1 LIGNOSPAN SPECIAL

LIGNOSPAN SPECIAL, Lidocaine hydrochloride (2%), adrenaline tartrate (1/80.000), injection solution 1.8mL

LIGNOSPAN SPECIAL, Lidocaine hydrochloride (2%), adrenaline tartrate (1/80.000), injection solution 2.2mL

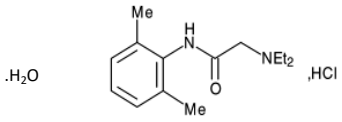
2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lidocaine hydrochloride

CAS [6108-05-0] Mr: 288.8

Local and regional anaesthetic

C_{14} H_{23} ClN_2 $O.H_2O$



2-diethylaminoaceto-2'6'-xylidide hydrochloride monohydrate

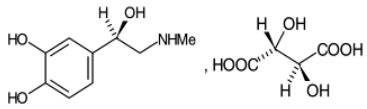
White crystalline powder practically odourless. Lidocaine hydrochloride

is very soluble in water, freely soluble in ethanol, and practically insoluble in ether.

Adrenaline acid tartrate

CAS [51-42-3] Mr: 333.3

C_{13} H_{19} NO_9



(R)-1-(3,4-di-hydroxyphenyl)-2-methylaminoethanol hydrogen tartrate

White to greyish-white or light brownish-grey, odourless, crystalline powder. Adrenaline acid tartrate 1.8 mg is approximately equivalent to 1 mg of adrenaline.

Cartridge	**2.2 mL**	**1.8 mL**
Lidocaine hydrochloride	44 mg	36 mg
Adrenaline	27.5 µg	22.5 µg
(as acid tartrate)		
Sodium chloride	14.3 mg	11.7 mg
Potassium metabisulfite	2.64 mg	2.16 mg
Disodium edetate	0.55 mg	0.45 mg
Sodium hydroxide solution (to adjust pH)		(to adjust pH)
Water for injection q.s. ad	2.2 mL	1.8 mL

For single patient use only. Contains no anti-microbial agent. Discard unused contents after use.

3 PHARMACEUTICAL FORM

Injection solution, clear colourless solution practically free from particles, packaged in a ready to use cartridge containing 1.8mL or 2.2mL

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidocaine solutions are indicated for the production of local anaesthesia in routine dental procedures and oral surgery by means of infiltration and nerve block techniques.

Lidocaine solutions with adrenaline are recommended for oral surgery requiring prolonged duration of anaesthesia and haemostasis.

4.2 Dose and method of administration

The lowest dosage that results in effective anaesthesia for the planned treatment should be used. The dosage will depend upon the area of the oral cavity to be anaesthetised, the vascularity of the oral tissues and the technique of anaesthesia. Toxic doses vary widely between patients and toxic effects may occur after any local anaesthetic procedure. Careful observation of the patient must be maintained after administration of the local anaesthetic.

Adults

For adults, a single cartridge (2.2 mL) is generally sufficient.

Two cartridges (4.4 mL) may be used in case of large interventions.

Adolescents

For adolescents between 14 and 17 years, usual dosage one cartridge (2.2 mL).

Do not exceed 2 cartridges (4.4 mL) in general cases.

Paediatric population

For children between 6 and 14, usual dose 3/4 of the cartridge (1.65 mL).

Do not exceed 1 1/2 cartridges (3.3 mL) in usual cases.

For children between 3 and 6, between 1/2 to 1 cartridge (1.1 mL to 2.2 mL).

Do not use on children under three years of age.

Method of administration

The product is injected either locally or in the vicinity of a dental nervous trunk.

The safe dose for people with acute or chronic disease may be substantially less than that for healthy individuals.

Cartridges are for single patient use only. Once opened, use immediately and discard remainder.

Use of a single cartridge in more than one patient is absolutely contraindicated

4.3 Contraindications

These may be of three types:

a. contraindications to Lidocaine :

- specific allergies to Lidocaine or to other anaesthetics of amide type,

- allergies of cross type procaine – lidocaine.

b. contraindications to the vasoconstrictor :

- cerebral arteriosclerosis,

- arterial hypertension,

- coronary disease,

- valvular cardiac disease (particularly sequelae to acute rheumatic fever).

- thyrotoxicosis, untreated,

- known sensitivity to sympathomimetic amines.

c. - hypersensitivity to sulfites (potassium metabisulfite is present in the formula as an antioxidant),
- injection by intravenous route,

- inflammation or sepsis in the region of the proposed injection.

4.4 Special warnings and precautions for use

General precautions

WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS. BECAUSE OF THE POSSIBILITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE LOCAL ANAESTHETIC IS INJECTED. DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDER VENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND DEATH.

INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE CEREBRAL SYMPTOMS EVEN AT LOW DOSES.

Note, however, that the absence of blood in the syringe does not assure that intravascular injection will be avoided. There should be careful monitoring of cardiovascular and respiratory vital signs after each injection.

Use with caution in the following circumstances:

- the lowest dosage that results in effective anaesthesia 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. However, this is unlikely to occur at the doses normally used in dentistry. 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.

- Lidocaine should be used with caution in patients with epilepsy, bradycardia, digitalis intoxication, severe shock or heart block. Lidocaine should also be used with caution in patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with prolongation of AV conduction produced by the drug. In patients with Stoke-Adams syndrome or Wolff-Parkinson-White syndrome care should be taken to avoid accidental arterio-venous injection.
- Local anaesthetic solutions containing adrenaline 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 hypersensitive vascular disease may exhibit

exaggerated vasoconstrictor response. Ischaemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anaesthetic agents, since cardiac arrhythmias may occur under such conditions.

- Inadvertent intravascular injection of small doses of Lidocaine injected into the head or neck area, including retrobulbar, dental and stellate injection blocks, may produce adverse effects similar to systemic toxicity seen with unintentional intravascular injection of larger doses.

- Lidocaine should be used with caution in patients with hepatic or renal disease, since amide-type local anaesthetics are metabolised by the liver and excreted via kidneys. Patients with hepatic or renal impairment, because of their inability to metabolise or excrete local anaesthetics normally, are at greater risk of developing toxic plasma concentrations.

- Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, benzocaine, etc) have not shown cross sensitivity to lignocaine.

- Solutions containing adrenaline should be used with extreme caution in patients with severe or untreated hypertension, arteriosclerotic heart disease, heart block, cerebral vascular insufficiency, thyrotoxicosis, advanced diabetes or any other pathological condition that might be aggravated by the effects of adrenaline. Adrenaline may induce anginal pain in patients suffering from ischaemic heart disease.

- The safety and effectiveness of Lidocaine depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various anaesthetic procedures.
- The patient should be advised to exert caution to avoid inadvertent trauma to the lips, tongue, check mucosa or soft palate when these structures are anaesthetised. Eating and drinking hot liquids should therefore be postponed until normal function returns.
- Lidocaine with adrenaline solutions contain 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. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.
- Prostatic hypertrophy.

4.5 Interaction with other medicines and other forms of interaction

The administration of local anaesthetic solutions containing adrenaline or noradrenaline to patients receiving monoamine oxidase inhibitors, butyrophenones, tricyclic antidepressants or phenothiazines may produce severe prolonged hypotension or hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Concurrent administration of vasopressor drugs and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

As the LIGNOSPAN SPECIAL solution contains a vasoconstrictor (adrenaline 1/80.000), concurrent use of either with a Beta-adrenergic blocking agent (propranolol, timolol, etc.) may result in dose-dependent hypertension and bradycardia with possible heart block.

The effects of adrenaline may be potentiated by thyroid hormones.

LIGNOSPAN SPECIAL should be administered with caution to patients under the following treatments:

- Hypoglycaemics: adrenaline-induced hyperglycemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemics.

- Anti-arrhythmic agents (e.g: procainamide, mexilitine, disopyramide): Lidocaine may increase their effects.

- Skeletal muscle relaxant (suxamethonium), combination with Lidocaine may lead to excessive neuro-muscular block.

- Cardiac glycosides (e.g: digoxin): adrenaline may interact with cardiac glycosides resulting in cardiac arrhythmias.

- Adrenergic neuron blocking agents (e.g: guanethidine) since the product contains adrenaline.

- Quinidine: combination with adrenaline may lead to cardiac arrhythmias.

- Cimetidine: increased serum levels of Lidocaine have been reported after concurrent cimetidine and Lidocaine administration.

- Amiodarone: combination with Lidocaine may reduce the clearance of Lidocaine and seizures, sinus bradycardia and a long sinoatrial arrest have been reported. Patients receiving the combination should be carefully monitored.

- Phenytoin and other antiepileptic drugs such as phenobarbitone, primidone and carbamazepine appear to enhance the metabolism of Lidocaine but the significance of this is not known. Phenytoin and Lidocaine have additive cardiac depressant effects.

- Lidocaine decreases the minimum effective concentration of inhalational anaesthetics, eg. nitrous oxide.

- Serious cardiac arrhythmias and acute pulmonary oedema if hypoxia present may occur if preparations containing adrenaline are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene or other halogenated compounds.

- Structurally related local anaesthetics, Lidocaine should be used with caution in patients receiving agents structurally related to local anaesthetics.

- Beta adrenoreceptor antagonists - Propranolol and metoprolol reduce the metabolism of intravenous lignocaine. It is possible that this effect may also occur with other beta-adrenoreceptor antagonists. If these drugs are used concurrently then the patient should be closely observed for the signs of Lidocaine toxicity.

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 lignocaine.

4.6 Fertility, pregnancy and lactation

Carcinogenicity and mutagenicity:

Studies of Lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

A two year oral toxicity study of 2,6-xylidine, a metabolite of lignocaine, has shown that in both male and female rats, 2,6-xylidine in daily doses of 900 mg/m 2 (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. No nasal tumours were observed in the low dose (15 mg/kg or control animals). In addition, the compound also caused subcutaneous fibromas and or fibrosarcomas in male and female rats (significant at 150 mg/kg)

The genotoxic potential of 2,6-xylidine has been studied with mixed results. Positive results were reported in assays for gene mutations (weakly positive in the Ames test with metabolic

activation and the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug precipitated from solution). No evidence of genotoxicity was found in *in vivo* assay for chromosomal damage (micronucleus assay) and DNA damage (unscheduled DNA synthesis). Covalent binding studies of DNA from liver and ethmoid turbinates in rates indicated that 2,6-xylidine may be genotoxic under certain conditions *in vivo*.

Use in pregnancy (category A):

The safe use of Lidocaine during pregnancy has not been established. Lidocaine has however been used extensively for dental procedure during pregnancy with no proven increase in frequency of malformations or of harmful effects to mother or foetus.

Use in lactation :

Lidocaine passes into breast milk.

The amount of Lidocaine appearing in breast milk from a breastfeeding mother receiving parental Lidocaine is unlikely to lead to significant accumulation of the parent drug in the breast-fed infant.

The remote possibility of an idiosyncratic or allergic reaction in the breast-fed infant from Lidocaine remains to be determined.

4.7 Effects on ability to drive and use machines

Depending on the dosage, or if given inadvertently intravenously, local anaesthetics may have a mild effect on mental function and may temporarily impair locomotion and coordination.

4.8 Undesirable effects

Common reactions (≥ 1 % and < 10%):

Excluding post procedural dental pain, local reactions at the injection site are the most common adverse events: infection, gingivitis, pain and edema. Headache, paresthesia and hyperaesthesia are also reported after use of anaesthetic injections during dental procedures.

Very rare reaction (≥ 0.1 % and < 1%):

Serious adverse experiences following the administration of Lidocaine are similar in nature to those observed with other amide local anaesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption, unintended intravascular injection or may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central nervous system (very rare)

CNS manifestations are excitatory and/or depressant and may be characterised by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, agitation, difficulty in swallowing and slurred speech, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest which are less common.

The excitatory manifestations 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 blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular system (very rare)

Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal

reaction, particularly if the patient is in an upright position.

Less commonly, they may result from a direct effect of the drug. Failure to recognize the premonitory signs such as sweating, a feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and seizure or serious cardiovascular catastrophe. Management consists of placing the patient in the recumbent position and ventilation with oxygen. Supportive treatment of circulatory depression may require the administration of intravenous fluids and, when appropriate, a vasopressor (e.g, ephedrine) as directed by the clinical situation.

Allergic reactions (very rare)

Allergic reactions are characterised by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions as a result of sensitivity to Lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value. Caution should be taken in asthmatic patients since LIGNOSPAN SPECIAL contains metabisulfites.

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose

The injection of excessive amounts of Lidocaine and adrenaline injection may, due to the vasoconstrictor, cause ischaemia. This can be followed by reactive hyperaemia resulting in post extraction bleeding.

Most systemic reactions to local anaesthetics are from overdose and in dentistry would most frequently be caused by accidental intravenous injection (for symptoms, see Adverse Reactions).

If unusual reactions develop resuscitative and/or supportive measures should be started promptly:

Treatment of overdose :

Contact the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 POISON (0800 764 766)

For all symptoms: If acute toxicity occurs the injection should be stopped immediately. A patent airway should be established and maintained, oxygen should be administered, and assisted or controlled ventilation should be provided as required.

Circulatory collapse: toxic cardiovascular reactions can include peripheral vasodilation, hypotension, bradycardia and cardiac arrest. Immediately resuscitate with oxygen and commence cardiovascular resuscitation procedures as appropriate, as well as treatment of acidosis are of vital importance

Convulsions: If convulsions occur, IV diazepam should be administered incrementally. Sodium thiopentone (5mg /kg) may be used if diazepam is unavailable or ineffective. If convulsions interfere with breathing and / or are not rapidly controlled by specific anticonvulsant medication, suxamethonium (1-2 mg/kg) may be used to paralyse the patient.

Artificial ventilation must then be instituted.

If not treated immediately, both convulsions and cardiovascular depression may result in hypoxia, acidosis, bradycardia, arrhythmia and cardiac arrest.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Lidocaine stabilises the neuronal membrane by decreasing its permeability to sodium ions and

reversibly blocks the initiation and conduction of nerve impulses thereby producing local anaesthesia.

Local anaesthetics of the amide type are thought to act within sodium channels of the nerve membrane.

The onset – considered as rapid – and duration of anaesthesia (1 to 3 hours) depend on the route of administration and the dosage (volume & concentration) employed.

The addition of adrenaline reduces the rate of local clearance of Lidocaine from the site of injection, thereby prolonging the duration of action.

Adrenaline acts on both adrenergic receptors of tissue innervated by sympathetic nerves, except for the sweat glands and arteries of the face. It is the most important alpha receptor activator. Adrenaline stimulates the heart to increase output, raises the systolic blood pressure, lowers the diastolic blood pressure, relaxes bronchial spasm and mobilises liver glycogen, resulting in hyperglycaemia and possibly glycosuria.

5.2 Pharmacokinetic properties

Absorption:

Information derived from diverse formulations, concentrations and usages reveals that Lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. The addition of adrenaline considerably slows the absorption of lignocaine. Peak plasma concentrations are reduced by 50% following subcutaneous injection if adrenaline in a proportion of 5 µg/ml is added. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

Distribution:

The plasma binding of Lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentration of 1 to 4 µg of freebase per ml, 60 to 80 per cent of Lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Since the degree of plasma protein binding in the foetus is less than that of the mother, although free Lidocaine concentration will be the same, the total plasma concentration will be greater than in the mother.

Metabolism:

Lidocaine is metabolised rapidly by the liver. Lidocaine has a total plasma clearance of 0.95 L/min, a volume of distribution at steady state of 91 L, an elimination half-life of 1.6 hr and an estimated hepatic extraction ratio of 0.65. Metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than those of lignocaine. Approximately 90% of Lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.

Excretion:

Studies of Lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5 to 2.0 hours. Because of the rapid rate at which Lidocaine is metabolised, any condition that affects liver function may alter Lidocaine kinetics, e.g. acute myocardial infarction and / or congestive heart failure. The half-life may be prolonged two-fold or more in patients with liver dysfunction, possibly because of altered perfusion. Renal dysfunction does not affect Lidocaine kinetics but may increase the accumulation of metabolites (see precautions).

5.3 Preclinical safety data

No information held.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Potassium metabisulfite

Disodium edetate

Sodium hydroxide solution (to adjust pH - if required)

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25^{o}C – Protect from light – Do not freeze.

6.5 Nature and contents of container

Box of 50 cartridges single use containing each 2.2 mL or 1.8 mL of solution.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

IVOCLAR VIVADENT Ltd

12 Omega Street, Rosedale, AUCKLAND 0632, NEW ZEALAND

9 DATE OF FIRST APPROVAL

03/04/1975

10 DATE OF REVISION OF THE TEXT

20/10/2011

SUMMARY TABLE OF CHANGES

01/08/2017 - Formatting changes only.