This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in June 2016

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Lidocaine B. Braun 2%
Solution for injection

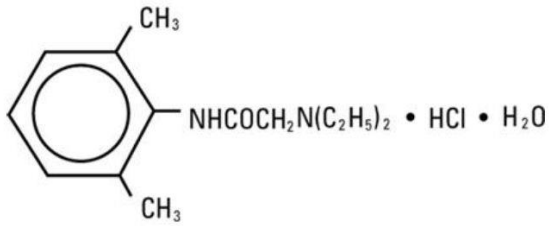
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 7.1mg/5.3 mg; Water for Injection q.s. Sodium hydroxide may have been added for pH adjustment

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

Local and regional anaesthesia

4.2 Posology and method of administration

Posology

Local and regional anaesthesia

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times.

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of

anesthesia required, and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Thus, an increase in volume and concentration of Lidocaine Hydrochloride Injection will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. However, increasing the volume and concentration of Lidocaine Hydrochloride Injection may result in a more profound fall in blood pressure when used in epidural anesthesia. Although the incidence of side effects with lidocaine is quite low, caution should be exercised when employing large volumes and concentrations, since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected

Maximum Recommended Dosages

Adults

For normal healthy adults, the individual maximum recommended dose of lidocaine HCl with epinephrine should not exceed 7 mg/kg (3.5 mg/lb) of body weight and in general it is recommended that the maximum total dose not exceed 500 mg. When used without epinephrine, the maximum individual dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight and in general it is recommended that the maximum total dose does not exceed 300 mg.

For continuous epidural or caudal anesthesia, the maximum recommended dosage should not be administered at intervals of less than 90 minutes. When continuous lumbar or caudal epidural anesthesia is used for non-obstetrical procedures, more drug may be administered if required to produce adequate anesthesia. The maximum recommended dose per 90 minute period of lidocaine hydrochloride for paracervical block in obstetrical patients and non-obstetrical patients is 200 mg total. One-half of the total dose is usually administered to each side. Inject slowly five minutes between sides.

For intravenous regional anesthesia, the dose administered should not exceed 4 mg/kg in adults.

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.

Table 1

	Recommended Dosages of Lidocaine Hydrochloride Injection, USP for Various Anesthetic Procedures in Normal Healthy Adults		
	Lidocaine Hydrochloride Injectoin, USP (without Epinephrine)		
Procedures	Conc. (%)	Vol. (mL)	Total Dose (mg)
Infiltration			
Percutaneous	0.5 or 1.0	1-60	5-300
Intravenous Regional	0.5	10-60	50-300
Peripheral Nerve Blocks, e.g.			
Brachial	1.5	15-20	225-300
Dental	2.0	1-5	20-100

Intercostal	1.0	3	30
Paravertebral	1.0	3-5	30-50
Pudendal (each side)	1.0	10	100
Paracervical			
Obstetrical Analgesia			
(each side)	1.0	10	100
Sympathetic Nerve Blocks, e.g.			
Cervical (stellate ganglion)	1.0	5	50
Lumbar	1.0	5-10	50-100
Central Neural Blocks			
Epidural*			
Thoracic	1.0	**	50-100
Lumbar			
Analgesic	1.0	25-30	250-300
Anesthesia	1.5	15-20	225-300
	2.0	10-15	200-300
Caudal			
Obstetrical Analgesia	1.0	20-30	200-300
Surgical Anesthesia	1.45	15-20	225-300
Spinal	1.5 or 5 in 7.5% glucose	1-2	100

*Dose determined by number of dermatomes to be anesthetized (2 to 3 mL/dermatome).
**Due to decrease compliance and volume in the thoracic epidural space, the maximum volume for each dose injected should NOT exceed 5 ml
Note: a test dose of 2 ml should be administered at least 5 minutes prior to injecting the total required volume for central neural blocks (epidural or caudal anesthesia).

THE ABOVE SUGGESTED CONCENTRATIONS AND VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES AND CONCENTRATIONS MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.

Table 1 (Recommended Dosages) summarizes the recommended volumes and concentrations of Lidocaine B. Braun for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults and refer to the use of epinephrine-free solutions. When larger volumes are required only solutions containing epinephrine should be used, except in those cases where vasopressor drugs may be contraindicated.
In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.
Paediatric population
It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age ~~and~~ body weight and nature of procedure. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child's age and weight. For example, in a child of 5 years weighing 22.679 kg (50 lbs.), the dose of lidocaine HCl should not exceed 75 — 100 mg (3.306 - 4.409 mg/kg / 1.5 — 2 mg/lb). The use of even more dilute solutions (i.e., 0.25 — 0.5%) and total dosages not to exceed 3 mg/kg (1.4 mg/lb) are recommended for induction of intravenous regional anesthesia in children.

Elderly patients and other special patient groups

- Dosages should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease.
- 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).
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- In patients with severe **renal insufficiency** the dose may need to be adapted due to reduced clearance and increased half-life of lidocaine
- 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.

Method of administration

Local and regional anaesthesia
Every local anaesthetic procedure should only be carried out by personnel adequately skilled in the respective anaesthetic technique.

Infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks, when the accepted procedures for these techniques as described in standard textbooks are observed.

Caudal and Lumbar Epidural Block: As a precaution against the adverse experiences sometimes observed following unintentional penetration of the subarachnoid space, a test dose such as 2−3 mL of 1.5% lidocaine hydrochloride should be administered at least 5 minutes prior to injecting the total volume required for a lumbar or caudal epidural block. The test dose should be repeated if the patient is moved in a manner that may have displaced the catheter. Epinephrine, if contained in the test dose (10−15 mcg have been suggested), may serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect an evanescent rise in systolic blood pressure. Adequate time should be allowed for onset of anesthesia after administration of each test dose. The rapid injection of a large volume of Lidocaine Hydrochloride Injection through the catheter should be avoided, and, when feasible, fractional doses should be administered.

4.3 Contraindications

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

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4.4 Special warnings and precautions for use

LIDOCAINE B. BRAUN, SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER

ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Local anesthetic solutions containing antimicrobial preservatives (e.g., methylparaben) should not be used for epidural or spinal anesthesia because the safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental.

PRECAUTIONS General:

Lidocaine should only be used with particular caution in patients with liver or kidney diseases or with myasthenia gravis, impaired cardiac conduction, cardiac insufficiency, bradycardia, impaired respiratory function and severe shock.
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.

The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various regional anesthetic procedures.

Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Syringe aspirations should also be performed before and during each supplemental injection when using indwelling catheter techniques. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and that the patient be monitored for central nervous system toxicity and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions that contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Lidocaine should also be used with caution in patients with severe shock or heart block. Lumbar and caudal epidural anesthesia should be used with extreme caution in persons with the following conditions: existing neurological disease, spinal deformities, septicemia and severe hypertension.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for the management of malignant hyperthermia should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Proper tourniquet technique, as described in publications and standard textbooks, is essential in the performance of intravenous regional anesthesia. Solutions containing epinephrine or other vasoconstrictors should not be used for this technique.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in the Head and Neck Area: Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injections of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded.

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.

Information for Patients:

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body following proper administration of epidural anesthesia.

Clinically Significant Drug Interactions:

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (for the treatment of hypotension related to obstetric blocks) and ergot-type oxytoxic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Drug Laboratory Test Interactions:

The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination without isoenzyme separation as a diagnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pediatric Use:

Dosages in pediatric patients should be reduced, commensurate with age, body weight and physical condition. See method of administration.

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.

- *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 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.

- *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 metabolized mainly via the cytochrome P 450 isoenzymes CYP 3A4 and CYP 1A2 concurrently administered drug substances that are ***substrates, inhibitors or inducers of hepatic enzyme, isoenzyme CYP 3A4and CYP 1A2***, 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 CYP 1A2 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

Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Labor and Delivery:

Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity. The potential for toxicity depends upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study, paracervical block anesthesia was associated

with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. However, spinal and epidural anesthesia have also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long-term significance of these observations is unknown. Fetal bradycardia may occur in 20 to 30 percent of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering paracervical block in prematurity, toxemia of pregnancy and fetal distress. Careful adherence to recommended dosage is of the utmost importance in obstetrical paracervical block. Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Case reports of maternal convulsions and cardiovascular collapse following use of some local anesthetics for paracervical block in early pregnancy (as anesthesia for elective abortion) suggest that systemic absorption under these circumstances may be rapid. The recommended maximum dose of each drug should not be exceeded. Injection should be made slowly and with frequent aspiration. Allow a 5-minute interval between sides.

Breastfeeding

Lidocaine metabolites are excreted in small amounts into human milk but at therapeutic doses of Lidocaine B. Braun no effects on the breast-fed newborns/infants are anticipated.

Fertility
Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

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.
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

Systemic: Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported.
Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of sensitivity to

lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.
Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Neurologic: The incidences of adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. In a prospective review of 10,440 patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were reported to be about 3 percent each for positional headaches, hypotension and backache; 2 percent for shivering; and less than 1 percent each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the local anesthetic.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally.

These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control, and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anesthetic procedures.

There have been reported cases of permanent injury to extraocular muscles requiring surgical repair following retrobulbar administration.

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

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution.

Management of Local Anesthetic Emergencies:The first consideration is prevention, best accomplished by careful monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

In the case of severe reaction, discontinue the use of Lidocaine B. Braun.

The first step in the management of convulsions, as well as underventilation or apnea due to unintended subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine). Bradycardia caused by increased vagal tone should be treated with intravenous atropine.

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

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

Centrally acting analeptics are contraindicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Anaesthetics, local, amides
ATC code: N01B B02

Mechanism of action
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 pKa 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 tissues, the local anaesthetic effect is reduced due to the lower pH in such regions.

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 anaesthesia.

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.

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 bioavailability 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 36mg of lidocaine , using a 2 % solution, the Cmax 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 (□-distribution phase). This phase is followed by redistribution into skeletal muscles and adipose tissue. The half life time during the □-distribution phase is approx. 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 □-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 is 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 two latter may accumulate during infusions of longer duration or in the presence of renal insufficiency due to their longer half life time as compared to lidocaine itself. In 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 Ndeethylation.

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 adults and approx. 3 hours in new-borns.

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 *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 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 *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 other special patient groups

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.

Elimination **half-life** and volume of distribution 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 data 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 mcg/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 B. Braun 2% is incompatible with solutions containing sodium bicarbonate and other alkaline solutions. It must therefore not be mixed with such solutions..

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.

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

- 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

Discard Unused Portion.

The container is for single use only. Discard container and any unused content after use.

Use only if solution is clear, colourless and seal intact.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

7. MANUFACTURER:

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