contains 200 mg lidocaine hydrochloride.

20 mg/ml:
Each ml of solution for injection contains 20 mg lidocaine hydrochloride.
Each 2 ml ampoule of solution for injection contains 40 mg lidocaine hydrochloride.
Each 5 ml ampoule of solution for injection contains 100 mg lidocaine hydrochloride.
Each 10 ml ampoule of solution for injection contains 200 mg lidocaine hydrochloride.
Each 20 ml vial of solution for injection contains 400 mg lidocaine hydrochloride.

Excipient(s) with known effect:
10 mg/ml: Each ml of solution for injection contains approximately 0.118 mmol sodium.

20 mg/ml: Each ml of solution for injection contains approximately 0.082 mmol sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution, practically free from visible particles
The pH of solution is 4.0 - 5.5
Osmolality of solution is 270 - 320 mOsmol/kg H_2O

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidocaine Accord is indicated for use in infiltration anaesthesia, intravenous regional anaesthesia, nerve blocks and epidural anaesthesia.

Lidocaine Accord 10 mg/ml is intended for adults and children over 1 year.
Lidocaine Accord 20 mg/ml is intended for adults and adolescents aged over 12 years.

4.2 Posology and method of administration

Posology

Adults and adolescents aged over 12 years

Lidocaine Accord should only be used by, or under the supervision of, doctors with experience of regional anaesthesia and resuscitative skills. Facilities for resuscitation should be available when administering local anaesthetics. The lowest possible dose producing the required effect should be given.

The table may serve as a guide for adults having a body weight of about 70 kilograms. The dose should be adjusted according to age, weight and condition of the patient.

Route of administration or procedure	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 anaesthesia:			
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 anaesthesia:			
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 surgery 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

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

Paediatric population
The doses are reduced to children and patients with poor general condition.
Special care has to be exercised when treating children below 4 years. 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 should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.
The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg 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 of lidocaine hydrochloride per kilogram of body weight.

Lidocaine Injection is not recommended for use in neonates (see section 5.2). The optimum serum concentration of lidocaine required to avoid toxicity, such as convulsions and cardiac arrhythmias, in this age group is not known.

Special population
The doses should be reduced in patients with renal impairment, hepatic impairment and the elderly, commensurate with age and physical status (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).
Lidocaine Accord 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 such as prilocaine, mepivacaine and bupivacaine or to any of the excipients listed in section 6.1.
Lidocaine Accord 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 carried out with equipment for resuscitation available. 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.
- Acidosis or hypoxia in the patient increases the risk and the severity of toxic reactions of the central nervous system or the cardiovascular system (see section 4.9).
- 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.
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- 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).

There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for lidocaine.

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.

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

Retrobulbar injections may rarely reach the cranial subarachnoid space, causing serious/severe reactions including cardiovascular collapse, apnoea, convulsions and temporary blindness. These complications should immediately be recognised and treated.

Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular motor dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves. 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. Vasoconstrictors and other additives can intensify tissue reactions and should only be used if indicated.

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

Intramuscular Lidocaine may increase creatinine phosphokinase concentrations which can interfere with the diagnosis of acute myocardial infarction.

Lidocaine has been shown to be porphyrinogenic in animals and should not be administered to patients with acute porphyria, unless absolutely unavoidable. Strict caution should be exercised in all patients with porphyria.

Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by intravenous administration of crystalloidal or colloidal solutions. Hypotension should be treated immediately, with, for example, ephedrine 5-10 mg intravenously, repeated as needed.

Paracervical block can sometimes cause foetal bradycardia or tachycardia and careful monitoring of the foetal heart rate is necessary (see section 4.6).

Each ml of solution for injection contains approximately 0.118 mmol sodium (if the strength 10 mg/ml is used) or 0.082 mmol sodium (if the strength 20 mg/ml is used). To be taken into consideration by patients on a sodium controlled diet.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which inhibit the metabolism of lidocaine (e.g. cimetidine or beta blockers) 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 should be used with caution in patients receiving other local anaesthetics or class Ib antiarrhythmic drugs, as the toxic effects are additive.
Specific interaction studies with lidocaine and class III anti-arrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised (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 (see section 5.2). 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. The risk to humans has, however, not been completely investigated.

Animal studies have shown reproductive toxicity (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. Breast feeding can therefore be continued during treatment with Lidocaine Accord.

4.7 Effects on ability to drive and use machines

Depending on dose and method of administration, lidocaine can have a temporary effect on motor function 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

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).

Very common (≥1/10)	*Vascular disorders*	Hypotension
	Gastrointestinal disorders	Nausea
Common (≥1/100 to <1/10)	*Nervous system disorders*	Paraesthesia, dizziness
	Cardiac disorders	Bradycardia
	Vascular disorders	Hypertension
	Gastrointestinal disorders	Vomiting
Uncommon (≥1/1,000 to <1/100)	*Nervous system disorders*	Symptoms of CNS toxicity (convulsions, circumoral paresthesia, numbness of tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, drowsiness, light-headedness, tinnitus, dysarthria)
Rare (≥1/10,000 to <1/1,000)	*Immune system disorders*	Hypersensitivity reactions, anaphylactic reaction/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.

Acute systemic toxicity

Systemic manifestations of toxicity can involve both the central nervous system and the cardiovascular system. Such reactions are caused primarily by high blood concentrations of the local anaesthetic, which can occur as a result of (accidental) intravascular injection, overdose or exceptionally rapid absorption from well perfused areas (see section 4.4). Central nervous system reactions are similar for all local anaesthetics of the amide type, while heart reactions are more drug-specific, both in quantitative and qualitative terms. In general, manifestations of cardiovascular toxicity are preceded by manifestations of central nervous system toxicity, unless the patient is undergoing general anaesthesia or is heavily sedated with drugs such as benzodiazepines or barbiturates.

Central nervous system toxicity develops gradually, with increasing severity of symptoms and manifestations. The first symptoms observed are a numb feeling around the mouth, numbness of the tongue, light-headedness, hyperacusis and tinnitus and visual disturbances. Dysarthria, twitching or tremors are more serious and may precede generalised convulsions. These manifestations should not be regarded as neurotic behaviour. Loss of consciousness and generalised tonic-clonic seizures may subsequently follow, varying in duration from a few seconds to minutes.

Hypoxia and hypercapnia develop quickly during the seizures as a consequence of increased muscular activity and interference with breathing. Apnoea can occur in severe cases. Acidosis, hyperkalaemia, hypokalaemia, hypocalcaemia and hypoxia increase and intensify the toxic effects of local anaesthetics. Recovery follows redistribution of the local anaesthetic from the central nervous system, followed by metabolism and excretion. Recovery can be rapid, unless large quantities have been injected.

Cardiovascular toxicity indicates more serious situations and is generally preceded by manifestations of central nervous system toxicity. Prodromal central nervous system symptoms may be absent in heavily sedated patients or patients under general anaesthesia. Hypotension, bradycardia, arrhythmias and even cardiac arrest can occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest occurred without prodromal effects on the CNS.

In children the first signals of CNS toxicity are difficult to identify if they occur during the block or under general anaesthesia.

Treatment of acute toxicity:

In the event of acute toxicity, the administration of local anaesthetic should be discontinued immediately. Intravenous fluid should be given in order to prevent hypoxia and acidosis, which potentiate local anaesthetic systemic toxicity (LAST) and exacerbate progression to cardiovascular collapse and seizure.

If convulsions occur, oxygenation should be maintained and circulation should be supported. If required, an anticonvulsant should be administered. Use of intravenous lipid emulsion should be considered.

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, dobutamine and, if necessary, noradrenaline, 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. For a successful outcome prolonged resuscitative efforts may be required.

Patients having manifested signs of LAST should be monitored for at least 12 hours, because cardiovascular depression can persist or recur after treatment.

Centrally acting analeptics are contra-indicated.

There is no specific antidote.

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 is a local anaesthetic of the amide type with rapid onset and average duration of effect. The mechanism of action is based on a decreased permeability of the membrane of the neuron for sodium ions. As a consequence of this, the depolarization rate is decreased and the threshold of excitation is increased, resulting in a reversible local numbness.

It is used to provide local anaesthesia by nerve blockade at various sites in the body and in the control of dysrhythmias. It acts by inhibiting the ionic refluxes required for the initiation and conduction of impulses, thereby stabilising the neuronal membrane. In addition to blocking conduction in nerve axons in the peripheral nervous system, lidocaine has important effects on the central nervous system and cardiovascular system. After absorption, lidocaine may cause stimulation of the CNS followed by depression and in the cardiovascular system, it acts primarily on the myocardium where it may produce decreases in electrical excitability, conduction rate and force of contraction. It has a rapid onset of action (about one minute following intravenous injection and fifteen minutes following intramuscular injection) and rapidly spreads through the surrounding tissues. The effect lasts about ten to twenty minutes and about sixty to ninety minutes following intravenous and intramuscular injection respectively.

5.2 Pharmacokinetic properties

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.

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 to4-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. The half life can be more than doubled in patients with hepatic impairment. Renal impairment does not affect the kinetics but can increase the accumulation of metabolites.

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.

Special population
The pharmacokinetics of lidocaine can be influenced by conditions affecting the liver function due to its rapid metabolism. The half-life can be increased by a factor of 2 or more in patients with hepatic dysfunction.

Renal function impairment has no effect on the pharmacokinetics of lidocaine but may lead to the accumulation of its metabolites.

In neonates, the α1-acid glycoprotein levels are low and protein binding may be reduced. As the free fraction may be higher, the use of lidocaine in neonates is not recommended.

Elderly
Elimination half-life and volume of distribution may appear to be prolonged resp. increased in the elderly due to reduced cardiac output and/or hepatic blood flow.

5.3 Preclinical safety data

In animal studies, the toxicity noted after high doses of lidocaine consisted of effects on the central nervous and cardiovascular systems.

In studies on reproduction toxicity, embryotoxic or fetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit. At doses below the maternal toxic range in the rat, lidocaine has no effect on the postnatal development of the offspring. An impairment of the fertility of male or female rats by lidocaine was not observed. Lidocaine crosses the placental barrier by means of simple diffusion.

Lidocaine showed no genotoxic potential in in-vitro and in-vivo genotoxicity tests. However, a metabolite of lidocaine, 2,6-dimethylaniline, showed evidence of genotoxic activity.

Cancer studies have not been performed with lidocaine. 2,6-dimethylaniline has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. The clinical relevance of these findings is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

To be use immediately after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Type I transparent glass ampoules and Type I transparent glass vials with chlorobutyl rubber stopper and aluminium flip-off seal

10 mg/ml

Glass ampoules:	5 x 2 ml, 10 x 2 ml, 20 x 2 ml
	5 x 5 ml, 10 x 5 ml, 20 x 5 ml
	10 x 10 ml, 20 x 10 ml

Glass vials: 1 x 20 ml

20 mg/ml
Glass ampoules: 5 x 2 ml, 10 x 2 ml, 20 x 2 ml
5 x 5 ml, 10 x 5 ml, 20 x 5 ml
5 x 10 ml, 10 x 10 ml, 20 x 10 ml

Glass vials: 1 x 20 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Use as directed by the physician.
Keep out of the sight and reach of children.
For single use only.
If only part of an ampoule and vial is used, discard the remaining solution.
The solution for injection should not be used if particles are present.

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

7 March 2024