PRESCRIBING INFORMATION

Lignospan® Forte
Lignospan® Standard
(Lidocaine Hydrochloride and Epinephrine Injection USP)

(lidocaine hydrochloride 2% with epinephrine 1:50,000 and with epinephrine 1:100,000)

Local Anaesthetic for Dental Use

Sponsor:	Manufacturer:	Date of Preparation:
Septodont, Inc. 58, RUE DU Pont de Creteil 94107 Saint-Maur-des-Fosses Cedex France	Novocol Pharmaceutical of Canada, 25 Wolseley Court, Cambridge, Ontario, N1R 6X3	June 30, 2015

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form/Strength**	**All Non-medicinal Ingredients**
Parenteral	Sterile Solution 20 mg/mL lidocaine hydrochloride solution with epinephrine contain 0.02 mg/mL (1:50,000) or 0.01 mg/mL (1:100,000) epinephrine	Sodium chloride (for isotonicity), potassium metabisulfite (as an antioxidant), Disodium Edetate (Chelating agent) water for injection, sodium hydroxide and/or hydrochloric acid to adjust pH 3.0 – 5.0 or pH 3.3 – 5.5

INDICATIONS AND CLINICAL USE

Adults (>18 years of age):

Lignospan solutions are indicated for the production of local anesthesia for dental procedures by nerve block or infiltration techniques.

Only accepted procedures for these techniques as described in standard textbooks are recommended.

Geriatrics (> 65 years of age):
Elderly patients should be given reduced doses commensurate with their age and physical condition (see DOSAGE AND ADMINISTRATION- Special Populations).

Pediatrics (< 18 years of age):
Children should be given reduced doses commensurate with their age, weight and physical condition (see DOSAGE AND ADMINISTRATION- Special Populations).

Lidocaine should be used with caution in children younger than two years of age as there are insufficient data to support the safety and efficacy of this product in the patient population at this time.

CONTRAINDICATIONS

Lignospan (Lidocaine Hydrochloride with Epinephrine) is contraindicated:

- In patients with a known hypersensitivity to local anesthetics of the amide type or to other components of the solution (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- In patients with a known history of hypersensitivity to sodium metabisulfite and/or citric acid (stabilizers used in solutions containing epinephrine).

WARNINGS AND PRECAUTIONS

General

LOCAL ANAESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MAY ARISE FROM THE BLOCK TO BE PERFORMED, AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (see ADVERSE REACTIONS and OVERDOSAGE). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

THE LOWEST DOSAGE OF LOCAL ANAESTHETICS THAT RESULTS IN EFFECTIVE ANESTHESIA OR ANALGESIA SHOULD BE USED TO AVOID HIGH PLASMA LEVELS AND SERIOUS ADVERSE REACTIONS. INJECTIONS SHOULD BE MADE SLOWLY OR IN INCREMENTAL DOSES, WITH FREQUENT ASPIRATIONS BEFORE AND DURING THE INJECTION TO AVOID INTRAVASCULAR INJECTION.

Major Peripheral Nerve Blocks: Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption which can lead to high plasma concentrations.

Repeat Dosing: Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition (see DOSAGE AND ADMINISTRATION-Special Populations).

Use of Parenteral Solutions containing Epinephrine: Lignospan containing epinephrine should not be used in areas of the body supplied by end arteries, such as digits, nose, ears or penis, or otherwise having a compromised blood supply (see also DRUG INTERACTIONS).

Inflammation and Sepsis: Local anesthetic procedures should not be used when there is inflammation and/or sepsis in the region of the proposed injection

Malignant Hyperthermia: 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 blockage 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.

Acute Porphyria: Lidocaine has been shown to be porphyrinogenic in animal models.

Lignospan Parenteral Solutions should only be used in patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken for all porphyric patients.

Cardiovascular

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

Patients with partial or complete heart block require special attention since local anaesthetics may depress myocardial conduction. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed. Dosage should be adjusted accordingly.

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

Solutions containing epinephrine should be used with caution in patients whose medical history and physical evaluation suggest the existence of untreated hypertension, ischemic heart disease, heart block, cerebral vascular insufficiency, peripheral vascular disorder, and any other pathological condition that may be aggravated by the effects of epinephrine.

Patients treated with antiarrhythmic drugs (e.g. amiodarone, mexiletine) should be under close surveillance and ECG monitoring, since cardiac effects of these drugs and lidocaine may be additive (see DRUG INTERACTIONS).

Peri-Operative Considerations

It is essential that aspiration for blood be done prior to injecting any local anesthetics, both the original and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.

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

Resuscitative equipment, oxygen, and other resuscitative drugs, should be available for immediate use (see OVERDOSAGE). During major regional nerve blocks, or using large doses, the patients should be in an optimal condition and should have i.v. fluids running via an indwelling catheter to assure a functioning intravenous pathway. The clinician responsible should have adequate and appropriate training in the procedure to be performed, should take the necessary precautions to avoid intravascular injection (see DOSAGE AND ADMINISTRATION), and should be familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see ADVERSE REACTIONS and OVERDOSAGE). THE LOWEST DOSAGE THAT RESULTS IN EFFECTIVE ANESTHESIA SHOULD BE USED TO AVOID HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. INJECTIONS SHOULD BE MADE SLOWLY, WITH FREQUENT ASPIRATIONS BEFORE AND DURING THE INJECTION TO AVOID INTRAVASCULAR INJECTION.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech,

lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Head/Neck
Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions caused by inadvertent injection to an artery. These reactions may be similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Inadvertent injections into an artery can cause cerebral symptoms even at low doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression leading to cardiac arrest have been reported. 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 (see DOSAGE AND ADMINISTRATION).

Endocrine
Solutions containing epinephrine should be used with caution in patients whose medical history and physical evaluation suggest the existence of poorly controlled hyperthyroidism or diabetes.

Hepatic
Because amide-type local anesthetics, such as Lidocaine, are metabolized in 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 anaesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Neurologic

Epilepsy: Lidocaine should be used with caution in patients with 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.

Besides the direct anesthetic effect, local anesthetics may have a very mild effect on mental function and co-ordination 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 ACTION and CLINICAL PHARMACOLOGY). Only a small fraction (3%) 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 LIGNOSPAN parenteral solutions are used for short treatment durations, according to dosage instructions (see DOSE 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.

Sensitivity
Lidocaine with epinephrine contains sodium metabisulfite, a sulfite that may cause allergic-type

reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in non asthmatic people.

Special Populations
Debilitated, 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.

Pregnant Women:
There are no adequate and well controlled studies in pregnant women of 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.

The use of lidocaine solutions containing epinephrine may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels.

Nursing Women:
Lidocaine and its metabolites are excreted in the breast milk. At therapeutic doses, the quantities of lidocaine and its metabolites in the breast milk are small and generally are not expected to be a risk for the infant. It is not known whether epinephrine enters breast milk, but is unlikely to affect the breast-fed infant.

Pediatrics: 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 DOSAGE AND ADMINISTRATION).

In children, the dosage should be calculated on a weight basis up to 7 mg/kg (see DOSAGE AND ADMINISTRATION).

Lidocaine 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.

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.

Carcinogenesis and Mutagenesis

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine 2,6 –dimethlaniline, showed weak evidence of activity in some genotoxicity tests. A chronic oral toxicity study of the metabolite 2,6 –dimethylanine (0,14,45,135 mg/kg) administered in feed to rats showed that there was a significantly greater incidence of nasal cavity tumours in male and female animals that had daily oral exposure to the highest dose of 2,6 –dimethylanine for two years. The lowest tumor-inducing dose tested in animals (135 mg/kg) corresponds to approximately 11 times the amount of 2,6 –dimethylanine to which a 50 kg

subject would be exposed following a single injection of 600 mg of lidocaine for injection, assuming 80% conversion of 2,6 –dimethylanine. Based on a yearly exposure (once daily dosing with 2,6 –dimethylanine in animals and 5 treatment sessions with 600 mg lidocaine for injection in humans), the safety margins would be approximately 1000 times when comparing the exposure in animals to man.

ADVERSE REACTIONS

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, rapid absorption, or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Table 1 Adverse Drug Reaction Frequencies

Common (≥ 1% and <10%)	Vascular disorders: hypotension, hypertension Gastrointestinal disorders: nausea, vomiting Nervous system disorders: parathesia, dizziness Cardiac disorders: bradycardia
Uncommon (≥ 0.1% and <1%)	Nervous system disorders: signs and symptoms of CNS toxicity (convulsions, paresthesia circumoral, numbness of the tongue, hyperacusis, visual disturbances, tremor, tinnitus, dysarthria, CNS depression).
Rare (≥ 0.01% and <10.1%)	Cardiac disorders: cardiac arrest, cardiac arrhythmias Immune system disorders: allergic reactions, anaphylactic reaction/shock Respiratory disorders: respiratory depression Nervous system disorders: neuropathy, peripheral nerve injury, arachnoiditis Eye disorders: diplopia

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 paresthsia, lightheadedness, 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, hypotenstion, 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 to local anesthetic agent or to other components in the formulation (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

Neurologic:
The incidence of adverse neurologic reactions may be related to the total dose of local anaesthetic administered but is also dependent upon the particular drug used, the route of the administration and the physical condition of the patient. Neurological effects may be related to local anaesthetic techniques, with or without a contribution from the drug.

DRUG INTERACTIONS

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 (3%) 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.

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.

Drug-Drug Interactions
<u>Local anesthetics and agents structurally related to amide-type local anesthetics</u>

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.

<u>Antiarrhythmic Drugs</u>
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 anti-arrymthmic 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.

Ergot-Containing Drugs
Lidocaine with epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur and cerebrovascular and cardiac accidents are possible.

Monoamine Oxidase (MAO) Inhibitors
LIGNOSPAN (Lidocaine with epinephrine) or solutions containing lidocaine with epinephrine and another vasoconstrictor should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAO) because severe prolonged hypertension may result . In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Antidepressants (triptyline, imipramine)
LIGNOSPAN (Lidocaine with epinephrine) or solutions containing lidocaine with epinephrine and another vasoconstrictor should be used with extreme caution in patients receiving antidepressants of the triptyline or imipramine types because severe, prolonged hypertension may result. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Antipsychotics (phenothiazines, butyrophenones)
LIGNOSPAN (Lidocaine with epinephrine) or solutions containing lidocaine with epinephrine and another vasoconstrictor should be used with extreme caution in patients receiving phenothiazines and butyrophenones. Phenothiazines and Butyrophenones may oppose the vasoconstrictor effects of epinephrine giving rise to hypotensive responses and tachycardia. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Sedatives
If sedatives are used to reduce patient apprehension, they should be used in reduced doses, since local anaesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

General Anaesthetics- Inhalation agents (halothane, enflurance)
Solutions containing epinephrine should be used with caution in patients undergoing general anesthesia with inhalation agents such as halothane and enflurane, due to the risk of serious cardiac arrhythmias.

Drug-Food Interactions
Interactions of Lidocaine with food have not been established.

Drug-Herb Interactions
Interactions of Lidocaine with herbal products have not been established.

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

Drug-Lifestyle Interactions
Interactions of Lidocaine with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General
Lignospan Solutions (lidocaine hydrochloride with epinephrine) should only be used by or under the supervision of clinicians experienced in regional anesthesia.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discoloured or which contain particulate matter should not be administered.

Recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of anesthesia required, and the physical condition of the patient (see Special Populations).

The lowest concentration of anesthetic and the lowest dosage needed to provide effective anesthesia should be administered. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional doses should be used when feasible.

The use of lidocaine with epinephrine will prolong the anesthetic action.

When LIGNOSPAN is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

Special Populations
Lidocaine should be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic or renal function and in severe shock (see WARNINGS AND PRECAUTIONS).

Debilitated patients, elderly patients, acutely ill patients, patients with sepsis and children should be given reduced doses commensurate with their age, weight and physical condition (WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

Careful aspiration before and during injection is recommended to prevent intravascular injection. The main dose should be injected slowly or in incremental doses, while closely observing the patient's vital functions and maintaining verbal contact.

Children

In children the dosage should be calculated on a weight basis up to 5 mg/kg. With the addition of epinephrine, up to 7 mg/kg can be used. Individual variations occur. 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.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration (i.e. total dose) of local anesthetic used. Thus, an increase in volume and concentration of LIGNOSPAN will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. Although the incidence of side effects with lidocaine is quite low, caution should be exercised when employing large volumes and concentrations since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected. The risk of reaching a toxic plasma concentration or inducing a local neural injury must be considered when prolonged blocks and/or repeated administration are employed.

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 ADVERSE REACTIONS and 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 DRUG INTERACTIONS).

Symptoms

With accidental intravascular injections, the toxic effect will be obvious within 1-3 min, while with overdosage, peak plasma concentrations may not be reached for 20-30 min depending on the site of injection, with signs of toxicity thus being delayed.

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, lightheadedness, 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 and loss of the airway. In severe cases apnea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

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.

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**. If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.**

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection consists of immediate attention to the establishment and 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, anticonvulsant should be given i.v. to facilitate adequate ventilation and oxygenation. Thiopental sodium 1-3 mg/kg i.v. is the first choice. Alternatively diazepam 0.1 mg/kg bw iv may be used, although its action will be slow. Prolonged convulsions may jeopardize 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 anaesthetics. Epinephrine (0.1 -0.2 mg intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary.

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

ACTION AND CLINICAL PHARMACOLOGY

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.

Onset of Action
The onset of action is 1-5 minutes following infiltration and 5-15 minutes following other types of administration. The duration of anesthesia depends on the concentration of lidocaine used, the dose, and the type of block. The 2% solution will last up to 5 hours with peripheral nerve blocks. The addition of epinephrine decreases the rate of absorption, reducing toxicity and increasing the duration of effect.

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

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

Pharmacokinetics

Absorption
Lidocaine is completely absorbed following parenteral administration. The rate of absorption depends on the dose, route of administration, and the vascularity of the injection site. Absorption is considerably slowed by the addition of epinephrine, although it also depends on the site of injection. Peak plasma concentrations are reduced by 50% following subcutaneous injection

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 with regard to the unbound concentration is rapidly reached. The degree of plasma protein binding in the fetus is less than in the mother, which results in lower total plasma concentrations in the fetus.

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.

Metabolism
Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. The main metabolites formed from lidocaine are monoethylglycine xylidide (MEGX), glycinexylidide (GX), 2,6-dimethylaniline and 4-hydroxy-2,6-dimethylaniline. The N-dealkylation to MEGX, is considered to be mediated by both CYP1A2 and CYP2A6, and the latter is the major urinary metabolite in man. Only 3% of lidocaine is excreted unchanged. About 70% appears in the urine as 4-hydroxy –2,6-dimethylaniline.

Excretion
Lidocaine has a terminal 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.

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.

The elimination half-life of lidocaine following intravenous bolus injection is typically 1.5 to 2.0 hours. The terminal half-life in neonates (3.2 h) is approximately twice that of adults, whereas clearance is similar (10.2 mL/min kg). 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.

STORAGE AND STABILITY

LIGNOSPAN Solutions (lidocaine hydrochloride with epinephrine) should be stored at controlled room temperature (15-30ºC). Do not freeze, protect from light.

SPECIAL HANDLING INSTRUCTIONS

Sterilization, and Technical Procedures
Adequate precautions should be taken to avoid prolonged contact between local anaesthetic solutions containing epinephrine (low pH) and metal surfaces (e.g. needles or metal parts of syringes), since dissolved metal ions, particularly copper ions, may cause severe local irritation (swelling, edema) at the site of injection and accelerate the degradation of epinephrine.

The solubility of lidocaine is limited at pH >6.5. This must be taken into consideration when alkaline solutions, i.e. carbonates, are added, since precipitation might occur. In the case of epinephrine containing solutions, mixing with alkaline solutions may cause rapid degradation of epinephrine.

Do not use if solution is coloured or if it contains a precipitate.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms
LIGNOSPAN Forte and LIGNOSPAN Standard (lidocaine hydrochloride with epinephrine) contains lidocaine hydrochloride 20 mg/mL, respectively. Solutions with epinephrine contain 0.02 mg/mL (1:50,000) or contain 0.010 mg/mL (1:100,000) epinephrine.

Composition
Non-medicinal Ingredients
Sodium chloride (for isotonicity), potassium metabisulfite (as an antioxidant), Disodium Edetate (Chelating agent), water for injection, sodium hydroxide and/or hydrochloric acid to adjust pH 3.0 – 5.0 or pH 3.3 – 5.5.

Packaging
LIGNOSPAN Forte and LIGNOSPAN Standard is available in single dose glass cartridges of 1.8 mL; boxes of 50 cartridges.

PART II: SCIENTIFIC INFORMATION

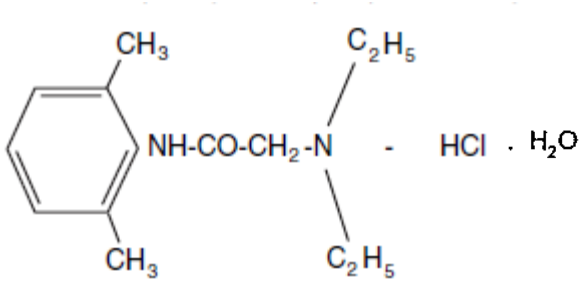
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: lidocaine hydrochloride

Chemical Name: 2-Diethylamino-N-(2,6-dimethylphenyl)-acetamide monohydrochloride monohydrate

Structural Formula:



Molecular Formula: $C_{14}H_{22}N_2O.HCl.H_2O$

Molecular mass: 288.8 g/mol

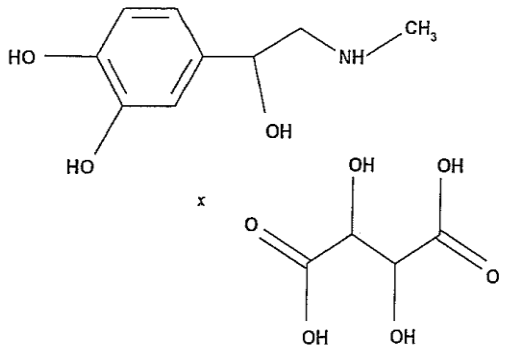
Physicochemical properties: White crystalline powder. Very soluble in water, freely soluble in alcohol. Melting range between 74 and 79ºC. pH of 4.0 to 5.5 (0.5% solution in H_2O).

Drug Substance

Proper Name: Epinephrine Bitartrate

Chemical Name: 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-(R)-[R-(R* , R*)]-2,3-dihydroxybutane dionate (1:1) salt

Structural Formula:



Molecular Formula: $C_9H_{13}NO_3$ x $C_4H_6O_6$

Molecular Mass: 333.30 g/mol

Physicochemical properties: white or greyish white or light brownish grey, odourless crystalline powder, which slowly darkens on exposure to light. Freely soluble in water. Slightly soluble in alcohol. Practically insoluble in chloroform and in ether. Solutions are acidic, with pH approximately 3.5.

REFERENCES

McNickle A, L'Heureux D, Provencher M, Romeo A, Cole B. Postsurgical Glenohumeral Arthritis in Young Adults. Am J Sports Med 2009; 37(9):1784-1791.

Solomon D, Navaie M, Stedje-Larsen E, Smith J, Provencher M. Glenohumeral Chondrolysis After Arthroscopy: A Systematic Review of Potential Contributors and Causal Pathways. J Arthr Rel Surg 2009; 25(11):1329-1342.

AstraZeneca Canada Inc.
Prescribing Information-Xylocaine® Parenteral Solutions, September 2011

PART III: CONSUMER INFORMATION

Lignospan® Forte
Lignospan® Standard
Lidocaine Hydrochloride and Epinephrine Injection USP
(lidocaine hydrochloride with epinephrine 1:50,000 and 1:100,000)

This leaflet is part III of a three-part "Package Insert" published when LIGNOSPAN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LIGNOSPAN. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
LIGNOSPAN is used to anesthetize part of the mouth for surgical operations and also for pain relief.

WHAT IT DOES:
LIGNOSPAN acts by preventing the nerves in the injected area from transmitting sensations of pain, heat or cold. However, you may still experience sensations such as pressure and touch. In this way the nerve(s) is anaesthetized in the part of the mouth, which will be subjected to surgery. In many cases this means that the nerves to the muscles in the area will also be blocked, causing temporary weakness or paralysis.

WHEN IT SHOULD NOT BE USED:
LIGNOSPAN should not be used in patients who:
- are allergic to lidocaine, any other "-caine" type anesthetics, or any of the non-medicinal ingredients in the product (see **NON-MEDICINAL INGREDIENTS** below)
- are allergic to sodium metabisulfite

WHAT THE MEDICINAL INGREDIENTS ARE:
Lidocaine hydrochloride 2% with epinephrine 0.010 mg/mL (1:100,000) or 0.02 mg/mL (1:50,000)

NON-MEDICINAL INGREDIENTS:
LIGNOSPAN with epinephrine contains sodium chloride, potassium metabisulfite, disodium edetate, water for injection, and sodium hydroxide and/or, hydrochloric acid.

Check with your doctor if you think you may be sensitive to any of the above ingredients.

WHAT DOSAGE FORMS IT COMES IN:
LIGNOSPAN is available in single –dose glass cartridges.

WARNINGS AND PRECAUTIONS

You should talk to your doctor prior to surgery:
- about all health problems you have now or have had in the past;
- about other medicines you take, including ones you can buy without prescription;
- if you are taking other medicines such as drugs used to treat irregular heart activity (anti-arrhythmics);
- if you think you may be allergic or sensitive to any ingredients in LIGNOSPAN (see above). Sodium metabisulfite might cause allergic reactions (e.g. facial swelling and respiratory difficulties) in susceptible people, especially those with a history of asthma or allergy;
- if you have a severe heart, liver or kidney disease;
- if you have poorly controlled hyperthyroidism and diabetes;
- if you have epilepsy;
- if you or someone in your family has been diagnosed with porphyria;
- if you are experiencing severe shock;
- if you are pregnant, plan to become pregnant or are breastfeeding;
- if you are planning to drive or operate any tools or machinery on the day of surgery, because LIGNOSPAN may temporarily interfere with your reactions and muscular coordination.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor/dentist/pharmacist if you are taking or have recently taken any medicines, even those that can be bought without a prescription.

Drugs that may interact with LIGNOSPAN include:
- anti-arrhythmic drugs for heart problems (e.g. mexiletine, amiodarone);
- other anesthetics;
- proranolol for heart problems or cimetidine for gastrointestinal problems;
- fluvoxamine for depression, if using high doses of LIGNOSPAN for long time and other medicines for depression;
- antimigraine therapy;
- antipsychotic therapy;
- medicines for high blood pressure.

Usage of such medicines at the same time as LIGNOSPAN may increase the risk of serious side effects.

PROPER USE OF THIS MEDICATION

USUAL DOSE:
LIGNOSPAN should be administered by a doctor. The dose given is decided by the doctor based on the clinical need and your physical condition.

Overdose:
Serious adverse effects resulting from getting too much LIGNOSPAN need special treatment and the doctor treating you is trained to deal with these situations. Early signs that too much LIGNOSPAN® Parenteral Solution has been given include:

- numbness of the lips and around the mouth;
- lightheadedness or dizziness;
- blurred vision;
- hearing problems;
- tingling in the ears

In the event of a serious overdosage, trembling, seizures or unconsciousness may occur.

If the early signs of overdosage are noticed and no further LIGNOSPAN is given, the risk of serious side effects occurring rapidly decreases. If you have any of these symptoms, or you think you have received too much LIGNOSPAN, **tell your doctor immediately**.

In the event of overdosage, contact your doctor, hospital emergency department or regional Poison Control Centre immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, LIGNSOSPAN may cause side effects in some people.

Medicines affect different people in different ways. Just because side effects have occurred in some patients, does not mean that you will get them. If any side effects bother you, or if you experience any unusual effects after exposure to LIGNOSPAN, check with your doctor as soon as possible.

LIGNOSPAN may temporarily interfere with your reactions and muscle co-ordination; therefore do not drive or use machines on the day of surgery.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor		Seek immediate emergency assistance
	Only if severe	In all cases	
Common			
Dizziness, abnormal sensations (pins and needles)		X	
Feeling of sickness/nausea, vomiting	X		
Decreased heart rate		X	
Increased blood pressure, decreased blood pressure		X	
Uncommon			
Toxicity symptoms such as: convulsions, seizures, lightheadedness, numbness of the lips and around the mouth, numbness of the tongue, hearing disturbances, visual disturbances, speech disturbances, trembling and other signs of central nervous system depression.			X
Rare			
Cardiac arrest and/or irregular heartbeat			X
Allergic reactions such as: Facial swelling and difficulties with breathing/respiratory shock			X
Nervous system disorders such as: nerve injury, paralysis or tingling of extremities		X	
Double vision		X	

This is not a complete list of side effects. Consult your doctor immediately if any of these symptoms or any unexpected effects appear.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by of the following 3 ways:

Report Online at www.healthcanada.gc.ca/medeffect
Call toll free telephone: 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  OTTAWA ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Important Note: This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor with any questions or concerns you have about using LIGNOSPAN Parenteral Solutions.

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information Leaflet plus the full Package Insert, prepared for health professionals can be found by contacting the sponsor, Septodont at 1-800-647-0643

This leaflet was prepared by
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