SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

0.4% LİDODEKS in 5% Dextrose Solution for I.V. Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:	**mg/ml**
Lidocaine hydrochloride	4 mg
Excipients:	
Dextrose anhydrous	50 mg
Water for injection	To be completed to 1.000 mL

For excipients, please see Section 6.1.

3. PHARMACEUTICAL FORM

Sterile and apyrogen solution for intraveineuse infusion.
0.4% LİDODEKS is a clear, colorless solution of which pH is between 3.0-7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lidocaine lowers cardiac irritability; therefore, 0.4% LİDODEKS is given as an intravenous infusion to control ventricular arrhythmias after myocardial infarction or during cardiac surgery. It is also used in patients with digitalis intoxication associated with life-threatening ventricular arrhythmias and general anesthesia susceptible to ventricular arrhythmia.

Generally, solutions containing lidocaine are used to maintain suppressed ectopic activity provided by bolus injection of lidocaine.

4.2 Posology and Method of Administration

Posology/Administration duration and frequency:

Adults

The speed and volume of application is decided by the doctor depending on the needs of the patient.
A plasma concentration of approximately 1-6 µg/ml is required to suppress ventricular arrhythmias.

Loading dose single i.v. bolus injection is 1.0-1.5 mg/kg. It is applied with a speed of 25-50 mg/min.
For solutions containing lidocaine, the subsequent loading doses are administered at 1-4 mg/min for 12-48 hours.

Adults (20-50 mcg/kg/min)			
	An adult with average 70 kg weight		
	mg/min	mL/h	mL/min
0.4% LİDODEKS in 5% Dextrose Solution for I.V. Infusion (4 mg Lidocaine HCl/mL)	1-4	15-60	0.25-1.0

Pharmacokinetic data show that lidocaine can extend the half-life of lidocaine up to 3 times longer in single-application infusions (24 hours). In order to avoid the toxic effect of lidocaine, it would be beneficial to adjust the infusion rate considering this feature of lidocaine.

More than 200-300 mg should not be administered in a 1 hour period. Smaller doses may be needed in patients under certain conditions (such as patients with congestive heart failure).

Method of administration:
0.4% LİDODEKS is administered as an intravenous infusion.
Concentrated lidocaine hydrochloride solutions (more than 0.2%) should be applied with carefully calibrated infusion devices.
Lidocaine hydrochloride infusion should not be added to the blood transfusion.

Additional information for different populations:

Renal failure:
Kidney dysfunction is unlikely to affect lidocaine clearance in the short term (24 hours). However, due to the accumulation of lidocaine and its metabolites, toxicity may develop with long-term or repeated applications.
Since lidocaine is known to be excreted by the kidneys, patients with impaired kidney function are more likely to experience toxic reactions.

Hepatic failure:
In patients with hepatic blood flow and dysfunction, and for whom lidocaine infusion has been administered for a long time, the half-life of lidocaine is longer and the clearance is lower. Therefore, the dose may need to be reduced. In order to reduce the risk of acute toxicity, two

consecutive bolus injections, which will be administered for 10-30 minutes, are preferred over as single bolus injection.
The half-life of lidocaine may decrease in patients with chronic cardiac output or with drug effect induced by hepatic microsomal enzymes; therefore, higher doses may be required in such patients.

Pediatric population:
In children, the dose should generally be reduced. Dosage will be adjusted according to the clinical response by evaluating the ECG changes.
The efficacy and safety of lidocaine in pediatric patients has not been reported. Therapy for children should start with 0.5-1 mg/kg as a single IV bolus. It is recommended that the continuation of the infusion should be performed at a speed of 30 mcg/kg/min (10-50 mcg/kg/min).

Geriatric population:
Dose selection should be done carefully in elderly patients, as kidney function generally decreases. It may be useful to monitor renal function. Patients with reduced hepatic function, impaired hepatic blood flow, or patients over the age of 70 are usually treated with half the loading dose and continued with lower levels of infusion. Dosing should be done according to body weight in patients over 65 years of age.

4.3. Contraindications

0.4% LİDODEKS should not be used in the following cases:

- In patients with hypersensitivity to amide-type local anesthetics.
- In patients known to be sensitive to corn products as it contains dextrose.
- In patients with hypovolemia.
- In heart block and other conduction disorders. (Stokes-Adams Syndrome, Wolff-Parkinson-White Syndrome, sinoatrial, atrioventricular or intraventricular block)
- Treatment of supraventricular arrhythmias
- bradycardia.
- Cardiac decompensation.
- Hypertension not due to treatable tachyarrhythmia.

4.4 Special warnings and precautions for use

Continuous infusion of lidocaine requires careful monitoring by electrocardiography. Conditions such as prolongation of the PR interval, widening of the QRS interval, or arrhythmias or symptoms of cardiac conduction depression should be monitored during the infusion of this agent and, if this occurs, the infusion should be stopped immediately. Emergency resuscitation equipment and medication may be necessary to tolerate adverse reactions affecting the cardiovascular, respiratory, or central nervous system. For this reason, resuscitative equipment

and medicines, oxygen should be available during the use of this product. Patients with atrial fibrillation may rarely experience accelerated ventricular rate when using lidocaine.
In emergencies, when ventricular rhythm disturbances are suspected, if ECG equipment is not available, the healthcare provider can perform a single dose of the patient, taking into account the potential benefit and possible harm.

This solution should be given with caution to patients with epilepsy, impaired cardiac or respiratory function, patients with liver damage, patients with severe kidney disease, or patients with Myesthenia Gravis. Lidocaine is metabolized in the liver and excreted from the kidneys. Therefore, it should be used with caution in cardiac and circulatory problems and similar situations that affect hepatic blood flow.

It should be used with caution in severe digitalis intoxication. It is used with caution in patients with digital toxicity with an atrioventricular block (see 4.3. Contraindications).

Antiarrhythmic drugs may be ineffective in patients with hypokalemia; therefore, serum potassium levels must be brought to normal before the product is applied. In addition, hypoxia and acid-base disorders that may increase ventricular arrhythmia should be corrected.

In patients with sinus bradycardia or incomplete heart block, administration of lidocaine intravenously to eliminate ventricular ectopic beats without accelerated heartbeat may result in more frequent and severe ventricular arrhythmias or completed heart block (see section 4.3.).

Extra caution should be exercised when using drugs that reduce the excitability of the cardiac muscles in patients with impaired myocardial function and high-dose lidocaine.

Strong anesthetic agents, amide-type local anesthetics and depolarized and polarized muscle relaxant agents in lidocaine have been associated with malignant hyperthermia.

In patients with dangerous myocardial function, special attention should be paid to these patients during lidocaine application to avoid fluid loading or to avoid conditions that may cause congenital heart failure or impairment of cardiac conduction.
Anaphylactic reactions may occur after administration of lidocaine hydrochloride. In such cases, stop using the drug.

Theoretical information suggests that lidocaine may have porphyrogenic properties, but its clinical significance is unknown. Care should be taken when applying this product in patients with acute porphyria.

Do not use in serial connections.

If the application is to be done with a controlled infusion pump, it should be noted that the pump has stopped running before the bag is completely emptied; otherwise, air embolism may occur.
The solution is administered intravenously through sterile sets. It is recommended that the sets used in intravenous administration are changed every 24 hours.

Use only if the solution is clear, the bag is strong and leakproof.

Laboratory tests
Clinical evaluation and periodic laboratory tests should be performed to monitor fluid balance, electrolyte concentrations, and changes in acid-base balance in the patient for long-term parenteral applications or where the condition of the patient requires.

Creatinine: In patients who have had lidocaine, creatinine measurements are 15-35% higher when compared with Jaffe method by enzymatic method. This is due to the intervention of a metabolite, N-etherline, into the analysis.

Evidence for its proper use in pediatric patients is limited. Newborns have clinical risk of methemoglobinemia due to low enzyme capacities.

In clinical studies, lidocaine clearance has been shown to decrease in patients over 65 years of age. This is due to both high risk of heart failure and lower body weight in elderly patients. Reducing the lidocaine dose may be necessary for elderly patients receiving dangerous cardiovascular and/or liver function and/or long-term infusion.

4.5 Interactions with other medicinal products and other forms of interaction
Interaction between lidocaine and beta-adrenergic blockers, cimetidine and phenytoin - moderate clinical significance.

Lidocaine may have combined effects when combined with phenytoin, procainamide, propranolol, amiodarone or other antiarrhythmic drugs such as quinine, or their antagonistic and toxic effects may be combined.

Co-administration of beta-adrenergic receptor antagonists such as propranolol, nadolol, metoprolol, or cimetidine with lidocaine may result in decreased plasma clearance. This can cause toxic buildup of the drug. Therefore, during the use of these drugs with lidocaine, the patient should be carefully monitored for lidocaine toxicity.

In a small prospective study of the combined therapy of amiodarone and lidocaine, two cases have been reported that amiodarone reduced lidocaine clearance, although amiodarone had no effect on lidocaine clearance and pharmacokinetics. This combination has been reported to cause seizures and severe sinus bradycardia and long sinoatrial involvement. Patients taking the

combination should be carefully monitored until more experience is obtained with the simultaneous use of lidocaine and amiodarone.
Phenytoin and other antiepileptic drugs such as primidone, carbamazepine, phenobarbitone can stimulate the hepatic metabolism of lidocaine, but the clinical significance of this effect is unknown. Phenytoin and lidocaine have cardiac depressant effects together.

Lidocaine should be used with caution in patients with digital toxicity accompanied by atrioventricular block.

Concomitant use of fluvoxamine and lidocaine greatly reduces the elimination of lidocaine.

Lidocaine reduces the minimum effective concentration of inhaled anesthetics such as nitrous oxide.

Muscle relaxants such as lidocaine and suxamethonium can cause excessive neuromuscular blockade, so caution should be exercised when used together.

There are no cases showing direct interaction between alcohol and lidocaine. However, acute severe alcohol intoxication can centrally depress the cardiovascular system, thereby prolonging the half-life of lidocaine.

Lidocaine is metabolised by CYP1A2 and CYP3A4 enzymes.

Concomitant use of drugs that are the substrate, inhibitor or stimulant of CYP1A2 and CYP3A4 enzymes and lidocaine affect the metabolism of the drug; therefore, plasma levels of lidocaine may be affected.

4.6 Pregnancy and Lactation

General advice
Pregnancy category: B.

Women with childbearing potential/Contraception
No clinical study available on humans.

Pregnancy period
Studies on animals do not show direct or indirect harmful effects with respect to pregnancy / embryonal / fatal development / birth or postnatal development (see section 5.3).

There are no data on the safety of this product during pregnancy. Reproductive studies of up to 5 times the human dose have been performed in rats, and no evidence has been found that lidocaine

hydrochloride causes harm to the fetus. However, there are not enough well-controlled studies in pregnant women. Animal experiments do not always give the answer in humans. It should therefore only be used if necessary. Despite the fact that lidocaine is widely used for surgical procedures during pregnancy and there is no evidence of negative effects on the mother and fetus, it should be decided to take into consideration the benefit and potential risk to the patient due to the lack of adequate and well-controlled studies showing the effect of lidocaine on the developing fetus in pregnant women.

Lactation period
There are no data on the safety of this product during the lactation period. It is not known whether this product passes into milk. Since many drugs are known to pass into milk, this product should be used with caution in nursing mothers.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Side effects of lidocaine are similar to those seen in other local anesthetics. Side effects are usually dose-dependent and may be due to high plasma levels, hypersensitivity, idiosyncrasy or tolerance.

Systemic toxicity is manifested by effects on the central nervous system and cardiovascular system. These undesirable effects are listed by the following categories:

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); unknown (cannot be estimated with the obtained data)

Blood and lymphatic system disorders
Unknown: Methemoglobinemia

Immune system disorders
Rare: Allergic reactions, urticaria, edema, anaphylactic reactions, skin lesions.
There are no data indicating cross-sensitivity between lidocaine hydrochloride-procainamide or lidocaine hydrochloride-quinidine.

Psychiatric disorders
Unknown: convulsions, psychosis.

Nervous system disorders
Unknown: Yawning, fainting, tiredness, excitement, euphoria, tension, irritability, anxiety, dizziness, tinnitus, eye tremor, blurred or double vision, numbness of tongue and perioral region, tremor, drowsiness, coma, temperature-cold feeling or numbness, loss of consciousness, disorientation, paraesthesia, difficulty swallowing, prolonged speech.

Cardiac disorders
Unknown: Myocardial depression, peripheral vasodilation, hypertension, hypotension, bradycardia, arrhythmia, ventricular tachycardia/ventricular fibrillation, cardiac arrest.

Respiratory, thoracic and mediastinal disorders
Unknown: respiratory distress-difficulty, respiratory depression or cessation.

Gastrointestinal disorders
Unknown: nausea, vomiting

Musculoskeletal and connective tissue disorders
Unknown: muscle twitching

4.9 Overdose treatment

Overdose symptoms on the central nervous system and the cardiovascular system are given under the heading of undesirable effects (see section 4.8. Undesirable effects).

Lidocaine toxicity is associated with systemic blood levels. Lidocaine with reduced clearance and a longer half-life should be taken into account in long-term infusions (24 hours). Application at a constant speed can cause toxic buildup of lidocaine. Infusion must be reduced by approximately one and a half times to compensate for reduced clearance. Concomitant use of propranolol or before may increase blood concentrations of about 30% in patients without cardiac and liver failure.

After discontinuation of lidocaine infusion therapy, circulation and respiration should be continued and convulsions should be checked. Respiratory airway should be continued by opening or giving oxygen. The circulation should be continued by infusing plasma or appropriate electrolytes. Vasopressor agents such as metaraminol, dopamine or dobutamine can be used to maintain blood pressure. Convulsions can be kept under control with ultra short-acting barbiturate administration such as intravenous diazepam or thiopentone. If these drugs are not available, short-acting barbiturates such as pentobarbitone can be used. If the patient is anesthetized, a short-acting muscle relaxant (such as suxamethonium) can be used. These drugs should only be administered by a healthcare professional who is familiar with the effects of the drug.

Overdose caused by continuous infusion of lidocaine can cause methemoglobinemia. This can be treated with an intravenous infusion of 1% methylene blue solution at a dose of 1-4 mg/kg.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antiarrhythmics Class IB
ATC code: C01BB01

Lidocaine hydrochloride is a class-1 anti-arrhythmic agent, reducing cardiac irritability. Lidocaine reduces the membrane's ability to respond, reduces the rate of transmission and extends the action potential time. It shows an antiarrhythmic effect by increasing the ventricular electrical stimulation threshold during diastole. It controls ventricular arrhythmias by suppressing automaticity in the His-Purkinje system. In the usual treatment doses, lidocaine hydrochloride does not provide a change in systemic arterial pressure, absolute refractory period or myocardial contractility.

5.2 Pharmacokinetic Properties

General aspects

Absorbation:
Following intravenous infusion, plasma concentrations rapidly decrease with a half-life of approximately 10 minutes. Antiarrhythmic concentrations were determined as 1.5-6 mg/ml.

Distribution:
After an intravenous dose of lidoakin, lidocaine is rapidly distributed to the heart, brain, kidneys and other organs. It diffuses to plesanta approximately a few minutes after injection. After rapid distribution, metabolism elimination phase and redistribution to skeletal muscles and adipose tissue are slower. Therefore, lidocaine has an initial half-life between 7-30 minutes and a terminal half-time between 1.5-2 hours. Lidocaine binds to plasma proteins, including α1-acid glycoprotein. Binding to plasma proteins is variable and concentration dependent. Approximately 60-80% of lidocaine is bound at concentrations of 1-4 µg/ml.

Biotransformation:
Approximately 90% of the administered dose is metabolized in the liver. The metabolic rate of lidocaine depends on the hepatic blood flow. Lidocaine is rapidly de-ethylated in the liver and turns into its active metabolites. Lidocaine has two main metabolites. These are monoethylglycinexilide and glycinexilide. These two metabolites play a role in the therapeutic and toxic effects of lidocaine. Cumulative accumulation of lidocaine metabolites can cause

toxicity in CNS. The half-life of these two metabolites is longer than that of lidocaine. The activity of monoethylglycinecilididine is lower, but its half-life is longer (about 2 hours).

Elimination:
Following intravenous infusion, plasma concentrations rapidly decrease with a half-life of approximately 10 minutes. The elimination half-life is about 2 hours. Metabolism products and 10% unchanged lidocaine are excreted in the urine together.

Linearity:
Not applicable.

5.3 Preclinical safety data

Long-term animal studies have not been conducted with 0.4% LİDODEKS in order to evaluate the effects on carcinogen, mutagen potential and fertility.

However, a 2-year oral toxicity study was conducted with 2,6-xylidine, a metabolite of lidocaine. Adenomas and carcinomas were found in the nasal cavity in studies performed with a daily dose of 900 mg/m^2 (150 mg/kg) in both male and female rats. Nasal tumors were not found at low doses (15 mg/kg) and control animals. In addition, subcutaneous fibromas and fibrosarcomas were observed in female and male rats (150 mg/kg).

The genoctoxic potential of 2,6-xylidine has been studied with mixed results: Positive results have been reported in gene mutation experiments (weekly positive and mouse lymphoma experiments in metabolic activation Ames tests) and chromosomal damage experiments (in chromosomal aberrations performed in Chinese Hamster ovary-CHO-cell culture). No indication of genotoxicity has been found in in vivo DNA damage experiments (unplanned DNA synthesis) and chromosomal damage experiments (micro-core analysis). Studies related to the liver DNA of rats and buckets with turbinate bones show that 2,6-xylidine can be genotoxic under certain in vivo conditions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Dextrose anhydrous
Water for injection
Sodium hydroxide (for pH adjustment, q.s.)
Hydrochloric acid (for pH adjustment, q.s.)

6.2 Incompatibilities

Solutions containing lidocaine hydrochloride are incompatible with amphotericin, methohexyl sodium, sulfadiazine sodium. It has incompatibility with pH due to ampicillin. Its incompatibility depends on the pH of the solution containing lidocaine.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

0.4% LİDODEKS; it is offered for sale in PP bags of 250 and 500 ml. It has 2 forms; with and without set.

6.6 Special precautions for disposal and other handling

Unused products should be discardedin accordance with the local regulations!

The solution should be checked before use.
Application is done intravenously with sterile pyrogen sets.

Only clear, particle-free and intact packaging integrity products should be used.
Application should be started as soon as possible after the application set is attached to the product.

Serial connections with other infusion fluids should not be made to prevent an air embolism that may occur due to residual air in the bag.

The solution should be applied using a aseptic technique through a sterile administration set. Liquid must be passed through the application set before use to prevent air from entering the system.

Additional drugs can be added before and during infusion with the help of a needle from the injection tip in aseptic conditions. The isotonicity of the resulting product must be determined before parenteral administration.
The added drug must be completely mixed with the solution before applying to the patient. Solutions containing additional drugs should be used immediately after the drug is added; should not be stored for later use.

Addition of the drug to the solution or wrong application technique may cause fever reaction due to pyrogen contamination to the product. In the event of an adverse reaction, infusion should be stopped immediately.
It is disposable.

Partially used solutions should not be stored.
Partially used bags should not be reconnected to the systems applied to the patient.
To open:
1. Check the integrity of the outer packaging and for leaks; do not use if the packaging is damaged.
2. Tear open the protective outer packaging.
3. Tightly check whether the bag in the protective packaging is intact. Check that the solution in the bag is clear and free from foreign matter.

Application preparations:
1. Hang the bag.
2. Remove the protective cap on the application tip.
3. Insert the spike of the application set firmly into the application tip.
4. The instructions for use of the set should be followed to apply the solution to the patient.

Adding additional medication:
Caution: As with all parenteral solutions, all substances to be added to the product must be compatible with the product. If additions will be made to the product, compatibility should be checked in the final mixture before applying to the patient.

Adding medication before application
1. The drug delivery tip is disinfected.
2. The drug to be added is added to the bag with a 19-22 gauge needle with a syringe.
3. The solution and the medication added are thoroughly mixed. In dense drugs such as potassium chloride, it is ensured that the bag is mixed by tapping the application outlet in the up position.
Caution: Bags with additional medication should not be stored.

Adding medication during application
1. The clamp of the set is closed.
2. The drug delivery tip is disinfected.
3. The drug to be added is applied through the injector tip with a 19-22 gauge needle.
4. The solution is removed from the rack and turned over.
5. While in this position, the application exit of the bag and the injection inlet are tapped gently to mix the solution and additional drug.
6. By opening the bag, the clamp is opened and the application is continued.

7. MARKETING AUTHORIZATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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