SUMMARY OF PRODUCT CHARACTERISTICS

"This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved.” Date of approval: August 2010.

1. NAME OF THE MEDICINAL PRODUCT

LIDOCADREN TEVA® Solution for injection
Lidocaine hydrochloride + Epinephrine (Adrenaline)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml de of solution for injection contains:

Lidocaine hydrochloride 20.0 mg
Epinephrine (adrenaline) 0.0125 mg
(as epinephrine tartrate) 0.02274 mg

Excipients:
Sodium chloride 5.80 mg
Sodium metabisulphite 0.55 mg

1 cartridge (1.8 ml) contains 36 mg of lidocaine hydrochloride (2%) and 0.0225 mg of epinephrine {(equivalent to 0.04095 mg of epinephrine tartrate) (1:80,000)}.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Production of local anaesthesia by nerve-block Infiltration technique.

LIDOCADREN TEVA is intended for use in adults, adolescents and children above 4 years of age.

4.2 Posology and method of administration

Posology
The dosage should be adjusted individually according to the area to be anaesthetised, vascularisation of the tissues and anaesthetic technique to be used.

The recommended doses according to the technique used are described in the table below.

<table>
<thead>
<tr>
<th>Anaesthetic technique</th>
<th>Recommended dose</th>
<th>Adults (70 kg)</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrations or terminal anaesthesia</td>
<td>in ml of solution</td>
<td>1 ml</td>
<td>0.3 ml</td>
</tr>
<tr>
<td></td>
<td>in mg of lidocaine HCl</td>
<td>20 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>Trunical anaesthesia</td>
<td>in ml of solution</td>
<td>1.5 – 2 ml</td>
<td>0.4 – 0.6 ml</td>
</tr>
<tr>
<td></td>
<td>in mg of lidocaine HCl</td>
<td>30 – 40 mg</td>
<td>8 – 12 mg</td>
</tr>
</tbody>
</table>
Maximum dose
Adults:
The maximum dose over a period of 24 hours is 500 mg of lidocaine (for a person of 70 kg), which must not exceed 7 mg/kg of body weight in adults.

Children:
The dose will be adjusted according to the patient’s age and weight, as well as the type of surgery to be performed, not exceeding 5 mg/kg of body weight.
The use of LIDOCADREN TEVA is contraindicated in children under 4 years of age.

Special population:
Increased plasma levels of LIDOCADREN TEVA can occur in older patients due to diminished metabolic processes and lower distribution volume.

The risk of accumulation of LIDOCADREN TEVA is increased in particular after repeated application. A similar effect can ensue from severely impaired hepatic function (see section 4.4.), thus a lower dose is recommended in these cases.

Method of administration
For injection/oromucosal use.
For use in dental anaesthesia only.
To avoid intravascular injection, aspiration control at least in two planes (rotation of the needle by 180°) must always be carefully undertaken. The injection rate should not exceed 0.5 ml in 15 seconds, i.e. 1 cartridge per minute.

4.3 Contraindications
LIDOCADREN TEVA is contraindicated in case of hypersensitivity to the active ingredients or any other of the components.
The use of LIDOCADREN TEVA is contraindicated in children younger than 4 years of age.

Due to the content in lidocaine, LIDOCADREN TEVA is contraindicated in case of:
- known allergy or hypersensitivity to local anaesthetics of the amide type
- severe disorders of atrioventricular conduction not compensated by a pacemaker.
- deficiency in plasma cholinesterase activity
- severe blood coagulation dysfunction
- degenerative nervous disorders

Due to the content in epinephrine (adrenaline); LIDOCADREN TEVA is contraindicated in case of:
- Unstable angina pectoris.
- Recent myocardial infarction.
- Recent coronary artery bypass surgery.
- Refractory arrhythmias and paroxistic or high rate tachycardia, continuous arrhythmia.
- Severe untreated or uncontrolled hypertension.
- Untreated or uncontrolled congestive heart failure.
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- Concomitant treatment with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants (see section 4.5).

Due to the content in metabisulphite, LIDOCADREN TEVA is contraindicated in case of:

- Allergy or hypersensitivity to sulphite.
- Severe bronchial asthma.

4.4 Special warnings and precautions for use

Warnings
Inadvertent intravascular injection may be associated with convulsions, followed by central nervous system or cardiorespiratory arrest. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use.

To minimize the likelihood of intravascular injection, aspiration should be performed before the local anesthetic solution is injected. If blood is aspirated, 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 assure that intravascular injection will be avoided.

It should be taken into consideration that during treatment with blood coagulation inhibitors (e.g. heparin or acetylsalicylic acid), an inadvertent vasopuncture when administering the local anaesthetic can lead to serious bleeding, and the hemorrhagic tendency may be increased (see section 4.5).

Athletes should be warned that this medicinal product contains an active substance likely to yield a positive result in anti-doping tests.

The injection of this medicinal product must be avoided in infected area.

The presence of sodium metabisulphite as an excipient may cause allergic reactions, including anaphylactic-type reactions and bronchospasm in susceptible patients, particularly those with an asthmatic or allergic history.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, i.e., essentially sodium-free.

Precautions for use
The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose due to 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.

If sedatives are employed to reduce patient apprehension, reduced doses should be used since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect. Young children should be given minimal doses of each agent. Lidocaine should be used with caution in patients with severe shock or heart block.
The product should be administered with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of atrioventricular conduction produced by these drugs (see section 4.3).

Local anesthetic solutions containing a vasoconstrictor should be used with caution 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.

LIDOCADREN TEVA should be used with precaution in patients with:
- angina pectoris
- arteriosclerosis
- impaired blood coagulation
- diabetes mellitus
- severe hepatic impairment Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations.
- lung diseases – particularly allergic asthma
- epilepsy
- phaeochromocytoma
- narrow-angle glaucoma
- thyrotoxicosis

Cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness should be monitored after each local anesthetic injection. Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness should alert the practitioner to the possibility of central nervous system toxicity. Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position: placing the patient in the recumbent position is recommended when an adverse response is noted after injection of a local anesthetic.

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 management 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 suspected triggering agent(s) and prompt treatment, including oxygen therapy, dantrolene (consult dantrolene sodium intravenous package insert before using) and other supportive measures. 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 injection 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.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its content in lidocaine, LIDOCADREN TEVA should be used with caution in patients that receive concomitant medication similar in structure to local anaesthetics (for example, Ib-class antiarrhythmic drugs), since the toxic effects are additive.

Due to its content in epinephrine, LIDOCADREN TEVA should be administered with caution in patients who are simultaneously receiving one of the following medications:

- Blood coagulation inhibitors (heparin), nonsteroidal anti-inflammatory drugs (NSAID), plasma substitutes (dextran), phenothiazines, butyrophenones: these drugs may reduce or reverse the vasopressor effect of epinephrine and may increase bleeding trend.

- Tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), ergotamine-like oxytocic drugs, non-selective beta blockers like propanol: these drugs may increase the vasopressor effect of epinephrine and may lead to serious hypertension and bradycardia.

4.6 Pregnancy and lactation

Pregnancy

Even if there is no evidence from animal studies of harm to the foetus, LIDOCADREN TEVA should not be given during pregnancy unless strictly necessary.

The administration of LIDOCADREN TEVA during pregnancy may cause foetal bradycardia due to its content in local anaesthetic, as well as a decrease in intrauterine blood flow due to its content in epinephrine, especially in case of inadvertent intravascular injection.

Lactation

Lidocaine may enter the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate. It is not known whether adrenaline enters breast milk or not, but it is unlikely to affect the breast-fed child. Thus, it is considered that LIDOCADREN TEVA may be used during lactation.

Pediatric use

Dosages in pediatric population should be reduced, commensurate with age, body weight and physical condition.
4.7 Effects on ability to drive and use machines

The influence of LIDOCADREN TEVA on the ability to drive or use machines is small or moderate, and may temporarily impair mental function and co-ordination depending on the dose of local anaesthetic.

The dentist has to assess in each case the possible impairment of safety when operating a motor vehicle or machinery. The patient should not leave the dental office earlier than at least 30 minutes after the injection.

4.8 Undesirable effects

Adverse effects strictly attributable to the local anaesthetic are limited. However, the physiological effects from nerve block are frequent, but these vary considerably depending on what type of block is administered.

Due to the content in lidocaine as a local anaesthetic, the following undesirable effects may occur:

Cardiovascular disorders  
*Rare* (≥1/10,000, <1/1,000)  
Drop in blood pressure, cardiac impulse conduction disorders, bradycardia, cardiovascular arrest.

Nervous system disorders  
*Rare* (≥1/10,000, <1/1,000)  
Metallic taste, tinnitus, dizziness, nausea, vomiting, anxiety, shaking, nervousness, nystagmus, headache, increase in respiratory rate. Paresthesias (loss of sensation, burning, tingling) of the lip, tongue, or both. Drowsiness, tonic-clonic seizures, coma and respiratory paralysis.

Respiratory disorders  
*Rare* (≥1/10,000, <1/1,000)  
Tachypnea, then bradypnea, which could lead to apnoea.

Allergic reactions  
*Very rare* (< 1/10,000)  
Rash, erythema, pruritus, oedema of the tongue, mouth, lips or throat and in more severe cases, anaphylactic shock.

Due to the content of epinephrine as a vasoconstrictor, the following undesirable effects can occur:

Cardiovascular disorders  
*Rare* (≥1/10,000, <1/1,000)  
Heat sensation, sweating, heart racing, migrainelike headache, blood pressure increase, angina pectoris disorders, tachycardias, tachyarrhythmias and cardiovascular arrest; acute oedematous thyroid swelling may not be discarded.
Due to the content of metabisulphite as excipient, the following undesirable effects can occur:

Allergic reactions
Very rare (<1/10,000)
Allergic reactions may particularly occur in bronchial asthmatics, which are manifested as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of consciousness or shock.

4.9 Overdose

4.9.1 Toxicity

Accidental intravascular injections of local anaesthetics may cause immediate systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15–60 minutes after injection). Toxicity is manifested first in the central nervous system, then followed by the cardiovascular system. In paediatric patients, when a local anaesthetic is administered under general anaesthesia, it is difficult to detect the first signs of toxicity to the local anaesthetic.

Central nervous system toxicity
Initially, symptoms include agitation, a feeling of intoxication, a sensation of numbness in the lips and tongue, paresthesias around the mouth, dizziness, vision and hearing disturbances, and buzzing in the ears. Speech problems, muscle stiffness and spasms are more serious symptoms and precede generalised seizures. Respiratory arrest may even occur in severe cases. Acidosis increases the toxic effects of local anaesthetics. Recovery depends on the metabolism of the local anaesthetic and the distribution away from the central nervous system. This occurs quickly providing large amounts of the drug are not injected.

Cardiovascular system
The symptoms associated to the local anaesthetic may include blood pressure drop, bradycardia, arrhythmia, and cardiac arrest as a result of high systemic concentrations of local anaesthetic. The symptoms associated to epinephrine are heat sensation, sweating, heart rhythm acceleration, headaches, blood pressure increase, anginous disorders, tachycardia, tachyarrhythmia, and cardiac arrest.

4.9.2 Treatment

General basic measures
If adverse reactions arise the application of the local anaesthetic has to be stopped. Measures should focus on maintenance/restoration of the vital functions of respiration and circulation, oxygen administration and intravenous access.

Special measures
- Hypertension: Elevation of the upper body, if necessary sublingual nifedipine.
- Convulsions: Protect patients from concomitant injuries, if necessary benzodiazepines (e.g. diazepam iv).
- Hypotension: Horizontal position, raise legs up, if necessary intravascular infusion of a complete electrolyte solution iv, vasopressors (e.g. ethylephrine iv).
- Bradycardia: Atropine iv.
- Anaphylactic shock: Infusion of a complete electrolyte solution, if necessary epinephrine iv, cortisone iv; contact emergency physician.
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- Cardiovascular arrest: Immediate cardiopulmonary resuscitation, contact emergency physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetics: amides, ATC code: N01BB52.

As other local anaesthetics, lidocaine reversibly blocks the propagation of the impulse along the nerve fibers, thus preventing the mobility of sodium ions through the nerve membrane.

At high doses lidocaine has a quinidine-like action on the myocardium, i.e., cardiac depressant. All local anaesthetics stimulate the central nervous system and may produce anxiety, restlessness and tremors.

The onset and duration of lidocaine action are increased by adding epinephrine as vasoconstrictor. Thus, the absorption of the anaesthetic is delayed and a greater concentration is obtained for a longer period. Also, the possibility of systemic adverse effects is reduced.

5.2 Pharmacokinetic properties

Lidocaine is rapidly absorbed after intramuscular injection and oromucosal injection. The distribution volume (Vdis) is 1.30 L/kg and the clearance (Cl) is 0.85 L/kg/hr. Lidocaine undergoes first-pass metabolism in the liver and less than 10% of the dose is excreted unchanged via the kidneys. Elimination half-life (t½) is 1.6 hours.

5.3 Preclinical safety data

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

As for other amide-type local anaesthetics, the active substance in high doses may cause reactions on the central nervous system and the cardiovascular system (see section 4.8. Undesirable effects).

6. PHARMACEUTICAL PARTICULARS

6.1 List of deexcipients

Sodium chloride
Sodium metabisulphite
Hydrochloric acid
Sodium hydroxide
Water for injection
6.2 Incompatibilities

In solutions with epinephrine, the mixture with alkaline solutions may cause a rapid degradation of the vasoconstrictor agent, as well as a greater risk of precipitation.

6.3 Special precautions for storage

Store below 25°C in the original package.

6.4 Nature and contents of container

Neutral, hydrolytic class type I glass cartridges, closed on one side with a grey-coloured bromobutyl stopper and on the other side with a bromobutyl coated disc and aluminium cap. LIDOCADREN TEVA is packed in boxes containing 50 or 100 cartridges.

6.5 Special precautions for disposal

Cartridges for single use.
Cartridges should not be used with other patients. The remaining of the product should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7  REGISTRATION NUMBER: 144 03 31072 00.

8. MANUFACTURER

Laboratories Inibsa, S.A., Bacelona, Spain.

8. LICENCE HOLDER

Abic Marketing Ltd., P.O.Box, 8077, Netanya, Israel.