SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Esracain® Gel

1.1 Qualitative and quantitative composition

Lidocaine hydrochloride 2%
1 ml of gel contains 20 mg lidocaine hydrochloride.

Excipients with known effect: Propylene glycol and benzalkonium chloride.
1 ml of gel contains approximatelohy 20 mg propylene glycol.
1 ml of gel contains 0.15 mg benzalkonium chloride.
For the full list of excipients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

1.2 Pharmaceutical form

Clear, colorless gel**.**

2 THERAPEUTIC INDICATIONS

Local anesthetic, not to be used for procedures requiring sterile products.

3 CONTRAINDICATIONS

- **Esracain® Gel** is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients of the gel or components of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.
- Patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components in the formulation (see 6 Dosage Forms, Strengths, Composition and Packaging).
- Not to be used for procedures requiring sterile products
- Patients with congenital or idiopathic methemoglobinemia and patients with glucose-6-phosphate dehydrogenase deficiency, which are more susceptible to drug-induced methemoglobinemia.
- Infants who require treatment with methemoglobin-inducing agents, e.g., sulfonamides and are 12 months of age or younger (see 9 DRUGS INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

The standard dosage is usually:
Dosage for adults (over the age of 18):
Use the smallest amount necessary to control your symptoms.

- Usually the effective dose is no more than 5 to 10 ml per application.
- No more than 6 doses should be used per day (24 hours).

Dosage in Children:

The gel is usually not intended for children under the age of 2 years and in any case children under the age of 3 will be treated under medical supervision only.
When using the gel on a child under the age of 2 years, do not use for more than one day (24 hours).

Dosage in children weighing less than 50 kg (and over the age of 2 years):

- The dosage depends on the child's weight. Use the smallest amount necessary to control the symptoms.
- For each dose, do not use more than 1 ml for every 5 kg of body weight. Do not exceed a maximum dose of 10 ml in each application. E.g.: for a child weighing 25 kg a maximum of 5 ml of gel can be used in each dose.
- No more than 4 doses should be used per day (24 hours). The gel can be applied once every six hours.

Dosage in Children weighing over 50 kg:

- Use the smallest amount necessary to control the symptoms.
- Usually the effective dose is no more than 5 to 10 ml per application.
- No more than 4 doses should be used per day (24 hours). The gel can be applied once every six hours.

4.2 Administration

- **Attention!** Not to be swallowed! The gel is intended for topical use only.
- Not to be used in sterile procedures.
- For use on the skin, mucous membranes and oral cavity.
- Apply the gel using a clean finger, a cotton swab or a piece of gauze.
- Wash your hands after use.
- Avoid contact with the eyes.

The patient should refer to the doctor if there is no improvement in his condition within 3-5 days or if there is a deterioration in his condition.

5 OVERDOSAGE

Acute systemic toxicity from local anesthetics is generally related to high plasma levels encountered during therapeutic use of local anesthetics and originates mainly in the central nervous and the cardiovascular systems (see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS). It should be kept in mind that clinically relevant pharmacodynamic drug interactions (i.e., toxic effects) may occur with lidocaine and other local anesthetics or structurally related drugs, and Class I and Class III antiarrhythmic drugs due to additive effects (see 9 DRUG INTERACTIONS).

Symptoms

Central nervous system toxicity is a graded response, with symptoms and signs of escalating severity. The first symptoms are circumoral paresthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalized convulsions. Unconsciousness and grand mal

convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration. In severe cases apnea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anesthetics.

Recovery is due to redistribution and metabolism of the local anesthetic drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular effects may be seen in cases with high systemic concentrations. Severe hypotension, bradycardia, arrhythmia and cardiovascular collapse may be the result in such cases.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anesthetic or is heavily sedated with drugs such as a benzodiazepine or barbiturate.

Methemoglobinemia

Rare cases of methemoglobinemia have been reported.

Mild methemoglobinemia is characterized by tissue cyanosis, a bluish-grey or brownish discoloration of the skin, especially around the lips and nail beds, which is not reversed by breathing 100% oxygen. Clinical signs may also include pallor and marbleization.

Severe methemoglobinemia (MetHb concentrations above approximately 25%) is associated with signs of hypoxemia, ie. dyspnea, tachycardia and depression of consciousness.

Drug-induced methemoglobinemia may occur with the use of drugs including but not limited to amino-amide, sulfonamides, acetanilid, aniline dyes, benzocaine, lidocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine.

Acetaminophen has been shown to induce methemoglobin formation *in vitro* and in animals. In humans, methemoglobin formation is very rare at therapeutic doses and overdoses of acetaminophen.

It should be kept in mind that **Esracain® Gel** is contraindicated for patients with congenital or idiopathic methemoglobinemia and for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs. Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methemoglobinemia (see also 3 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Treatment

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

The first step in the management of systemic toxic reactions 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. This may prevent convulsions if they have not already occurred.

If convulsions occur, the objective of the treatment is to maintain ventilation and oxygenation and support circulation. Oxygen must be given, and ventilation assisted if necessary (mask and bag or tracheal intubation). Should convulsions not stop spontaneously after 15-20 seconds, an anticonvulsant should be given iv to facilitate adequate ventilation and oxygenation. Thiopental sodium 1-3 mg/kg iv is the first choice. Alternatively, diazepam 0.1 mg/kg bw iv may be used, although its action will be slow. Prolonged convulsions may jeopardise the patient's ventilation and oxygenation. If so, injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg bw) will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation is required when succinylcholine is used to control motor seizure activity.
If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg i.v. should be given and may be repeated, if necessary, after 2-3 minutes.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Continual oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance since hypoxia and acidosis will increase the systemic toxicity of local anesthetics. Epinephrine (0.1-0.2 mg as intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary.

Children should be given doses of epinephrine commensurate with their age and weight.

In neonates, methemoglobin concentrations of up to 5 - 6% are not considered to be of clinical significance, with treatment of symptomatic methemoglobinemia not typically necessary unless methemoglobin concentrations are above 25 - 30%. However, the severity of clinical symptoms should be the primary consideration in the decision to initiate treatment, rather than the level of methemoglobin. Most patients recovered spontaneously after removal of the jelly. Methemoglobinemia may be treated with a slow intravenous injection of methylene blue. It has been reported in published literature that methylene blue should be used cautiously as a treatment for methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency because it may not be effective for these patients and may cause hemolytic anemia.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Local oral, topical, mucosal	Lidocaine hydrochloride 2% (20 mg/ml) gel in 30 g tube	Glycerin anhydrous, propylene glycol, hydroxyethyl cellulose, benzalkonium chloride, sodium hydroxide and purified water.

Packaging

Esracain® Gel is packed in 30 g aluminium tube.

7 WARNINGS AND PRECAUTIONS

General

EXCESSIVE DOSAGE, OR SHORT INTERVALS BETWEEN DOSES, CAN RESULT IN HIGH PLASMA LEVELS OF LIDOCAINE OR ITS METABOLITES AND SERIOUS AS WELL AS LIFE-TREATENING ADVERSE EFFECTS, including methemoglobinemia. Absorption from the mucous membranes is variable. Such applications may therefore result in rapidly rising or excessive plasma concentrations, with an increased risk for toxic symptoms, such as convulsions and methemoglobinemia. PATIENTS SHOULD BE INSTRUCTED TO STRICTLY ADHERE TO THE RECOMMENDED DOSAGE. This is especially important in children where doses vary with weight. The management of serious adverse reactions may require the use of resuscitative equipment, oxygen and other resuscitative drugs (see 5 OVERDOSAGE).

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Tolerance to elevated blood levels varies with the status of the patient.

Lidocaine should be used with caution in patients with sepsis and/or traumatized mucosa at the area of application, since under such conditions there is the potential for rapid systemic absorption.

When using Esracain® Gel in younger children, especially infants under the age of 3 months, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see 4 DOSAGE AND ADMINISTRATION). Children should be closely observed during and after use of lidocaine, as they are at greater risk than adults for serious adverse events (e.g., methemoglobinemia).

Avoid contact with eyes.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It has been shown that the use of amide local anesthetics in malignant hyperthermia patients is safe. However, there is no guarantee that neural blockade will prevent the development of malignant hyperthermia during surgery. It is also difficult to predict the need for supplemental general anesthesia. Therefore, a standard protocol for the management of malignant hyperthermia should be available.

When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food or chewing gum should not be taken while the mouth is anesthetized. See also patient leaflet.

Esracain® Gel is ineffective when applied to intact skin.

Lidocaine has been shown to be porphyrinogenic in animal models. **Esracain® Gel** should only be prescribed to patients with acute porphyria on strong or urgent indications, when they can be closely monitored. Appropriate precautions should be taken for all porphyric patients.

Carcinogenesis and Mutagenesis

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2,6-dimethylaniline, showed weak evidence of activity in some genotoxicity tests. A chronic oral toxicity study of the metabolite 2,6-dimethylaniline (0, 14, 45, 135 mg/kg) administered in feed to rats showed that there was a significantly greater incidence of nasal cavity tumors in male and female animals that had daily oral exposure to the highest dose of 2,6-dimethylaniline for 2 years. The lowest tumor-inducing dose tested in animals (135 mg/kg) corresponds to approximately 50 times the amount of 2,6-dimethylaniline to which a 50 kg subject would be exposed following the application of 20 g of lidocaine jelly 2% for 24 hours on the mucosa, assuming the highest theoretical extent of absorption of 100% and 80% conversion to 2,6-dimethylaniline. Based on a yearly exposure (once daily dosing with 2,6-dimethylaniline in animals and 5 treatment sessions with 20 g lidocaine jelly 2% in humans), the safety margins would be approximately 3400 times when comparing the exposure in animals to man.

Cardiovascular

Lidocaine should be used with caution in patients with bradycardia or impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by amid-type local anesthetics.

Lidocaine should be used with caution in patients in severe shock.

Driving and Operating Machinery

With the recommended doses, **Esracain® Gel** has no effect on the ability to drive and use machines. However, in case of overdosage it will not be the case. It is suggested that the patient should know how he/she feels and be aware that due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Hepatic

Because amide-type local anesthetics such as lidocaine are metabolized by the liver, these drugs, especially repeated doses, should be used cautiously 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.

Neurologic

Epilepsy: The risk of central nervous system side effects when using lidocaine in patients with epilepsy is very low, provided that the dose recommendations are followed. (See 4 DOSAGE AND ADMISTRATION).

Locomotion and Coordination: Topical lidocaine formulations generally result in low plasma concentrations because of a low degree of systemic absorption. However, depending on the dose, local anesthetics may have a very mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

Renal

Lidocaine is metabolized primarily by the liver to monoethylglycinexylidine (MEGX, which has some CNS activity), and then further to metabolites glycinexylidine (GX) and 2,6-dimethylaniline (see 10 ACTION AND CLINICAL PHARMACOLOGY). Only a small fraction (2%) of lidocaine is excreted unchanged in the urine. The pharmacokinetics of lidocaine and its main metabolite

were not altered significantly in haemodialysis patients (n=4) who received an intravenous dose of lidocaine. Therefore, renal impairment is not expected to significantly affect the pharmacokinetics of lidocaine when **Esracain® Gel** is used for short treatment durations, according to dosage instructions (see 4 DOSAGE AND ADMINISTRATION).
Caution is recommended when lidocaine is used in patients with severely impaired renal function because lidocaine metabolites may accumulate during long term treatment (see 4 DOSAGE AND ADMINISTRATION).

Sensitivity/Resistance

Lidocaine should be used with caution in persons with known drug sensitivities.

Esracain® Gel is contraindicated in patients with known hypersensitivities to local anesthetics of the amide type and to other components in the formulation.

Esracain® Gel contains propylene glycol and benzalkonium chloride which may cause skin irritation (see 1.1 Qualitative and quantitative composition and 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

7.1 Special Populations

Debilitated patients, acutely ill patients, and patients with sepsis should be given reduced doses commensurate with their age, weight and physical condition because they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses.

Esracain® Gel is contraindicated for patients with congenital or idiopathic methemoglobinemia and patients with glucose-6-phosphate dehydrogenase deficiency which are more susceptible to drug-induced methemoglobinemia (see also 3 CONTRAINDICATIONS).

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women on the effect of lidocaine on the developing fetus.

It is reasonable to assume that a large number of pregnant women and women of child-bearing age have been given lidocaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations. However, care should be given during early pregnancy when maximum organogenesis takes place.

Labor and Delivery: Lidocaine is not contraindicated in labor and delivery. Should **Esracain® Gel** be used concomitantly with other products containing lidocaine during labor and delivery, the total dose contributed by all formulations must be kept in mind.

7.1.2 Breast-feeding

Lidocaine and its metabolites are excreted in the breast milk. At therapeutic doses, the quantities of lidocaine and its metabolites in breast milk are small and generally are not expected to be a risk for the infant. The patient should not apply this medicine to the breasts because the baby may take it in with the milk.

7.1.3 Pediatrics

Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious adverse events (e.g., methemoglobinemia).

When using **Esracain® Gel** in younger children, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see 4 DOSAGE AND ADMINISTRATION).

Esracain® Gel should not be applied to the genital mucosa of children or infants due to insufficient data on absorption.

Parents should be reminded of the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

The gel is not intended for relieving teething pains in children and infants.

Pediatrics (2-18 Years): Children should be given reduced doses commensurate with their age, weight and physical condition because they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses (see 4 DOSAGE AND ADMINISTRATION).

Pediatrics(< 2 Years): **The gel is usually not intended for children under the age of 2 years and in any case children under the age of 3 will be treated under medical supervision only. Esracain® Gel** should be used with caution in children under the age of 2 as there is insufficient data to support the safety and efficacy of this product in this patient population at this time. **Esracain® Gel** is contraindicated for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs (see also 3 CONTRAINDICATIONS).

7.1.4 Geriatrics

Elderly patients may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses and may require dose reductions.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 overdosage or rapid absorption, 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:

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by the following signs and symptoms of escalating severity: circumoral

paresthesia, light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, hyperacusis, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations (e.g., twitching, tremors, convulsions) 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 lidocaine plasma level and may occur as a consequence of rapid absorption.

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

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or, in the most severe instances, anaphylactic shock. Allergic reactions of the amide type are rare (<0.1%) and may occur as a result of sensitivity either to the local anesthetic agent or to other components in the formulation (see 6 DOSAGE FORM, COMPOSITION AND PACKAGING).

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

9 DRUG INTERACTIONS

9.1 Overview

Lidocaine is mainly metabolized in the liver by CYP1A2 and CYP3A4 to its two major metabolites, monoethylglycinexylidine (MEGX) and glycinexylidine (GX), both of which are pharmacologically active. Lidocaine has a high hepatic extraction ratio. Only a small fraction (2%) of lidocaine is excreted unchanged in the urine. The hepatic clearance of lidocaine is expected to depend largely on blood flow.

Strong inhibitors of CYP1A2, such as fluvoxamine, given concomitantly with lidocaine, can cause a metabolic interaction leading to an increased lidocaine plasma concentration. Therefore, prolonged administration of lidocaine should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine. When co-administered with intravenous lidocaine, two strong inhibitors of CYP3A4, erythromycin and itraconazole, have each been shown to have a modest effect on the pharmacokinetics of intravenous lidocaine. Other drugs such as propranolol and cimetidine have been reported to reduce intravenous lidocaine clearance, probably through effects on hepatic blood flow and/or metabolism.

When lidocaine is used topically, plasma concentrations are of importance for safety reasons (see 7 WARNINGS AND PRECAUTIONS, General; 8 ADVERSE REACTIONS). However, with the low systemic exposure and short duration of topical application, the abovementioned metabolic drug-drug interactions are not expected to be of clinical significance when **Esracain® Gel** is used according to dosage recommendations.

Clinically relevant pharmacodynamic drug interactions may occur with lidocaine and other local anesthetics or structurally related drugs, and Class I and Class III antiarrhythmic drugs due to additive effects.

Co-administration of **Esracain® Gel** and other methemoglobin-inducing agents to patients 12 months of age or younger may result in clinical signs of methemoglobinemia (see 3 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS, 8 ADVERSE REACTIONS)

9.2 Drug-Drug Interactions

Local anesthetics and agents structurally related to amide-type local anesthetics

Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics (e.g. antiarrhythmics such as mexiletine), since the toxic effects are additive.

Antiarryhythmic Drugs

Class I Antiarrhythmic drugs Class I antiarrhythmic drugs (such as mexiletine) should be used with caution since toxic effects are additive and potentially synergistic.

Class III Antiarrhythmic drugs

Caution is advised when using Class III antiarrhythmic drugs concomitantly with lidocaine due to potential pharmacodynamic or pharmacokinetic interactions with lidocaine, or both. A drug interaction study has shown that the plasma concentration of lidocaine may be increased following administration of a therapeutic dose of intravenous lidocaine to patients treated with amiodarone (n=6). Case reports have described toxicity in patients treated concomitantly with lidocaine and amiodarone. Patients treated with Class III antiarrhythmic drugs (e.g. amiodarone) should be kept under close surveillance and ECG monitoring should be considered, since cardiac effects of these drugs and lidocaine may be additive.

Strong Inhibitors of CYP1A2 and CYP3A4

Cytochrome CYP1A2 and CYP3A4 are involved in the formation of the pharmacologically active lidocaine metabolite MEGX.

Fluvoxamine: Strong inhibitors of CYP1A2, such as fluvoxamine, given during prolonged administration of lidocaine to areas with a high extent of systemic absorption (e.g., mucous membranes) can cause a metabolic interaction leading to an increased lidocaine plasma concentration. The plasma clearance of a single intravenous dose of lidocaine was reduced by 41 to 60% during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor, to healthy volunteers.

Erythromycin and Itraconazole: Erythromycin and itraconazole, which are strong inhibitors of CYP3A4, have been shown to reduce clearance of lidocaine by 9 to 18%, following a single intravenous dose of lidocaine to healthy volunteers.
During combined co-administration with fluvoxamine and erythromycin the plasma clearance of lidocaine was reduced by 53%.

13-blockers and cimetidine

Following a single intravenous dose of lidocaine, administered to healthy volunteers, the clearance of lidocaine has been reported to be reduced up to 47% when co-administered with propranolol and up to 30% when co-administered with cimetidine. Reduced clearance of lidocaine when co-administered with these drugs is probably due to reduced liver blood flow and/or inhibition of microsomal liver enzymes. The potential for clinically significant interactions with these drugs should be considered during long-term treatment with high doses of lidocaine.

Methemoglobinemia
In patients treated concomitantly with **Esracain® Gel** and other methemoglobin-inducing agents including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine, **Esracain® Gel** may induce the formation of methemoglobin and result in overt clinical signs of methemoglobinemia (see 3 CONTRAINDICATIONS and 5 OVERDOSAGE).

Acetaminophen has been shown to induce methemoglobin formation *in vitro* and in animals. In humans, methemoglobin formation is very rare at therapeutic doses and overdoses of acetaminophen.

9.3 Drug-Food Interactions

Interactions of lidocaine with food have not been established.

9.4 Drug-Herb Interactions

Interactions of lidocaine with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions of lidocaine with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action. Local anesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

10.2 Pharmacodynamics

Hemodynamics

Lidocaine, like other local anesthetics, may also have effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating from the central nervous and cardiovascular systems.

Central nervous system toxicity (see 5 OVERDOSAGE) usually precedes the cardiovascular effects since it occurs at lower plasma concentrations. Direct effects of local anesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

10.3 Pharmacokinetics

Absorption: The rate and extent of absorption depends upon concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application to wound surfaces and mucous membranes is high.

Distribution: Lidocaine has a total plasma clearance of 0.95 L/min and a volume of distribution at steady state of 91 L.

Lidocaine readily crosses the placenta, and equilibrium in regard to free, unbound drug will be reached. Because the degree of plasma protein binding in the fetus is less than in the mother, the total plasma concentration will be greater in the mother, but the free concentrations will be the same.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 µg of free base per ml, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein. Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Metabolism: Lidocaine is metabolized rapidly by the liver, and its metabolites and the unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. Only 2% of lidocaine is excreted unchanged. Most of it is metabolized first to monoethylglycinexylidide (MEGX) and then to glycinexylidide (GX) and 2,6-dimethylaniline. Up to 70% appears in the urine as 4-hydroxy- 2,6-dimethylaniline. The pharmacological/toxicological actions of MEGX and GX are similar to, but less potent than those of lidocaine. GX has a longer half-life (about 10 h) than lidocaine and may accumulate during long-term administration.

Elimination: Lidocaine has an elimination half-life of 1.6 h and an estimated hepatic extraction ratio of 0.65. The clearance of lidocaine is almost entirely due to liver metabolism, and depends both on liver blood flow and the activity of metabolizing enzymes. Approximately 90% of the lidocaine administrated intravenously is excreted in the form of various metabolites, and less than 10% is excreted unchanged in the urine. The primary metabolite in urine is a conjugate of 4-hydroxy- 2,6-dimethylaniline, accounting for about 70-80% of the dose excreted in the urine.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. The elimination half-life in neonates (3.2 h) is approximately twice that of adults. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Special Populations and Conditions

Acidosis increases the systemic toxicity of lidocaine while the use of CNS depressants may increase the levels of lidocaine required to produce overt CNS effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above

6.0 µg free base per ml.

11 STORAGE, STABILITY AND DISPOSAL

Store below 25°C.
The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 6 months, when stored below 25°C.

12 SPECIAL HANDLING INSTRUCTIONS

No special instructions.

13 MANUFACTURER AND REGISTRATION HOLDER

Rafa Laboratories Ltd, POB 405, Jerusalem 9100301, Israel.

14 REGISTRATION NUMBER

19 26 21043

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