Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lidocaine/Adrenaline (Epinephrine) 20 mg/ml + 5 microgram/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lidocaine/Adrenaline (Epinephrine) 20 mg/ml + 5 mcg/ml
Each ml of solution for injection contains lidocaine hydrochloride monohydrate equivalent to 20 mg of lidocaine hydrochloride and adrenaline (epinephrine) tartrate equivalent to 5 micrograms of adrenaline (epinephrine).

Each 10 ml ampoule contains lidocaine hydrochloride monohydrate equivalent to 200 mg of lidocaine hydrochloride and adrenaline (epinephrine) tartrate equivalent to 50 micrograms of adrenaline (epinephrine).

Excipients with known effect
Each ml of solution for injection contains 2.48 mg of sodium and 0.5 mg of sodium metabisulfite (E223).

Each 10 ml ampoule contains 24.8 mg of sodium and 5 mg of sodium metabisulfite (E223).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear colourless aqueous solution, practically free from visible particles.
pH = 3.0 to 4.0
Osmolality:
Lidocaine/Adrenaline (Epinephrine) 20 mg/ml + 5 mcg/ml: 330-370 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidocaine/Adrenaline (Epinephrine) is indicated for local or regional anaesthesia.

Lidocaine/Adrenaline (Epinephrine) 20 mg/ml + 5 mcg/ml is intended for adults and adolescents over 12 years.

4.2 Posology and method of administration

Lidocaine adrenaline should only be used by or under the supervision of a doctor with experience in regional anaesthesia. The lowest concentration and smallest possible dose for adequate anaesthesia should be given (see section 4.4).
Dose should be adjusted according to age, weight and condition of the patient.

Posology
Adults

The recommended doses of lidocaine adrenaline in adults are shown in Table 1.

Table 1: Recommended dosage in adults

Indication	Lidocaine hydrochloride		
	Concentration	Dose	Recommended total dose
Infiltration anaesthesia	10 mg/ml 20 mg/ml	1-20 ml 0.5-10 ml	10-200 mg 10-200 mg
Peripheral nerve blocks			
Brachial plexus block	10 mg/ml 20 mg/ml	20-35 ml 10-17.5 ml	200-350 mg 200-350 mg

Paravertebral block	10 mg/ml 20 mg/ml	3-5 ml 1.5-2.5 ml	30-50 mg (per segment) 30-50 mg (per segment)
Intercostal nerve block	10 mg/ml 20 mg/ml	3-5 ml 1.5-2.5 ml	30-50 mg (per segment) 30-50 mg (per segment)
Sciatic nerve block	10 mg/ml 20 mg/ml	10-40 ml 5-20 ml	100-400 mg 100-400 mg
Pudendal block (on each side)	10 mg/ml 20 mg/ml	10-20 ml 5-10 ml	100-200 mg 100-200 mg
Paracervical block (on each side)	10 mg/ml 20 mg/ml	10 ml 5 ml	100 mg 100 mg
Retrobulbar block	10 mg/ml 20 mg/ml	2-5 ml 1-2.5 ml	20-50 mg 20-50 mg
Epidural anaesthesia			
Lumbar anaesthesia	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
Obstetric anaesthesia	10 mg/ml 20 mg/ml	20-30 ml 10-15 ml	200-300 mg 200-300 mg
Caudal - Surgical anaesthesia	10 mg/ml 20 mg/ml	40 ml 20 ml	400 mg 400 mg

Maximum recommended doses
The maximum dose of lidocaine hydrochloride with adrenaline should not exceed 500 mg.

Special populations
Elderly or frail subjects
Elderly or frail patients may be more sensitive to standard doses, which increases the risk and severity of toxic reactions affecting the central nervous system and cardiovascular system and calls for close clinical monitoring. Doses are calculated individually according to the age and body weight of the patients. Doses may need adaptation as cardiac output and hepatic blood flow decrease with advanced age indicating a decreased clearance of lidocaine (see section 5.2).

Patients with renal impairment
Patients should be monitored as renal impairment may cause toxic effects due to the accumulation of active metabolites (see section 4.4 and 5.2). The dose may need to be adapted due to reduced clearance and increased half-life of lidocaine.

Patients with hepatic impairment
The dose may need to be reduced up to a half in patients with hepatic insufficiency (see section 4.4).

Patients with cardiac insufficiency
The dose may need to be reduced up to a half in patients with cardiac insufficiency (see section 4.4).

Other special population
Doses may need to be reduced in patients with poor general condition or in those with reduced protein binding capacity (resulting e.g. from renal insufficiency, liver insufficiency, cancer, pregnancy).

Paediatric population
Lidocaine/Adrenaline (Epinephrine) 20 mg/ml + 5 mcg/ml should not be used in children aged less than 12 years because of safety concern and toxic reaction (see sections 4.8 and 4.9).

Adolescents (12-18 years)
The posology is the same as for adults.

Children aged 1 to 11 years
Dose should be calculated based on weight up to a maximum of 7 mg/kg.
For calculation in overweight children, the average weight for the age is to be considered.

Method of administration

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

Extreme care should be taken to prevent accidental intravascular injection. Aspiration should always be done carefully. A test dose of 3–5 mL of short-acting local anaesthetic is recommended for epidural anaesthesia.

Verbal contact with the patient and repeated monitoring of the heart rate for 5 minutes following the administration of the test dose should take place. Re-aspiration should be done before administration of the full dose. The full dose should be injected slowly, under constant verbal contact with the patient.
If mild toxic symptoms occur, administration should be stopped immediately.

For surgical anaesthesia (e.g. epidural administration), the higher concentration and dose (higher than the concentration and dose for postoperative pain relief) should generally be used. However, use the minimum effective concentration and dose whenever possible and do not exceed the maximum dose.

The volume of solution used plays a role in the extent of the anaesthetic diffusion area.

It is preferable to bring the solution to body temperature before injection because injecting cold solutions is painful.

4.3 Contraindications

- Hypersensitivity to lidocaine and other amide-type local anaesthetics or any of the excipients listed in section 6.1.
- Hypersensitivity to sulphite in the medical history is a contraindication to the use of adrenaline-containing local anaesthetics.
- Lidocaine should not be used for epidural anaesthesia in patients with severe hypotension such as cardiogenic and hypovolaemic shock.
- The use of adrenaline in anaesthesia of organs with terminal arteries such as fingers, toes, the nose, ears or penis should be avoided.

4.4 Special warnings and precautions for use

Administration of regional or local anaesthesia should be done in a suitably equipped and staffed room. Regional or local anaesthetic procedures, except those of the most trivial nature, should always be performed in close proximity to resuscitation equipment. Medication and other supplies for monitoring and resuscitation should be within reach.

For major blocks, an intravenous cannula should be inserted before injecting the local anaesthetic.

Like all local anaesthetics, lidocaine can cause acute central nervous and cardiovascular toxic effects from high concentrations in the blood, especially after unintentional intravascular administration. Physicians should be familiar with the techniques to be used and should be aware of the diagnosis and treatment of systemic toxicity and other complications that may occur with the use of local anaesthetics (see section 4.9).

In rare cases, cardiac arrest has been described without prior central nervous system symptoms. This cardiac arrest was probably a symptom of overdose due to inadvertent intravascular injection (see section 4.9).

Extreme caution should be exercised in the use of adrenaline-containing solutions in patients with severe or untreated hypertension, hyperthyroidism, ischaemic heart disease, disorders of atrioventricular conduction, cerebrovascular insufficiency, diabetes or other diseases that may worsen due to the effects of adrenaline. Adrenaline can provoke angina pains in patients with angina.

Warnings regarding special patient groups
To minimise the risk of dangerous adverse reactions, special attention is needed in the following groups of patients:

- Patients with a partial or total AV block, as local anaesthetics can decrease myocardial conductivity.
- Elderly people and patients in poor overall condition.
- Patients with severe hepatic and/or renal insufficiency.

- Patients treated with class III anti-arrhythmic agents (e.g. amiodarone) should be supervised and ECG monitoring should be considered as concomitant cardiac effects are possible (see section 4.5).
- Patients with acute porphyria. Lidocaine/Adrenaline (Epinephrine) solution for injection is probably porphyrinogenic and should only be prescribed on strict indication to patients with severe or urgent cases of acute porphyria. Appropriate precautions should be taken in all patients with porphyria.

The use of local anaesthetics in an inflamed area should be avoided.

There have been post-marketing reports of chondrolysis in patients receiving post- operative intraarticular 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. Intraarticular continuous infusion is not an approved indication for lidocaine.

Warnings regarding administration technique
Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by intravenous administration of crystalloid or colloidal solutions.

Rare cases of neuropathies have been reported after administration of high concentrations of lidocaine in the intrathecal space. Signs of spinal block should be monitored to recognise unintentional intrathecal injection.
Serious adverse reactions have been described for some local anaesthetic techniques - independent of the local anaesthetic used.

For example:

- *Epidural anaesthesia* can lead to hypotension and bradycardia, especially in hypovolaemic patients. This risk can be reduced by filling the circulation with a crystalline or colloidal solution prior to administration of the anaesthetic. Hypotension should be treated immediately with intravenous administration with sympathomimetics, which may be repeated if necessary.
- Caution should be exercised when using epidural anaesthesia in patients with reduced cardiovascular reserve, as they may be less able to compensate for the slowing of atrioventricular conduction induced by lidocaine.
- A *paracervical block* affects the foetus more than other blocks used in obstetrics. Foetal cardiac action should be monitored during paracervical anaesthesia, as foetal bradycardia or tachycardia has been frequently observed and may be accompanied by foetal acidosis and hypoxia. The potential undesirable effects of a paracervical block should be weighed against the benefits.
- With *retrobulbar injection*, in rare cases the local anaesthetic may leak into the subarachnoid space, causing toxic reactions even at low doses of local anaesthetic, in particular temporary blindness, cardiovascular collapse, apnoea, convulsions, etc. These complications should be recognised and treated immediately.
- There is a small risk of persistent ocular muscle dysfunction with *retro- and peribulbar injections* of local anaesthetics. Primary causes include trauma and/or local toxic effects on muscle and/or nerve tissue. The severity of the tissue reaction depends on the severity of the trauma, the strength of the injection fluid used and the length of time the tissue was exposed to the local anaesthetic. Therefore, it is recommended to choose the lowest effective concentration and dose for all local anaesthetics. Vasoconstrictors and other additives may potentiate tissue reactions and should be used only on indication.
- Injections in the head-neck region in particular can inadvertently become intravascular, causing cerebral toxicity even at low doses.

Other warnings
Possible cross-sensitivity with other amide-type local anaesthetics should be taken into account.

Sodium
This medicinal product contains 2.48 mg of sodium per ml, equivalent to 1.24% of the WHO-recommended maximum daily intake of 2 g sodium for an adult.

Sodium metabisulphite
This medicinal product contains sodium metabisulphite. In rare cases, this can result in severe hypersensitivity reactions and bronchospasms.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with lidocaine
Pharmacodynamic interactions

Class I antiarrhythmics
Simultaneous administration of lidocaine and other class I antiarrhythmics should be avoided because of the risk that serious cardiac adverse effects occur.

Other anti-arrhythmics
If lidocaine is combined with other anti-arrhythmic medicinal products such as beta receptor blockers or calcium channel blockers, the inhibitory effect on atrioventricular and intraventricular conduction and on contractility may be enhanced.

Combination with other local anaesthetics
Combination of different local anaesthetics may lead to additive effects on the cardiovascular and the central nervous system.

Muscle relaxants
The effect of muscle relaxants (e.g. Suxamethonium) is prolonged by lidocaine.

Sedatives, hypnotics
Lidocaine should be administered with due caution to patients receiving medication with sedatives that also affect the function of the CNS and therefore may alter the toxicity of lidocaine. There may be an additive effect between the local anaesthetic effect and sedatives or hypnotics.

Volatile anaesthetics
If lidocaine and volatile anaesthetics are given simultaneously, the depressive effects of both may be intensified.

Medicinal products that can lower the seizure threshold
As lidocaine itself may reduce the seizure threshold co-administration with other medicinal products lowering the seizure threshold (e.g. tramadol or bupropion) may increase the risk of seizures.

Medicinal products that can raise the seizure threshold
Simultaneously administered diazepam raises the threshold for Lidocaine to produce convulsions. This must be kept in mind when monitoring patients for signs of toxicity of Lidocaine.

Pharmacokinetic interactions

Lidocaine is mainly metabolized via the cytochrome P 450 isoenzymes CYP 3A4 and CYP 1A2 (see section 5.2). Concomitant administration with active substances that are substrates, inhibitors or inducers of hepatic enzymes, isoenzyme CYP3A4 and CYP1A2, may have an influence on the pharmacokinetics of lidocaine and thus also on its effect.

Inhibitors of CYP 3A4 and/or CYP 1A2

Concurrent administration of lidocaine with inhibitors of CYP3A4 and/or CYP1A2 may lead to accelerated plasma concentrations of lidocaine. Increased plasma levels have been reported for e.g:

- Amiodarone (CYP3A4 inhibitor): Amiodarone decreases hepatic metabolism of lidocaine, thus leading to the risk of increase of lidocaine levels, with subsequent increase of neurological and cardiovascular toxicity. Clinical monitoring, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after amiodarone therapy.
- Cimétidine (CYP3A4 and CYP1A2 inhibitor): Cimetidine used at doses equal or higher than 800 mg/day: increase of plasma concentration of lidocaine with subsequent increase of neurological and cardiovascular toxicity. Clinical survey, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after cimetidine therapy.

- Fluvoxamine (CYP3A4 and CYP1A2 inhibitor): Increase of lidocaine levels, thus enhancing risk of neurological and cardiovascular toxicity. Clinical monitoring, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after the association.
- Betablockers (except esmolol): Lidocaine intravenous: increase of lidocaine levels, with subsequent increase of neurological and cardiovascular toxicity. Clinical monitoring, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after betablockers therapy.
- Other known inhibitors of CYP3A4: protease inhibitors (e.g. ritonavir), macrolides antibiotics (e.g. erythromycine), antifungals (e.g. ketoconazole, itraconazole).
- Other known inhibitors of CYP1A2: ciprofloxacin.

Inducers of CYP 3A4 and/or CYP 1A2

Active substances inducing CYP3A4 and/or CYP 1A2 such as barbiturates (mainly phenobarbital), carbamazepine, phenytoin or primidone, accelerate the plasmatic clearance of lidocaine and thus reduce the efficacy of lidocaine.

Other pharmacokinetic interactions

Medicinal products that alter the metabolism, hepatic blood flow, cardiac output or peripheral distribution of lidocaine may influence plasma levels of lidocaine.

Medicinal products that cause hypokalaemia
The electrophysiological effects of lidocaine are highly dependent on the extracellular potassium concentration and can be almost completely blocked by hypokalemia. Concomitant use of medicinal products that can cause severe hypokalemia (e.g. acetazolamide, loop diuretics and thiazides) should therefore be avoided or used under careful monitoring of serum potassium concentration.

Interactions with adrenaline

Non-selective beta-receptor blockers
Non-selective beta-receptor blockers, such as propranolol, enhance the pressor effect of adrenaline, which can lead to intense hypertension and bradycardia. The combination may necessitate a dose adjustment.

Inhalation anaesthetics
Adrenaline can cause serious cardiac arrhythmias when injected under general anaesthesia with halothane. The combination may necessitate a dose adjustment.

Tricyclic antidepressants
The pressor effect of adrenaline in combination with tricyclic antidepressants can cause a prolonged elevation in blood pressure. In acute toxicity studies with high-dose intravenous adrenaline, the effect has been shown to be enhanced 2- to 3-fold.
A combination of adrenaline-containing solutions and ergot-type *oxytocin-like* medicinal products can produce a strong, sustained increase in blood pressure and possibly cause cerebrovascular and cardiac damage.

Phenothiazine derivatives and *butyrophenone derivatives* may reduce or inhibit the pressor effect of adrenaline.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of lidocaine/adrenaline in pregnant women.
Lidocaine crosses the placenta. It is reasonable to presume that lidocaine has been used in a large number of pregnant women and women of childbearing potential. There is no evidence that lidocaine cause disturbances in the reproductive process such as increased rates of malformations or has any direct or indirect foetal effects. However, the risks to humans have not been fully investigated.

Animal studies are incomplete with respect to the effects of lidocaine and adrenaline on pregnancy, embryonic/foetal development, delivery and development after birth (see section 5.3).
Animal studies have shown a teratogenic risk during organogenesis for adrenaline (see section 5.3). However, prolonged experience with use of adrenaline in pregnancy over several decades does not identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes.

For occasional use during pregnancy and childbirth, the benefits are considered to outweigh the potential risks. Paracervical block or pudendal block with lidocaine increases the risk of reactions such as foetal bradycardia/tachycardia. The foetal heart rate must therefore be carefully monitored. Adrenaline can reduce uterine blood flow and uterine contraction during childbirth, especially after intravenous injection (see also section 5.2).

Lactation

Adrenaline is excreted in breast milk. However, adrenaline is not absorbed when orally ingested. Small amounts of lidocaine are excreted in breast milk, and it is poorly absorbed by the infant. The mother's need for treatment with Lidocaine adrenaline and the benefits of breast-feeding must be weighed against the potential risks to the child.

4.7 Effects on ability to drive and use machines

Lidocaine/Adrenaline (Epinephrine) may have influence on the ability to drive and use machines. After injection of local anaesthetics, a transient sensory loss and/or motor blockade, may occur. Until the effects subside patients should not drive vehicles or use machines.

4.8 Undesirable effects

Summary of the safety profile

The frequency and severity of the undesirable effects of lidocaine depend upon the dose, the method of administration and the patient's individual sensitivity.

The undesirable effects related to local anaesthetics are rare in the absence of an overdose, abnormal rapid systemic absorption or accidental intravascular injection; in such cases, they can be very serious, in particular in terms of cardiac and neurologic function.

Adverse reactions caused by lidocaine may be difficult to distinguish from the physiological effects of the nerve block (e.g. hypotension, bradycardia), events caused directly (e.g. neurological lesions) or indirectly by needle puncture.

Symptoms of local toxicity may occur after the administration of lidocaine. Systemic adverse effects may be expected at plasma concentrations of lidocaine exceeding 5-10 mg/l. They become manifest in the form of both CNS symptoms and cardiovascular symptoms.

The possible undesirable effects after administration of lidocaine as local anaesthetic are largely the same as those produced by other amide-type local anaesthetics.

The adverse reactions listed in this section fall in to the following frequency categories: 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) and not known (cannot be estimated from the available data).

MedDRA System Organ Class	**MedDRA preferred term**				
	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)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					Methaemoglobinae-mia
Immune system disorders				Allergic reactions*, anaphylactoid reactions, bronchospasm, and in severe	

				cases anaphylactic shock	
Nervous system disorders		Paraesthesia, loss of consciousness, transient neurological symptoms.	Signs and symptoms of CNS toxicity (circumoral paraesthesia, numbness of the tongue, hyperacusis, dysarthria)	Neuropathy, convulsion (overdose), peripheral nerve damage, cranial nerve lesions, persistent anaesthesia, paresis, headache accompanied by tinnitus and photophobia, neurosensory deafness. Regional applications in the thoracic or head/neck region may induce sympathetic blockade resulting in transient symptoms such as Horner's syndrome, Harlequin syndrome.	
Eye disorders				Double vision	
Cardiac disorders		Bradycardia		Arrhythmia, myocardial depression or possibly cardiac arrest (overdose or inadvertent intravascular injection)	
Vascular disorders		Hypertension, hypotension			
Respiratory, thoracic and mediastinal disorders				Respiratory depression	
Gastrointestinal disorders	Nausea	Vomiting			
Skin and subcutaneous tissue disorders				rash, urticaria, oedema	

*Skin testing for allergy to lidocaine is not considered to be reliable

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

In elderly patients the incidence of undesirable effects may be increased.

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Depending on the individual sensitivity, toxic reactions occur from a concentration of approximately 5 - 10 mg lidocaine per litre upward in venous blood.

The lethal plasma concentration for humans is in the range 6 to 33 mg lidocaine per litre.

An overdose, or an accidental intravascular injection can produce excessive plasma concentrations of lidocaine; this results in signs of acute toxicity, which can lead to very serious undesirable effects. The toxic effects of lidocaine depend on the level of the plasma concentration; the higher the plasma concentration and the more rapid its rise, the more frequent and more serious are the toxic reactions. Such toxic reactions concern the central nervous system and the cardiovascular system.

Symptoms
Low toxic overdoses of lidocaine result in stimulation of the CNS. Gross overdose, producing high toxic plasma concentrations, causes depression of the central functions.

Central nervous system toxicity is a graded response with symptoms and sign of escalating severity.

Initially, symptoms are observed such as: dizziness, vertigo, agitation, hallucination, euphoria, apprehension, yawning, logorrhoea, headaches, nausea, vomiting, labial paresthesia, numbness of the tongue, tinnitus and dysarthria, impaired hearing and vision.

Other subjective central nervous system symptoms include: disorientation, occasional feeling of drowsiness. Tachycardia, hypertension and flushing have also been reported.

These signs of alarm necessitate attentive surveillance : muscular twitching, tremors, shivering, and generalised seizures. Simultaneously administered diazepam raises the threshold for lidocaine to produce convulsions. This must be kept in mind when monitoring patients for signs of toxicity of lidocaine.

In cases of very high dose administered: generalized depression of central nervous system, respiratory depression, coma and respiratory arrest.

Cardiovascular toxicity may be seen in severe cases : cardiac rhythm disorders such as ventricular extrasystole, ventricular fibrillation, unpalpable pulse, pallor, major bradycardia, disorders of atrioventricular conduction, decrease in cardiac contractility, hypotension and cardiac arrest.

Treatment

If signs of acute toxicity occur during administration of the local anaesthetic, administration of the anaesthetic should be stopped 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.

If cardiovascular depression is evident (hypotension, bradycardia) treatment with intravascular fluid substitution, vasopressoric, chronotropic and/or inotropic drugs should be taken in consideration.

In case of circulatory arrest, immediate cardiopulmonary resuscitation should be initiated. 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.

Lidocaine cannot be eliminated by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics
ATC code: N01BB52.

Lidocaine adrenaline contains lidocaine, an amide-type local anaesthetic, and the vasoconstrictor adrenaline (epinephrine). Lidocaine reversibly blocks impulse conduction in nerve fibres by inhibiting the transport of sodium ions across the nerve membrane. Similar effects can also be observed in excitable membranes in the brain and cardiac muscle.

The onset and duration of the local anaesthetic effect of lidocaine depend on the administration site and dose. The presence of adrenaline may prolong the duration of action for infiltration and peripheral nerve blocking, but it has a less pronounced effect on epidural blocking.

Central nervous system toxicity occurs at lower plasma concentrations of lidocaine than cardiac toxicity. Therefore, in case of overdose, symptoms of central nervous system toxicity appear first, before symptoms of cardiac toxicity.

Effects of systemically circulating local anaesthetics on the heart may include delay of the stimulus threshold and conduction, negative inotropy, negative chronotropy and hypotension. These effects can lead to cardiac arrest in rare cases.

5.2 Pharmacokinetic properties

Absorption

Plasma levels depend on the site and method of administration. However, there is a poor relationship between the amount of local anaesthetic injected and peak plasma levels.

Maximum concentrations are achieved within latest 30 minutes, in the majority of patients maximum concentrations are met within 10-20 minutes.

Intercostal blocks produce the highest plasma concentrations, while subcutaneous injections into the abdomen produce the lowest plasma concentrations

After intramuscular injectionof 400 mg of lidocaine hydrochloride monohydrate for intercostal block the maximum plasma concentration (C_{max}) has been determined to be 6.48 mg/l, attained after 5 – 15 min (t_{max}).

After subcutaneous administration, C_{max} values reached 4.91 mg/l (vaginal injection) or 1.95 mg/l (abdominal injection), respectively. In a study involving 5 healthy volunteers, after maxillar-buccal infiltration anaesthesia with 36 mg of lidocaine, using a 2 % solution, the C_{max} value reached 0.31 mg/l.

The adrenaline additive (5 µg/ml) slows the rate of absorption and reduces the maximum plasma concentration by 20-50%, depending on the injection site.

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

Distribution

Lidocaine follows a biphasic elimination kinetic. After intravenous administration the active substance is first rapidly distributed from the central compartment into intensively perfused tissues and organs (alpha-distribution phase). This phase is followed by redistribution into skeletal muscles and adipose tissue. The half-life time during the alpha-distribution phase is approximately 4-8 minutes. Distribution into peripheral tissues is predicted to occur within 15 min.

The plasma protein binding rate is approximately 60 – 80 per cent in adults. It is dependent on the active substance concentration and additionally on the concentration of the alpha-1-acid glycoprotein (AAG). The AAG is an acute phase protein that is binding free lidocaine and may be increased e.g. after trauma, surgery or burns depending on the pathophysiological condition of the patient. To the contrary it had been shown that AAG concentrations are low in new-born infants and patients suffering from liver impairment leading to a marked reduction of lidocaine plasma protein binding.

The volume of distribution at steady state is 91 litres. The volume of distribution may be altered in patients suffering from further diseases, e.g. heart insufficiency, liver insufficiency or renal insufficiency.

Biotransformation

Lidocaine is rapidly metabolised in the liver by mono-oxygenases mainly via oxidative N-dealkylation, hydroxylation at the aromatic ring and hydrolysis of the amide bond. Hydroxylated derivatives undergo conjugation.

In total, approx. 90 % of lidocaine is metabolised to 4-hydroxy-2,6-xylidine, to 4-hydroxy-2,6-xylidine glucuronide and to a lower degree to the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX).

The latter may accumulate during longer lasting infusions or in the presence of severe renal insufficiency due to their longer half life time as compared to lidocaine itself. In the presence of liver diseases the metabolic rate may be reduced to 10 – 50 per cent of normal.

Results with human liver microsomes and recombinant human CYP isoforms demonstrated that CYP1A2 and CYP3A4 enzymes are the major CYP isoforms involved in lidocaine N-deethylation.

Elimination

Less than 10 per cent of lidocaine are excreted unchanged in urine, the remaining proportion in the form of the metabolites.

The elimination half-life time is 1.5 – 2 hours in adults and approx. 3 hours in newborns. The elimination half-life maybe increased in case of severe heart failure (up to 4 – 12 hours), or chronic liver disease (up to 4.5 – 6 hours).

The half-life times of the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX) are 2-6 hours and 10 hours, respectively. Since their plasmatic half-lives are longer than that of lidocaine, accumulation of metabolites, particularly GX, may occur during prolonged infusion.

Additionally, the elimination rate depends on the pH; it can be increased by acidification of the urine. The plasmatic clearance is about 0.95 ml/min.

The hepatic blood flow appears to limit the rate of lidocaine metabolism.

Special populations

Patients with renal impairment

The plasmatic half-life time of lidocaine seemed to be unaltered except for some accumulation of GX during infusion of 12 hours or more. This accumulation seemed to be associated with long-term administration of the drug. However, in patients with severe renal insufficiency clearance of lidocaine was approximately halved and half-life time of lidocaine was about twice the amount than in healthy patients.

Patients with liver impairment

The plasmatic half-lifeof lidocaine and its metabolites may be prolonged, and significant effects on pharmacokinetics and dosage requirements of lidocaine are to be expected, in patients with impaired liver perfusion, e.g. after acute myocardial infarction, in the presence of cardiac insufficiency, liver disease or congestive heart failure.

Elderly

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

Pregnant or breast-feeding woman

Lidocaine passes across the placental barrier by simple diffusion and reaches the fetus within a few minutes of administration.
After paracervical block, markedly higher concentrations of lidocaine have been found in umbilical blood.
The fetus is able to metabolise lidocaine. The levels in fetal blood are approximately 60% of the concentrations in the maternal blood. Due to a lower plasma protein binding in fetal blood, the concentration of the pharmacologically active free lidocaine is 1.4 fold the maternal concentration.
Lidocaine is secreted into breast milk only in small amounts.

Paediatric population

In new-born infants, 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 new-born infants is not recommended.

5.3 Preclinical safety data

Reproductive toxicity
No teratogenic effects were observed in rat and rabbit embryo/foetal development studies with lidocaine dosing during organogenesis. Embryotoxicity was observed in rabbits at the maternally toxic dose. The offspring of rats treated with a maternally toxic dose during late gestation and lactation showed reduced postnatal survival.

At very high doses, adrenaline caused malformations in rats. Apart from these, there are no reproductive toxicological studies on adrenaline in animals.

Genotoxicity and carcinogenicity
Genotoxicity studies of lidocaine were negative. The carcinogenicity of lidocaine has not been studied. The lidocaine metabolite 2,6-dimethylaniline has genotoxic potential *in vitro*. In a carcinogenicity study in rats with in utero, postnatal or lifetime exposures to 2,6-dimethylaniline, tumours were observed in the nasal cavity, subcutaneous tissue and liver. The clinical relevance of the tumour findings in short-term/intermittent use of lidocaine is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid, concentrated (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Sodium metabisulphite (E223)
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

Unopened ampoules: 2 years.
This medicinal product may be stored at temperatures not exceeding 25 °C for a maximum period of 3 months. In all cases, once initially removed from refrigerated storage, the medicinal product should be discarded after 3 months.

After first opening of the ampoule:
The solution for injection is to be administered immediately after opening the container. Discard any unused portion.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

10 ml solution in colourless glass ampoule. Each pack contains 10 ampoules.

6.6 Special precautions for disposal and other handling

Instruction for use:
The product should be inspected visually for particles and discoloration prior to administration. Only clean and 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

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8 MARKETING AUTHORISATION NUMBER

PA1968/027/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2025

10 DATE OF REVISION OF THE TEXT