The format of this leaflet has been determined by the Ministry of Health and its content has been examined and approved in November 2016

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lidocaine B. Braun 2%

Solution for injection

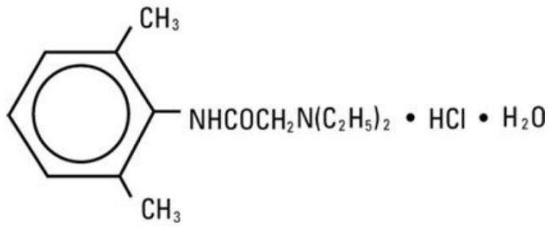
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lidocaine B. Braun is a sterile, nonpyrogenic solution of lidocaine hydrochloride in water for injection for parenteral administration with characteristics as follows:

Each mL contains: Lidocaine HCl 20 mg; Sodium Chloride 5.3 mg; Water for Injection q.s. Sodium hydroxide

Lidocaine is a local anesthetic of the amide type.

Lidocaine B. Braun is chemically designated 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide monohydrochloride monohydrate, a white powder freely soluble in water. The molecular weight is 288.82. It has the following structural formula:



3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless aqueous solution
The pH is 6.5 (5.0 to 7.0)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Method of administration and Posology

Method of administration
Intravenous use
Administer as slow direct 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.

Posology

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

Bolus:
For Direct Injection–The usual dose is 50 to 100 mg administered intravenously under ECG monitoring. The rate of injection should not exceed 25 to 50 mg/min. Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. If the initial injection of 50 to 100 mg does not produce a desired response, a second dose may be repeated after 5 minutes.

NO MORE THAN 200 TO 300 MG OF LIDOCAINE B. BRAUN SHOULD BE ADMINISTERED DURING A ONE HOUR PERIOD.

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 i.v. 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 i.v. or intraosseous infusion should be started at a rate of 20-50 µg/kg b.w. per min.

Elderly patients
For elderly patients, the doses are calculated individually according to the patients' 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.

Other special patient groups
The dose should be reduced in patients with cardiac insufficiency, hepatic insufficiency, in patients receiving drugs that intensify the effects of lidocaine and during pregnancy.

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.

4.3 Contraindications

General

- Lidocaine is contraindicated in patients with a known history of hypersensitivity to lidocaine, local anesthetics of the amide type or to any of the exipients listed in section 6.1.

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- Severe conduction disorders including STOKES-ADAMS syndrome, Wolff-Parkinson-White syndrome, or with severe degrees of sinoatrial, atrioventricular or intraventricular block.
- Myocardial infarction within the preceding 3 months
- Markedly decreased cardiac output unless there is life threatening ventricular cardiac arrhythmia

4.4 Special warnings and precautions for use

General

Caution should be employed in the repeated use of Lidocaine B. Braun in patients with severe liver or renal disease because accumulation may occur and lead to toxic phenomena since Lidocaine B. Braun is metabolized mainly in the liver and excreted by the kidneys. This drug should also be used with caution in patients with hypovolemia and shock and all forms of heart block.

In patients with sinus bradycardia or incomplete heart block, the administration of Lidocaine B. Braun intravenously or the elimination of ventricular ectopic beats without prior acceleration in heart rate may promote more frequent and serious ventricular arrhythmias or complete heart block.

Lidocaine should only be used with particular caution in patients with *myasthenia gravis* and impaired respiratory function.

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.

Toxicity may be manifest as central nervous system depression (sedation) or irritability (twitching), which may progress to frank convulsions accompanied by respiratory depression and/or arrest. Early recognition of premonitory signs, assurance of adequate oxygenation and (where necessary) establishment of artificial airway with ventilatory support are essential to management of the problem. Should convulsions persist despite ventilatory support, small doses of anticonvulsant drugs may be used intravenously. Examples of such drugs include benzodiazepines (e.g., diazepam, lorazepam), or an ultrashort acting barbiturate (e.g., thiopental or thiamylal). If the patient is under anesthesia, a short-acting muscle relaxant (succinylcholine) may be used. Longer acting drugs should be used only when recurrent convulsions are evidenced.

Many potent anesthetic drugs, neuromuscular blocking agents and possibly amide local anesthetics may serve as triggering agents for the fulminant hypermetabolic process termed malignant hyperthermia. Key to successful outcome of fulminant hypermetabolism is early recognition of premonitory signs, i.e., unexplained or unexpected tachycardia and increased metabolic rate as evidenced by respiratory and/or metabolic acidosis. Treatment includes administration of oxygen and discontinuation of lidocaine hydrochloride administration and where necessary administration of dantrolene sodium. For additional information on management, see prescribing information for dantrolene sodium.

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.

Constant monitoring of the electrocardiogram and blood pressure is essential in the proper administration of Lidocaine B.Braun intravenously. If hypotension or excessive depression of cardiac conductivity (such as prolongation of the PR interval and QRS complex and the appearance of aggravation of arrhythmias) is seen, administration of Lidocaine B. Braun should be discontinued.

The safe use of Lidocaine B. Braun requires careful ECG observation in an environment equipped and by persons trained for resuscitation.

Occasional acceleration of ventricular rate may occur when Lidocaine B. Braun is administered to patients with atrial fibrillation.

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

Safety and effectiveness in children have not been established by controlled clinical studies.

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 20 ml ampoule. To be taken into consideration for patients on a controlled sodium diet.

4.5 Interactions 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.

- ***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.

- ***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.

- ***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, 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. **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 not indicate 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 fetus/neonate.

Lidocaine should only be used in pregnancy if there is an imperative indication. Then doses should be as low as possible.

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 Lidocaine B. Braun 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 Lidocaine B. Braun has negligible influence on the ability to drive and use machines. 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)

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.

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 suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

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 func tions.

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

Antiarrhythmics, class Ib: ATC code: C01BB01

Mechanism of action
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 repolarization 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

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 anti-arrhythmic 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, 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 Cmax 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 (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 drug 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 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 t1/2 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 adults and approx. 3 hours in newborns.

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 plasma t1/2 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 ml/min.

Paediatric population
After epidural anaesthesia of the mother, the elimination half-life time in the new-born 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 t1/2 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

• 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. 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 fetus within a few minutes of administration. After epidural administration, the fetal 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 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 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 fetal 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 B. Braun is incompatible with solutions containing sodium bicarbonate and other alkaline solutions. It must therefore not be mixed with those.

6.3 Shelf life

Unopened

- Polyethylene ampoules of 5 ml: 2 years
- Polyethylene ampoules of 10 and 20 ml: 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.
Solution has to be stored in the outer carton to keep it protected from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Lidocaine B. Braun 2% is supplied in

Ampoules of low-density polyethylene 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

The container is for single use.

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

8. REGISTRATION HOLDER:

Lapidot Medical Import and Marketing Ltd.
8 Hashita street, Industrial Park Caesarea 3088900, ISRAEL