SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LIDOCAINE HYDROCHLORIDE S.A.L.F. 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the solution for injection contains 10mg of Lidocaine Hydrochloride (1% w/v).
Accordingly, the contents per ampoule are as follows:
One ampoule of 5ml contains 50mg of Lidocaine Hydrochloride.
One ampoule of 10ml contains 100mg of Lidocaine Hydrochloride.

Excipients with known effect:
Sodium (as sodium chloride and sodium hydroxide).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Local and regional anaesthesia.

4.2 Posology and method of administration

Posology
Local and regional anaesthesia.
As a matter of principle the smallest possible dose that produces adequate anesthesia should be administered. The dosage should be adjusted individually according to the particulars of each case.
Adults:
When injected into tissues with marked systemic absorption, without combination with a vasoconstrictor, a single dose of lidocaine Hydrochloride monohydrate should not exceed 4.5 mg/kg body weight (BW) (or 300 mg). If combined with a vasoconstrictor, 7 mg/kg BW (or 500 mg) of lidocaine Hydrochloride monohydrate per single dose should not be exceeded.
For the clinical uses listed below, recommendations for single doses and strengths of the injection solution to be administered to adults with average body weight (70 kg) are as follows:

Type of anaesthesia	Concentration [%]	Usual volume [ml]	Maximum dose [mg]
Infiltration	0.5-1		300 500 (with epinephrine)
Major nerve blocks	1-2	30-50	500 (with epinephrine)
Minor nerve blocks	1	5-20	200
Epidural	1-2	15-30*	500 (with epinephrine)
Spinal	1.5 or 5 in 7.5% glucose	1-2	100
Intravenous regional anaesthesia (IVRA) - upper limb -lower limb	0.5 0.25	40 50-100	

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

Pediatric population
For children, the doses are calculated individually according to the patients' age, body weight and the nature of the procedure. Up to 5 mg/kg BW may be administered. With the addition of epinephrine, up to 7 mg/kg can be used. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. For anaesthesia in children, only a low strength (0.5 % w/v) of the local anaesthetic should be used. To achieve a complete motor block, a higher strength (1 % w/v) may be required.
Lidocaine should be used with caution in children younger than two years of age as there are limited data to support the safety and efficacy of this product in this patient population at this time.

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

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

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

4.3 Contraindications

- hypersensitivity towards lidocaine, amide-type local anaesthetics 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.

4.4 Special warnings and precautions for use

General
In the case of known allergy towards other amide-type local anaesthetics, group allergy towards lidocaine should be considered.
Lidocaine should only be used with particular caution in patients with liver or kidney diseases or with myasthenia gravis, impaired cardiac conduction (see also section 4.3), cardiac insufficiency, bradycardia, impaired respiratory function and severe shock (see also section 4.2).
In general, prior to injection of lidocaine, it must be made sure that all equipment for resuscitation and emergency medication for the treatment of toxic reactions are instantly available.
Patients with **epilepsy** should be carefully monitored for the occurrence of central nervous symptoms. An increased tendency to convulsions should be considered even with doses below maximum.

Local and regional anaesthesia
Sudden arterial hypotension may occur as a complication of spinal and epidural anaesthesia, in particular in elderly patients.
Particular caution should also be exercised if the local anaesthetic is to be injected into inflamed (infected) tissue because of increased systemic absorption due to higher blood flow and decreased effect due to the lower pH of infected tissue.
A risk of post-spinal headache is associated with spinal anaesthesia mainly in adolescents and in adults up to the age of 30 years. This risk of post-spinal headache can be markedly reduced by choosing sufficiently thin injection cannulae.
When removing the tourniquet after intravenous regional anaesthesia there is an increased risk of adverse effects. Therefore the local anaesthetic should be drained off in several portions.
During anaesthetic procedures in the neck and head region patients are at increased risk of central nervous toxic effects of the drug. See also section 4.8.

Special warnings/precautions regarding excipients
5 ml ampoule
This medicinal product contains sodium, but less than 1 mmol (23 mg) per ampoule, i.e. it is 'essentially sodium free'.
10 ml ampoule
This medicinal product contains about 1 mmol (23.6 mg) sodium per 10 ml ampoule. To be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

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 sedative medications 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 with 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 (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 regarding the possibility of accumulation of lidocaine.
As lidocaine is metabolized mainly via the cytochrome P450 isoenzymes, CYP 3A4 and CYP 1A2 concurrently administered drug substances that are ***substrates, inhibitors or inducers of hepatic enzyme, isoenzyme CYP 3A4 and 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 CYP 3A4 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 CYP 3A4 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 is 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 foetus/neonate.

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

Local and regional anaesthesia
Use of lidocaine for epidural, pudendal, caudal or paracervical block may cause varying degrees of foetal and neonatal toxicity (e.g. bradycardia, hypotonia or respiratory depression). An accidental subcutaneous injection of lidocaine in the foetus during paracervical or perineal block may cause apnoea, hypotension and convulsive fits and may thus put the newborn at vital risk.

Breastfeeding
Lidocaine metabolites are excreted in small amounts into human milk but at therapeutic doses of LIDOCAINE HYDROCHLORIDE S.A.L.F. 10 mg/ml no effects on the breast-fed newborns/infants are anticipated.

Fertility
No data available

4.7 Effects on ability to drive and use machines

In general, LIDOCAINE HYDROCHLORIDE S.A.L.F. 10 mg/ml has negligible influence on the ability to drive and use machines.
However, when outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is fully restored. So when using this medicinal product, the doctor has to asses in each individual case whether a patient is able to take part in traffic or to operate machinery.

4.8 Undesirable effects

General
The frequency and severity of the undesirable effects of lidocaine depend upon the dose, the method of administration and the patient's individual sensitivity.
Symptoms of local toxicity may occur after the administration of lidocaine. Systemic adverse effects may be expected at plasma concentrations of lidocaine exceeding 5-10 mg/l. They become manifest in the form of both CNS symptoms and cardiovascular symptoms (see also section 4.9).

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:	(frequency cannot be estimated from the available data)

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

Nervous system disorders
Common: Transient neurological symptoms especially after spinal and epidural anaesthesia (up to 5 days).
Rare: Neurological complications following central nervous blocks - mainly spinal anaesthesia - such as persistent anaesthesia, paraesthesia, paresis up to paraplegia cauda equina syndrome (i.e. bilateral leg weakness up to paraplegia, saddle anaesthesia, urinary retention and fecal incontinence), headache accompanied by tinnitus and photophobia. Cranial nerve lesions, neurosensory deafness (if administered in head and neck regions).
Not known: Horner's syndrome, associated with epidural anaesthesia or regional applications in the head/neck region.

Gastrointestinal disorder
Very common: Nausea, vomiting.

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

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 liter upward in venous blood.

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

Symptoms
Effects on the CNS:
Low toxic overdose of lidocaine results in stimulation of the CNS. Gross overdose, producing high toxic plasma concentrations, causes depression of the central functions.
Two phases of lidocaine intoxication can be distinguished:

Stimulation
At the beginning of intoxication with lidocaine patients mainly show symptoms of excitation: unrest, vertigo, disturbances of hearing and vision, unpleasant perioral sensations, agitation, hallucination, euphoria,

paraesthesias (e.g. circumoral paraesthesia and numbness of the tongue), dizziness, tinnitus, blurred visions, nausea, vomiting, dysarthria. Shivering and muscular twitching may be signs of imminent attacks of generalized convulsion. Subconvulsive plasma levels of lidocaine often also lead to sleepiness and sedation. Tachycardia, hypertension and flushing may occur as a sign of initial stimulation of the sympathetic nervous system.

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

Effects on cardiovascular circulation:
Unpalpable pulse, pallor, hypotension, bradycardia, arrhythmias, cardiovascular collapse, ventricular fibrillation, cardiac arrest. Sudden hypotension is often the first sign of cardiovascular toxicity of lidocaine. The hypotension is mainly caused by an impairment 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 contraindicated.
There is no specific antidote.
Lidocaine cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 fibers 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 fibers.

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 fibers and the cardiac impulse conducting system. Lidocaine reversibly inhibits the conduction in sensitive nerve fibers 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.

Pediatric population
There is 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 up to 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) since the 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 C_{max} value reached 0.31 mg/l.

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

No data are available on pharmacokinetics after intrathecal administration.

Distribution
Lidocaine follows a biphasic elimination kinetic. After intravenous administration the drug substance is first rapidly distributed from the central compartment into intensively perfused tissues and organs (α-distribution phase). This phase is followed by redistribution into skeletal muscles and adipose tissue. The half-life time during the α-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 percent in adults. It depends on the drug concentration and additionally on the concentration of the α-1-acid glycoprotein (AAG). The AAG is an acute phase protein that binds free lidocaine and may be increased e.g. after trauma, surgery or burns depending on the pathophysiological condition of the patient. On 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 percent of normal.
Results with human liver microsomes and recombinant human CYP isoforms demonstrated that CYP1A2 and CYP3A4 enzymes are the major CYP isoforms involved in lidocaine N-deethylation.
The hepatic blood flow appears to limit the rate of lidocaine metabolism. As a consequence the plasma $t_{1/2}$ of lidocaine and its metabolites may be prolonged and significant effects on pharmacokinetics and dosage requirements of lidocaine are to be expected in patients with impaired liver perfusion, e.g. after acute myocardial infarction, in the presence of cardiac insufficiency, liver disease or congestive heart failure.

Elimination
Less than 10 percent 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 $t_{1/2}$ 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.

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

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 tumors 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/ Hydrochloric acid
Water for injections

6.2 Incompatibilities

Lidocaine Hydrochloride is incompatible with solutions containing sodium bicarbonate, with injectable preparations of amphotericin B, methohexitone sodium, phenytoin and other alkaline solutions. Therefore, LIDOCAINE HYDROCHLORIDE S.A.L.F. 10 mg/ml must not be mixed with such solutions.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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

Store below 25°C.
Store in the original package to protect from light.
Do not freeze.
For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

LIDOCAINE HYDROCHLORIDE S.A.L.F. 10 mg/ml is supplied in:
- glass ampoules, contents: 5ml and 10ml available in packs of:
  5 × 5 ml
  5 × 10 ml

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements for disposal.

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

7. MANUFACTURER

S.A.L.F. S.p.A. Laboratorio Farmacologico
Cenate Sotto (BG) - Italy.

8. MARKETING AUTHORISATION HOLDER

RAZ PHARMACEUTICS LTD, ISRAEL
6 Hamatechet st., Kadima, Israel.

9. MARKETING AUTHORISATION NUMBER

165-32-35867-00

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