Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

2% w/v Lidocaine Hydrochloride Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the solution for injection contains 20mg Lidocaine hydrochloride monohydrate.
Accordingly, the contents per ampoule are as follows:

- One ampoule of 5ml contains 100mg of Lidocaine hydrochloride monohydrate
- One ampoule of 10ml contains 200mg of Lidocaine hydrochloride monohydrate
- One ampoule of 20ml contains 400mg of Lidocaine hydrochloride monohydrate

Excipients with known effect:
Sodium (as sodium chloride and sodium hydroxide) 95 µmol/ml
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless aqueous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Local and regional anaesthesia.

Severe symptomatic ventricular tachycardia or tachy-arrhythmia, if assessed to be life-threatening.

4.2 Posology and method of administration

Posology

Local and regional anaesthesia
As a matter of principle the smallest possible dose that produces adequate anaesthesia should be administered. The dosage should be adjusted individually according to the particulars of each case.

Adults
When injected into tissues with marked systemic absorption, without combination with a vasoconstrictor, a single dose of lidocaine hydrochloride monohydrate should not exceed 4.5 mg/kg body weight (BW) (or 300 mg). If combined with a vasoconstrictor, 7 mg/kg BW (or 500 mg) of lidocaine hydrochloride monohydrate per single dose should not be exceeded.

For the clinical uses listed below, recommendations for single doses and strengths of the injection solution to be administered to adults with average body weight (70 kg) are as follows:

Type of anaesthesia	**Concentration [%]**	**Usual volume [ml]**	**Maximum dose [mg]**
Infiltration	0.5-1		300 500 (with epinephrine)
Major nerve blocks	1-2	30-50	500 (with epinephrine)
Minor nerve blocks	1	5-20	200
Epidural	1-2	15-30*	500 (with epinephrine)
Spinal	1.5 or 5 in 7.5% glucose	1-2	100

Type of anaesthesia	**Concentration [%]**	**Usual volume [ml]**	**Maximum dose [mg]**
Intravenous regional anaesthesia (IVRA) - upper limb -lower limb	 0.5 0.25	 40 50-100	

*1.5 ml per segment in average

For prolongation of anaesthesia lidocaine may be combined with a vasoconstrictor, e.g. epinephrine. Addition of epinephrine at a concentration of 1:100 000 to 1:200 000 has proven useful.

Paediatric population

For children, the doses are calculated individually according to the patient's age, body weight and the nature of the procedure. Up to 5mg/kg BW may be administered. With the addition of epinephrine, up to 7 mg/kg can be used. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. For anaesthesia in children, only a low strength (0.5 % w/v) of the local anaesthetic should be used. To achieve a complete motor block, a higher strength (1 % w/v) may be required.

Lidocaine should be used with caution in children younger than two years of age as there are insufficient data to support the safety and efficacy of this product in this patient population at this time.

Elderly patients

For elderly patients, the doses must be calculated individually according to the patient's age and body weight. Dosages may need adaptation as cardiac output and hepatic blood flow may decrease with advanced age indicating a decreased clearance of lidocaine (see section 5.2).

Other special patient groups

- Doses should be reduced in patients in **poor general condition** or in those with reduced **protein binding capacity** (resulting e.g. from renal insufficiency, liver insufficiency, cancer, pregnancy).
- In patients with severe **renal insufficiency** the dose may need to be adapted due to reduced clearance and increased half-life of lidocaine (see section 5.2).
- Patients with **liver diseases show reduced** tolerance towards amide-type local anaesthetics. This may be due to reduced hepatic metabolism and decreased protein synthesis resulting in a lower protein binding rate of the local anaesthetic. Dose reduction is advisable in such cases.
- The dose should be reduced in patients showing clinical signs of **cardiac insufficiency**. Nevertheless, local or regional nerve blockage can be the anaesthetic method of choice in such patients.
- During pregnancy, the dose may need to be reduced depending on the type of anaesthesia. Regional anaesthetic blocks in which usually large doses are required should be avoided during the first trimester. For use in anaesthetic blocks in which smaller doses are administered the dosage may need to be reduced because of the altered anatomical and physiological characteristics in late pregnancy.

Antiarrhythmic therapy

Adults

The dosage must be adjusted according to individual requirements and the therapeutic effect.

Bolus:

Usual loading doses are 50-100 mg or 1 – 1.5 mg/kg BW of lidocaine hydrochloride monohydrate as direct intravenous injection, corresponding to approximately 2.5 - 5 ml or 0.05 - 0.075 ml/kg BW of 2% w/v Lidocaine Hydrochloride Injection BP.

The rate of injection should not exceed 25-50 mg/min, corresponding to approximately 1.25 – 2.5 ml/min 2% w/v Lidocaine Hydrochloride Injection BP.

If the therapeutic effect of the first dose is insufficient within the first 5 – 10 minutes, the initial dose may be repeated once or twice up to a maximum dose of 200 – 300 mg in 1 hour.

Maintenance:
To maintain therapeutic plasma lidocaine concentrations (1.5 - 5 µg/ml), lidocaine hydrochloride monohydrate is infused at a rate of 20 - 50 µg/kg BW/min (about 1-4 mg/min), corresponding to approximately 0.001 – 0.0025 ml/kg BW/min.

Infusions can be prepared by adding 1000 mg of lidocaine hydrochloride monohydrate, corresponding to 50 ml 2% w/v Lidocaine Hydrochloride Injection BP, to 500 ml of glucose solution or physiological saline.

The infusion should be terminated as soon as the patient's basic cardiac rhythm appears to be stable or at the earliest signs of toxicity. It should rarely be necessary to continue the infusion beyond 24 hours. As soon as possible, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

Paediatric patients
The safety and the efficacy of the use of lidocaine in children have not yet been definitely established. The dose should be adapted according to the clinical situation and the nature of the procedure.

Infants and children may be given an initial IV bolus of 0.5 - 1 mg/kg BW. This dose may be repeated according to the response of the patient, but the total dose should not exceed 3-5 mg/kg BW. If required, a maintenance IV infusion of 10 - 50 µg/kg BW/min may be given via an infusion pump.

For advanced cardiovascular life support in children, the recommended dosage is an initial rapid IV or intraosseous injection (i.e. bolus) of 1 mg/kg BW up to a maximum initial dose of 100 mg.

If ventricular tachycardia or ventricular fibrillation is not corrected following defibrillation (or cardioversion) and an initial recommended dose of lidocaine, an IV or intraosseous infusion should be started at a rate of 20-50 µg/kg BW/min.

Elderly patients
For elderly patients, the doses are calculated individually according to the patient's age and body weight. Dosages may need adaptation as cardiac output and hepatic blood flow decrease with advanced age indicating a decreased clearance of lidocaine (see section 5.2).

Other special patient groups

Cardiac insufficiency, hepatic insufficiency, co-medication, pregnancy
The dose should be reduced in patients with cardiac insufficiency, hepatic insufficiency, in patients receiving drugs that intensify the effects of lidocaine (see section 4.5) and during pregnancy (see section 4.6). See also section 5.2.

Renal insufficiency
Renal insufficiency as a rule does not require specific dose adjustment. However, such patients should be monitored for toxic effects caused by accumulation of active metabolites. In cases of severe renal insufficiency the dose may need to be adapted (see also section 5.2).

Method of administration
Local and regional anaesthesia
Intradermal, intramuscular, subcutaneous, or submucosal use (infiltration), perineural (injection into the surroundings of peripheral nerves), epidural or spinal use. Intravenous use regarding intravenous regional anaesthesia (Bier`s block). Every local anaesthetic procedure should only be carried out by personnel adequately skilled in the respective anaesthetic technique.

Antiarrhythmic therapy
Intravenous use. Intraosseous use.
Administer as slow intravenous injection or intravenous infusion after dilution in a suitable vehicle solution.
Because of the relatively short duration of action of lidocaine, the injection should be followed by continuous infusion, if possible, using an infusion pump.

4.3 Contraindications

General

- hypersensitivity towards lidocaine, amide-type local anaesthetics or to any of the exipients listed in section 6.1

Local and regional anaesthesia
The special contraindications for spinal and epidural anaesthesia must also be observed:

- uncorrected hypovolaemia,
- coagulopathy (acquired, induced, genetic)
- increased intracranial pressure
- intracranial or intraspinal haemorrhage.

Antiarrhythmic therapy

- Severe conduction disorders
- Myocardial infarction within the preceding 3 months or markedly decreased cardiac output unless there is life threatening ventricular cardiac arrhythmia.

4.4 Special warnings and precautions for use

General
In the case of known allergy towards other amide-type local anaesthetics, group allergy towards lidocaine should be considered.

Lidocaine should only be used with particular caution in patients with liver or kidney diseases or with *myasthenia gravis,* impaired cardiac conduction (see also section 4.3), cardiac insufficiency, bradycardia, impaired respiratory function and severe shock. See also section 4.2.

In general, prior to injection of lidocaine, it must be made sure that all equipment for resuscitation and emergency medication for the treatment of toxic reactions are instantly available.

Patients with **epilepsy** should be carefully monitored for the occurrence of central nervous symptoms. An increased tendency to convulsions should be considered even with doses below maximum.

Local and regional anaesthesia
Sudden arterial hypotension may occur as a complication of spinal and epidural anaesthesia, in particular in elderly patients.

Particular caution should also be exercised if the local anaesthetic is to be injected into inflamed (infected) tissue because of increased systemic absorption due to higher blood flow and decreased effect due to the lower pH of infected tissue.

A risk of post-spinal headache is associated with spinal anaesthesia mainly in adolescents and in adults up to the age of 30 years. This risk of post-spinal headache can be markedly reduced by choosing sufficiently thin injection cannulae.

After removing the tourniquet after intravenous regional anaesthesia there is an increased risk of adverse effects. Therefore the local anaesthetic should be drained off in several portions.

During anaesthetic procedures in the neck and head region patients are at increased risk of central nervous toxic effects of the drug. See also section 4.8.

Antiarrhythmic therapy
In acidosis, the plasma protein binding of lidocaine is reduced and therefore the concentration of free lidocaine is increased. Hence the effect of lidocaine may be intensified in acidosis.

Hypokalaemia, hypoxia, and disorders of acid-base balance need to be corrected prior lidocaine is used in patients who require large doses of antiarrhythmic agents.

During prolonged parenteral therapy with lidocaine, fluid balance, serum electrolytes and acid-base balance should be monitored regularly.

Administration of lidocaine should be accompanied by continuous monitoring of ECG, blood pressure, state of concsiousness and respiration. Especially adjustment of the dose of the anti-arrhythmic drug requires careful cardiological monitoring. Cardiological emergency equipment must be available. If one or more parameters indicate worsening of cardiac function, revision of therapy, which may include discontinuation of lidocaine, is necessary.

Note:
In narcotised patients central nervous disorders may remain unrecognised and cardiac adverse effects may suddenly occur without other previous warning symptoms.

Special warnings/precautions regarding excipients

5 ml and 10 ml ampoule:
This medicinal product contains sodium, but less than 1 mmol (23 mg) per ampoule, i.e. it is 'essentially sodium free'.

20 ml ampoule:
This medicinal product contains 1.9 mmol (43.7 mg) sodium per ampoule, equivalent to 2.2% 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

Pharmacodynamic interactions

- ***Vasoconstrictors***

The local anaesthetic effect is prolonged by combination with a vasoconstrictor, e.g. epinephrine.
If lidocaine is given as antiarrhythmic agent, additional medication with epinephrine or norepinephrine may lead to potentiation of the cardiac side effects.

- ***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.

- ***Muscle relaxants***

The effect of muscle relaxants is prolonged by lidocaine.

- ***Combination with other local anaesthetics***

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

- ***Volatile anaesthetics***

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

- ***Class I antiarrhythmic agents***

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

- ***Other anti-arrhythmic agents***

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

- ***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.

Pharmacokinetic interactions

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

- ***Beta receptor blockers, vasoconstrictors, cimetidine***

Beta receptor blockers (e.g. propranolol, metoprolol see also below), cimetidine (see also below), and vasoconstrictors like norepinephrine reduce cardiac output and/or hepatic blood flow and therefore reduce the plasma clearance of lidocaine prolonging its elimination half life. Therefore, due account should be taken of the possibility of accumulation of lidocaine.

- As lidocaine is mainly metabolized via the cytochrome P 450 isoenzymes CYP 3A4 and CYP 1A2 concurrently administered drug substances that are ***substrates, inhibitorsor 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. **erythromycine, fluvoxamine, amiodarone, cimetidine, protease inhibitors.**

Inducers of CYP 3A4 and/or CYP 1A2
Drugs inducing CYP3A4 and/or CYP 1A2, e.g. barbiturates (mainly **phenobarbital**), **carbamazepine, phenytoin or primidone**, accelerate the plasmatic clearance of lidocaine and thus reduce the efficacy of lidocaine.

Substrates of CYP 3A4 and/or CYP 1A2
Co-administration with other substrates of CYP 3A4 and/or CYP 1A2 may lead to increased plasma levels of the drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or a limited amount of data from the use of lidocaine in pregnant women. Animal studies do notindicate direct or indirect harmful effects with respect to reproductive toxicity (see 5.3).
However, lidocaine rapidly crosses the placenta. Therefore high plasma concentrations of lidocaine in the mother`s plasma may cause central nervous depression, alteration of the peripheral vascular tone and cardiac function in the foetus/neonate.
Lidocaine should only be used in pregnancy if there is an imperative indication. Then doses should be as low as possible.

Local and regional anaesthesia
Use of lidocaine for epidural, pudendal, caudal or paracervical block may cause varying degrees of foetal and neonatal toxicity (e.g. bradycardia, hypotonia or respiratory depression). An accidental subcutaneous injection of lidocaine in the fetus during paracervical or perineal block may cause apnoea, hypotension and convulsive fits and may thus put the new-born at vital risk.
In general lidocaine in strengths of 10 mg/ml should be preferred during pregnancy.

Breastfeeding
Lidocaine/metabolites are excreted in small amounts into human milk, but at therapeutic doses of 2% w/v Lidocaine Hydrochloride Injection BP no effects on the breastfed newborns/infants are anticipated.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

In general 2% w/v Lidocaine Hydrochloride Injection BP has negligible influence on the ability to drive and use machines. However, when outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is fully restored. So when using this medicinal product, the doctor has to asses in each individual case whether a patient is able to take part in traffic or to operate machinery.

4.8 Undesirable effects

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

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 (see also section 4.9).

Considering the method of administration systemic undesirable effects are more frequently associated with the use of lidocaine as antiarrhythmic agent.

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

Undesirable effects are listed according to their frequencies as follows:

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 from the available data)

Local and regional anaesthesia

Blood and the lymphatic system disorders

Not known: Methaemoglobinaemia

Immune system disorders
Rare: Anaphylacticreactions manifesting as urticaria, oedema, bronchospasm, respiratory distress and circulatory symptoms up to anaphylactic shock.

Nervous system disorders
Common: Transient neurological symptoms especially pain after spinal and epidural anaesthesia(up to 5 days).
Rare: Neurological complications following central nervous blocks – mainly spinal anaesthesia – such as persistent anaesthesia, paraesthesia, paresis up to paraplegia, *Cauda equina* syndrome (i.e. bilateral leg weakness up to paraplegia, saddle anaesthesia, urinary retention and fecal incontinence), headache accompanied by tinnitus and photophobia.
Cranial nerve lesions, neurosensory deafness (if administered in head and neck regions).
Horner's syndrome, associated with epidural anaesthesia or regional applications in the head/neck region.

Gastrointestinal disorder
Very common: Nausea, vomiting

Injury, poisoning and procedural complications
Rare: Trauma, transient radicular irritation due to spinal anaesthesia, compression of the spinal cord after development of haematoma

General disorders and administration site conditions
Rare: Shivering (after epidural use)

Antiarrhythmic therapy
The most frequently seen undesirable effects after administration of lidocaine as antiarrhythmic agent are those on the nervous system. Further heart function and circulation may be affected. Most of the reactions observed are associated with high injection speed or infusion rate.

Immune system disorders
Rare: Anaphylactic reactions manifesting as urticaria, oedema, bronchospasm, respiratory distress and circulatory symptoms up to anaphylactic shock.

Psychiatric disorders
Common: Confusion, restlessness, irritability, euphoria, hallucinations and depression.
Very common: Dysphoria

Nervous system disorders
Common: Somnolence, dizziness, vertigo, dysarthria, tinnitus, trembling, tingling and paraesthesia (skin), blurred vision
Rare: Muscular twitching, up to generalised convulsions, depressed level of consciousness up to coma.

Cardiac disorders
Rare: Bradycardia, atrioventricular block up to cardiac arrest
Very rare: Ventricular tachycardia

Vascular disorders
Rare: Hypotension

Gastrointestinal disorders
Very common: Nausea, vomiting, dysphagia,

Respiratory, thoracic and mediastinal disorders
Rare: Respiratory depression or even arrest.

Information on particular undesirable effects
none

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

Elderly patients
In elderly patients the incidence of undesirable effects may be increased (see section 4.4).

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

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.

Depending on the individual sensitivity, toxic reactions occur from a concentration of approximately 5 - 9 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.

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

Two phases of lidocaine intoxication can be distinguished:

Stimulation
At the beginning of intoxication with lidocaine patients mainly show symptoms of excitation: unrest, vertigo, disturbances of hearing and vision, unpleasant perioral sensations, agitation, hallucination, euphoria, paraesthesias (e.g. circumoral paraesthesia and numbness of the tongue), dizziness, tinnitus, blurred visions, nausea, vomiting, dysarthria. Shivering and muscular twitching may be signs of imminent attacks of generalized convulsion. Subconvulsive plasma levels of lidocaine often also lead to sleepiness and sedation. Tachycardia, hypertension and flushing may occur as a sign of initial stimulation of the sympathetic nervous system.

Depression
During progress of the intoxication of the CNS increasing impairment of the brain stem functions appears in the form of respiratory depression and coma, even up to death.

Effects on cardiovascular circulation:
Unpalpable pulse, pallor, hypotension, bradycardia, arrhythmias, cardiovascular collapse, ventricular fibrillation, cardiac arrest. Sudden hypotension often is the first sign of cardiovascular toxicity of lidocaine. The hypotension is mainly caused by the reduction or block of cardiac impulse conduction. These toxic effects, however, are less relevant than those on the CNS.

Treatment
The occurrence of central nervous or cardiovascular symptoms demands the following emergency treatment:

- Immediately discontinue administration.
- Ensure patency of the airways.
- Supply additional oxygen. If necessary provide artificial ventilation with pure oxygen – assisted or controlled – initially via mask and air bag, then intubate. The oxygen therapy must be continued until all vital functions have returned to normal.
- Monitor blood pressure, pulse and pupil width carefully.
- Maintain the circulation by sufficient supply of intravenous fluid.
- Immediately start cardio-pulmonary resuscitation, if necessary.

These measures are also applicable in the case of accidental total spinal anaesthesia, first manifesting as unrest, whispering voice, and sleepiness. The latter can proceed to unconsciousness and respiratory arrest.

Further therapeutic measures include the following:

Acute life-threatening hypotension should be treated with intravenous vasopressors. Bradycardia caused by increased vagal tone should be treated with intravenous atropine. Convulsions not reacting to sufficient oxygenation should be treated with intravenous benzodiazepins or ultra-short-acting barbiturates.

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
Anaesthetics, local, amides: ATC code: N01B B02
Antiarrhythmics, class Ib: ATC code: C01BB01

Mechanism of action

Local and regional anaesthesia
Lidocaine is a local anaesthetic agent of the amide type.
Lidocaine reduces the permeability of cell membranes for cations, in particular sodium ions, at higher concentrations also for potassium ions. This leads, depending on the concentration of lidocaine, to reduced excitability of the nerve fibres because the increase of sodium permeability producing the action potential is slowed down. From inside the cell the lidocaine molecule enters the open sodium channel and blocks it by binding to a specific receptor. A direct effect of incorporation of lidocaine in the cell membrane is much less relevant.
Because lidocaine, before reaching its site of action, must pass into the cell, its effect depends on its pK_a and on the environmental pH, i.e. on the proportion of the free base which is the moiety predominantly migrating through the lipophilic membranes of nerve fibres.
In inflamed tissue the local anaesthetic effect is reduced due to the lower pH in such regions.

Antiarrhythmic therapy
In membranes of myocardial fibres lidocaine inhibits the large transient increase in the permeability of the membrane for sodium channels during the plateau of the action potential and increases the potassium efflux during repolarisation period.
In Purkinye fibres the duration of action potentials and their effective refractory time are shortened while impulse conduction is slowed down.
Impulse conduction in the sinus node and supraventricular regions remains virtually unaffected.

Clinical efficacy and safety
Local and regional anaesthesia
Lidocaine inhibits the function of excitable structures such as sensor, motor and autonomic nerve fibres and the cardiac impulse conducting system. Lidocaine reversibly inhibits the conduction in sensitive nerve fibres in the area of application. The order of loss of nerve function is as follows: pain, temperature, touch, and pressure.
The local anaesthetic effect of lidocaine lasts for about 30 minutes- 3 hours depending on the type of anasesthesia.

Antiarrhythmic therapy
In the myocardium the excitation and fibrillation thresholds are raised.
Lidocaine suppresses heterotopic pacemakers and action potentials originating from delayed potentials and tachyarrhythmias caused by circus rhythm.
The sodium channels more avidly bind lidocaine when the membrane is depolarized. Therefore the antiarrhythmic effect of lidocaine is particularly marked in cases of increased excitation frequency.
The effect of lidocaine is enhanced if the resting potential is less negative, e.g. in hyperkalaemia and/or myocardial ischaemia.
In situations of hyperpolarisation, e.g. due to hypokalaemia, the effect of lidocaine is reduced.
Lidocaine has been shown to eliminate re-entrant ventricular arrhythmias in the late myocardial phase by further depression and blocking of conduction in the re-entrant pathway.
Therapeutic plasma concentrations should lie between 1.5 and 5 mg/l. Beyond 5 mg/l, toxic effects on the CNS and the cardiovascular system are to be expected.

Other pharmacological effects
Lidocaine shows weak parasympatholytic activity.
Intradermally administered lidocaine acts at low concentrations as a mild vasoconstrictor and at higher concentrations as vasodilator.

Antiarrhythmic therapy
The effects of lidocaine on myocardial contractility, blood pressure, cardiac output and heart rate are very small.
Patients with impaired function of the sinus node, however, may respond particularly markedly to the conduction suppressing effect of lidocaine.

In the period immediately following myocardial infarction the coronary blood flow may be increased by lidocaine.

Paediatric population
There are no data indicating that the pharmacodynamic properties of lidocaine in children should be different from those established for adults.

5.2 Pharmacokinetic properties

Absorption
Plasma levels depend on the site and mode of administration. However, there is a poor relationship between the amount of local anaesthetic injected and peak plasma levels. After intravenous administration the bio-availability is 100 %.
Maximum concentrations are achieved within latest 30 minutes, in the majority of patients maximum concentrations are met within 10-20 minutes.

After ***intramuscular injection*** of 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 ***intravenous administration***, onset of the therapeutic effect of lidocaine is rapid. Therapeutic plasma concentrations are reached within 1 - 2 min. The effect of a bolus injection lasts for 10 - 20 min; in order to maintain the therapeutic effect of lidocaine, its administration must be continued in the form of an intravenous infusion.

After ***continuous infusion*** and when no loading dose is given the steady state of plasma concentration was achieved not earlier than 5 hours (range, 5 – 10 hours) of beginning of the infusion. However, therapeutic concentrations had already been achieved after 30 – 60 min.

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 hydrochloride monohydrate, using a 2 % solution, the C_{max} value reached 0.31 mg/l.

After ***epidural injection*** the measured maximum plasma concentrations do not seem to be directly proportional to the dose applied. Administration of 400 mg resulted in C_{max} values of 3 - 4 mg/l.

No data are available on pharmacokinetics after intrathecal administration.

Distribution
Lidocaine follows a biphasic elimination kinetic. After intravenous administration the drug substance is first rapidly distributed from the central compartment into intensively perfused tissues and organs (a-distribution phase). This phase is followed by redistribution into skeletal muscles and adipose tissue. The half life time during the a-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 dependant on the drug concentration and additionally on the concentration of the a-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 neonates and patients suffering from liver impairment leading to a marked reduction of lidocaine plasma protein binding.
The distribution volume may be altered in patients suffering from further diseases, e.g. heart insufficiency, liver insufficiency or renal insufficiency.

Biotransformation
Besides distribution of Lidocaine in other compartments (e.g. cerebrospinal fluid), the drug rapidly metabolised in the liver by mono-oxygenases mainly via oxidative desalkylation, 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.

The hepatic blood flow appears to limit the rate of lidocaine metabolism. As a consequence the plasma $t_{1/2}$ of 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.

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 healthy adults and approx. 3 hours in newborns.

The half-life times of the active metabolites MEGX and GX are about 2-6 hours and 10 hours, respectively. Since their plasma $t_{1/2}$ 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 plasma clearance is about 0.95 l/min.

Paediatric population
After epidural anaesthesia of the mother, the elimination half-life time in the newborn was approximately 3 hours; after infiltration of the perineum and after paracervical block lidocaine was found in the urine of the new-born during 48 hours following anaesthesia.

The plasma $t_{1/2}$ is increased 2-3 fold in neonates, due to a slower rate of metabolism and in parts to the expanded distribution volume. Absorption and elimination may be faster in children than adults, although other studies suggested that differences in pharmacokinetics (between children and adults) decrease by correcting for BW.

Pharmacokinetics in special clinical situations

Renal impairment
In the presence of ***renal insufficiency*** the plasma 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.

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.

Pregnancy and lactation
Lidocaine passes across the placental barrier by simple diffusion and reaches the foetus within a few minutes of administration. After epidural administration, the foetal to maternal plasma concentration ratio is 0.5 – 0.7.
After infiltration of the perineum and after paracervical block, markedly higher concentrations of lidocaine have been found in umbilical blood.
The foetus is able to metabolise lidocaine. The levels in foetal blood are approximately 60% of the concentrations in the maternal blood. Due to a lower plasma protein binding in foetal 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to development.

Single-dose toxicity
Numerous studies on acute toxicity of lidocaine have been carried out in various animal species. Toxicity manifested in the form of CNS symptoms. These included also convulsions with lethal outcome.
In man, toxic plasma lidocaine concentrations leading to cardiovascular or central nervous symptoms have been reported to be in the range of 5 – 10 mg/l

Mutagenic and tumorigenic potential
Mutagenicity studies with lidocaine showed negative results. However, there are findings indicating that a metabolite of lidocaine, 2,6-xylidine, appearing in rats and possibly also in man, might be mutagenic. The mutagenic effect was shown in *in-vitro* tests applying very high, nearly toxic doses of the metabolite.
At present there are no indications of a mutagenic effect of lidocaine itself.
In a carcinogenicity study with transplacental exposure of rats to 2,6-xylidine and subsequent treatment with the same substance for 2 years a tumorigenic potential was shown. This highly sensitive test demonstrated the incidence of benign and malignant tumours in the nasal cavity (*ethmoturbinalia*).
A relevance of these findings for humans cannot be definitely ruled out if high-dose were administered over long periods. However as lidocaine is usually not used over longer periods no risks are to be expected if used according to the directions given.

Reproduction toxicity
Investigations of reproduction toxicity did not reveal embryotoxic or teratogenic effects. Only a reduction of foetal weight has been observed.
When administered to pregnant rats at doses almost as high as the therapeutic maximum doses applied in man, neurological behavioural deviations in the offspring had been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injections.

6.2 Incompatibilities

Lidocaine Hydrochloride is incompatible with solutions containing sodium bicarbonate and other alkaline solutions. It must therefore not be mixed with those.

6.3 Shelf life

Unopened: 3 years

After first opening

Containers once opened must not be stored for later use (see section **6.6**). The solution is to be administered immediately after opening the container.

After dilution
From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

2% w/v Lidocaine Hydrochloride is supplied in:

• low density round or oval polyethylene ampoules (Mini-Plasco), contents: 5 ml, 10 ml and 20 ml available in packs of:

20 × 5 ml
20 × 10 ml
20 × 20 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Only to be used if the solution is clear and colourless and the container and its closure are undamaged.
Containers are for single use only. Discard container and any unused content after use.

7 MARKETING AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Straße 1
34212 Melsungen
Germany

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