1 NAME OF THE MEDICINAL PRODUCT

LIGNOSPAN SPECIAL, solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains:

Lidocaine hydrochloride	20 mg (expressed as anhydrous)
Adrenaline	0.0125 mg (as Adrenaline tartrate 0.02275 mg).

One cartridge of 1.8 ml of solution for injection contains 36 mg of lidocaine hydrochloride and 0.0225 mg of adrenaline.

Excipient(s) with known effect: LIGNOSPAN SPECIAL contains potassium metabisulfite (E224), sodium chloride, disodium edetate, sodium hydroxide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

pH adjusted to 5.0 with sodium hydroxide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LIGNOSPAN SPECIAL is a local anaesthetic indicated for the local and loco-regional anaesthesia in dental surgery in adults and in children and adolescents aged 4 to 18 years of age.

LIGNOSPAN SPECIAL is appropriate for procedures of long duration and when there is a risk of significant bleeding into the operative field.

4.2 Posology and method of administration

For professional use by dentists and stomatologists.

LIGNOSPAN SPECIAL is indicated in children and adolescents aged 4 to 18 years of age.

For adults and children over 4 years of age only, because of the unsuitability of the anaesthetic technique under this age.

4.2.1 Posology

- *Adults*

As occurs with all local anaesthetics, doses vary and depend on the area to be anaesthetised, on the vascularity of tissues, on the number of nerve segments to be blocked, on the individual tolerance (degree of muscular relaxation and condition of the patient) and on the technique and depth of anaesthesia. The lowest dose leading to efficient anaesthesia should be

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used. The necessary dosage must be determined on an individual basis.

Various volumes may be used provided that the total maximum recommended dose is not exceeded.

For a healthy adult of 70 kg, the maximum dose of lidocaine administered by submucosal infiltration and/or nervous block should not exceed 4.4 mg/kg (0.22 ml/kg) of body weight with an absolute dose of 200 mg of lidocaine per session and 200 µg of adrenaline whatever the lowest.

The maximum recommended doses are reported in the following table depending on the cartridge volume and on the patient's weight.

				Equivalent in cartridge numbers
Weight (kg)	Lidocaine dose (mg)	Adrenaline dose (mg)	Volume (ml)	1.8 ml
50 To 100	200	0.1	10	5.9
	200	0.125	10	5.9
	200	0.2	10	5.9

- *Children (over 4 years of age)*

Due to the paediatric worksharing consensus, the quantity to be injected depends on child's age and on the type of operation to be performed.

The average dose to be used is 20 mg to 30 mg lidocaine hydrochloride per session. The recommended dose in mg of lidocaine hydrochloride which can be administered in children may be calculated from the expression: child's weight (in kilograms) x 1.33. Do not exceed the dose of 2.2 mg of lidocaine per kilogram of body weight.

- *Special populations*

Due to the lack of clinical data, particular precaution should be used in order to administer the lowest dose leading to efficient anaesthesia in elderly patients over 70 years old and in patients with renal or hepatic impairment.

4.2.2 Method of administration:

Infiltration and perineural use in oral cavity.

The rate of injection should not exceed 1 ml of solution per minute.

4.3 Contraindications

- Hypersensitivity to lidocaine (or to any local anaesthetics agent of the amide type) or to adrenaline or to any of the excipients.
- Children (age below 4 years old).

Due to lidocaine

- Severe conduction disturbances;
- Poorly controlled epileptic patient.

Due to adrenaline:

- Uncontrolled/severe hypertension;

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- Severe ischemic heart disease;
- Persistent/refractory tachyarrhythmia;
- Thyrotoxicosis;
- Pheochromocytoma.

4.4 Special warnings and precautions for use

4.4.1 Special warnings

LIGNOSPAN SPECIAL must be used with caution in:

Patients with cardiovascular disorders:

- Peripheral vascular disease
- Arrhythmias particularly of ventricular origin;
- Heart failure;
- Hypotension.

LIGNOSPAN SPECIAL should be administered with caution in patients with impaired cardiac function since they may be less able to compensate changes due to prolongation of atrio-ventricular conduction.

Epileptic patients:

Because of their convulsive actions, all local anaesthetics should be used very cautiously. For poorly controlled epileptic patients, see section 4.3.

Patients with an hepatic disease:

The lowest dose leading to efficient anaesthesia should be used, see section 4.2.

Patients receiving treatment with antiplatelets / anticoagulants:

The increased risk of severe bleeding following accidental vessel puncture and during oro-maxillo-facial surgery should be considered. INR monitoring should be increased in patients taking anticoagulants.

Patients with porphyria:

LIGNOSPAN SPECIAL should be used cautiously.

Patients with uncontrolled diabetes:

LIGNOSPAN SPECIAL should be used cautiously due to hyperglycemic effect of adrenaline.

Patients with susceptibility of acute angle-closure glaucoma:

LIGNOSPAN SPECIAL should be used cautiously due to the presence of adrenaline.

Patients with bleeding diathesis due to needle / technique/ surgery.

Elderly patients:

Dosages should be reduced in elderly patients over 70 years old (lack of clinical data).

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LIGNOSPAN SPECIAL must be used safely and effectively under appropriate conditions:

The local anaesthetic effects may be reduced when LIGNOSPAN SPECIAL is injected into an inflamed area or into an infected area.

Risk of biting trauma (lips, cheeks, mucosa, and tongue) exists, especially in children; the patient should be told to avoid chewing gum or eating until normal sensation is restored.

LIGNOSPAN SPECIAL contains potassium metabisulfite, a sulfite that may rarely cause hypersensitivity reactions and bronchospasm.

LIGNOSPAN SPECIAL contains less than 1 mmol sodium (23 mg) per cartridge, i.e. it is considered as essentially 'sodium free'.

Sportsmen should be warned that the presence of LIGNOSPAN SPECIAL in blood may yield positive results on doping tests undergone by professional athletes.

4.4.2 Precautions for use

Before using LIGNOSPAN SPECIAL, it is important:

- To make inquiries into the patient's diathesis, current therapies and history;
- To maintain verbal contact with the patient.
- To have resuscitative equipment at hand (see section 4.9).

Risk associated with an accidental intravascular injection:

Accidental intravascular injection (e.g.: inadvertent intravenous injection into the systemic circulation, inadvertent intravenous or intra-arterial injection in the head area and neck area) may be associated with severe adverse reactions, such as convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest, due to the sudden high level of lidocaine and/or adrenaline in the systemic circulation.

Thus, to ensure that the needle does not penetrate a blood vessel during injection, aspiration should be performed before the medicinal product is injected. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Risk associated with intraneural injection:

Accidental intraneural injection may lead the drug to move in retrograde manner along the nerve.

In order to avoid intraneural injection and to prevent nerve injuries in connection with nerve blockades, the needle should always be slightly withdrawn if electric shock sensation is felt by the patient during injection or if the injection is particularly painful. If needle nerve injuries occur, the neurotoxic effect could be aggravated by lidocaine potential chemical neurotoxicity and by the presence of adrenaline as it may impair the perineural blood supply and prevent lidocaine local wash-out.

Concomitant use of other medicinal products may require thorough monitoring (see section 4.5).

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4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Due to the presence of lidocaine

Interactions requiring precautions for use

Other local anaesthetics: Toxicity of local anaesthetics is additive. It is not relevant considering dental anaesthesia doses and blood levels, but it is a concern in children.

The total dose of administered lidocaine should not exceed the maximum recommended dose.

H2 antihistaminics (cimetidine)**:** Increased serum levels of amide anaesthetics have been reported following concomitant administration of cimetidine.

Sedatives (central nervous system depressants): Reduced doses of LIGNOSPAN SPECIAL should be used due to additive effects.

Non-selective beta-adrenergic blockers **(**e.g., propranolol, nadolol): Reduced doses of LIGNOSPAN SPECIAL should be used due to possible increase in blood pressure.

Close cardiovascular monitoring status is recommended.

4.5.2 Due to the presence of adrenaline

Interactions that are not recommended:

Postganglionic adrenergic blocking agents (e.g., guanadrel, guanethidine, and rauwolfia alkaloids): Reduced doses of LIGNOSPAN SPECIAL should be used under strict medical supervision followed by careful aspiration due to possible increase response to adrenergic vasoconstrictors: risk of hypertension and other cardiovascular effects

Interactions requiring precautions for use:

Halogenated volatile anaesthetics (e.g.: halothane): Reduced doses of LIGNOSPAN SPECIAL should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia.

Non-selective beta-adrenergic blockers (e.g., propranolol, nadolol): Reduced doses of LIGNOSPAN SPECIAL should be used due to possible increase in blood pressure.

Close cardiovascular monitoring status is recommended

(TCAs) Trycyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, maprotiline, and protriptyline): Dose and rate of administration of LIGNOSPAN SPECIAL should be reduced due to strengthening of adrenaline activity.

Close cardiovascular monitoring is recommended.

MAO inhibitors [both A-selective (e.g., brofaromine, moclobemide, toloxatone) and non-selective (e.g., phenelzine, tranylcypromine, linezolide)]:

Use under strict medical supervision due to possible potentialization of the effects of adrenaline.

(COMT inhibitors) Catechol-O-Methyl Transferase inhibitors (e.g., entacapone, tolcapone):

Arrhythmias, increased heart rate and blood pressure variations may occur.

Cardiovascular monitoring is recommended.

(SSRIs) Selective Serotonin Reuptake Inhibitors *(*e.g., venlafaxine, milnacipran, sertraline):

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Dose and rate of administration of LIGNOSPAN SPECIAL should be reduced due to additive or synergistic effects on blood pressure and heart rate.

Cardiovascular monitoring (preferably by ECG) is recommended.

Drugs causing arrhythmias (e.g., antiarrhythmics like digitalis, quinidine): Dose of administration of LIGNOSPAN SPECIAL should be reduced due to additive or synergistic effects on heart rate.

Careful aspiration prior to administration and cardiovascular monitoring (ECG) are recommended.

Ergot-type oxytocic drugs (e;g; methysergide, ergotamine, ergonovine): Use LIGNOSPAN SPECIAL under strict medical supervision due to additive or synergistic increases in blood pressure and/or ischemic response.

Sympathomimetic vasopressors (e.g., mainly cocaine but also amphetamines, phenylephrine, pseudoephedrine, oxymetazoline): There is a risk of adrenergic toxicity. If cocaine has been used within 24 hours, the planned dental treatment should be postponed.

Other sympathomimetics (e.g., isoproterenol, levothyroxine, methyldopa, antihistamines (e.g, chlorpheniramine, diphehydramine)): Reduced doses of LIGNOSPAN SPECIAL should be used.

Phenothiazines (and other neuroleptics): Use under strict medical supervision and cardiovascular monitoring in case of patients with hypotension due to possible inhibition of adrenaline effect.

4.6 Fertility, pregnancy and lactation

4.6.1 Fertility

No data is available regarding the potential impact of LIGNOSPAN SPECIAL on fertility.

4.6.2 Pregnancy

There are no or limited amount of data from the use of lidocaine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

LIGNOPSAN SPECIAL is not recommended during pregnancy and in women of childbearing potential not using contraception.

4.6.3 Breastfeeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to lidocaine is negligible. LIGNOSPAN SPECIAL can be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Patients should not leave the dental office within 30 minutes following administration of LIGNOSPAN SPECIAL.

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4.8 Undesirable effects

a) Summary of the safety profile

Adverse reactions following administration of LIGNOSPAN SPECIAL are similar to those observed with other local amide anaesthetics combined with vasoconstrictors. These adverse reactions are, in general, dose-related and may result from high plasma levels caused by overdose, rapid absorption or unintended intra-vascular injection. They may also result from hypersensitivity, idiosyncrasy, or diminished tolerance by patient.

Serious adverse reactions are generally systemic. The presence of adrenaline increases LIGNOSPAN's safety profile due to its sympathomimetic effects.

b) Tabulated list of adverse reactions

The reported adverse reactions come from spontaneous reporting and literature.

The frequencies classification follows the convention: Very common (≥ 1/10), Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), and Very rare (<10,000). Frequency "not known": "not known (cannot be estimated from the available data)".

The seriousness of adverse reactions is classified from 1 (most serious) to 3 (less serious) in the following table):

MedDRA System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Rare	Hypersensitivity
		1. Anaphylactic / anaphylactoid reactions Angioedema (face / tongue / lip / throat / larynx[1] / periorbital oedema) 2. Bronchospasm / asthma[2] Urticaria
Psychiatric disorders	Not known	Euphoric mood Anxiety
Nervous system disorders	Common	1. Neuropathy[3] : Neuralgia (Neuropathic pain), Paresthesia (i.e., burning, prickling, itching, tingling, local sensation of heat or cold, with no apparent physical cause) of oral and perioral structures; Hypoesthesia / numbness (oral and perioral) [3] Dysesthesia (oral and perioral), *including* Dysgeusia (e.g., taste metallic, taste disturbance) [3] Ageusia [3] 2. Headache, Dizziness (light headedness) Tremor

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MedDRA System Organ Class	Frequency	Adverse Reactions (continued)
Nervous system disorders	Not known	1. Deep CNS depression: Loss of consciousness Coma Convulsion[4] (including tonic clonic seizure) 2. Presyncope, syncope Confusional state, disorientation, Vertigo Speech disorder (e.g., dysarthria, logorrhea) Restlessness, agitation Balance disorder (disequilibrium) Somnolence
Eye disorders [5]	Rare	1. Horner's syndrome: eyelid ptosis, enophthalmos Diplopia (paralysis of oculomotor muscles) Amaurosis 2. Mydriasis Miosis Nystagmus Visual impairment Vision blurred Accommodation disorder
Ear and labyrinth disorders	Not known	Tinnitus
Cardiac disorders	Common	Palpitations
	Rare	Tachycardia Conduction disorders (atrioventricular block) Bradyarrhythmia, Bradycardia
	Not known	Myocardial depression Cardiac arrest Tachyarrhythmia (including ventricular extrasystoles and ventricular fibrillation)[6] Angina pectoris
Vascular disorders	Common	Hypotension (with possible circulatory collapse) Hypertension Pallor (local, regional, general)
	Not known	Hyperaemia (local, regional) Vasodilatation Vasoconstriction Hot flushes
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Not known	1. Respiratory depression Apnoea (respiratory arrest) Hypoxia [4](including cerebral) 2. Tachypnoea Bradypnoea Hypercapnia [4] 3. Yawning Dysphonia (Hoarseness[1])
Gastrointestinal disorders	Rare	Nausea, Vomiting
	Not known	1. Gingival / oral exfoliation (sloughing) / ulceration / necrosis [7] 2. Dysphagia [1] Swelling of tongue, lip, gums [8] Stomatitis, glossitis, gingivitis Salivary hypersecretion Diarrhoea

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MedDRA System Organ Class	Frequency	Adverse Reactions (continued)
Skin and subcutaneous tissue disorders	Common	Rash (eruption) Pruritus
Musculoskeletal and connective tissue disorders	Common	Myalgia Arthralgia
	Not known	Muscle twitching Trismus
General disorders and administration site conditions	Common	Hyperhidrosis Chest pain
	Uncommon	Fatigue, asthenia (weakness) Chills (shivering) Feeling cold Feeling hot Burning sensation
	Not known	Swelling (facial, submandibular , local) Discomfort
Injury, poisoning and procedural complications	Rare	Procedural pain Post procedural pain Pain Injection site haematoma Injection site pain

c) Description of selected adverse reactions

[1] Laryngo-pharyngeal oedema may characteristically occur with hoarseness and / or dysphagia;

[2] Bronchospasm (bronchoconstriction) may characteristically occur with dyspnoea;

[3] These neural pathologies may occur with the various symptoms of abnormal sensations (i.e., paresthesia, hypoesthesia, dysesthesia, hyperesthesia, etc) of the lips, tongue and oral tissues.

[4] Hypoxia and hypercapnia are secondary to respiratory depression and/or to seizures and sustained muscular exertion;

[5] These neurally mediated effects are due to the presence of local anaesthetic/vasoconstrictor at excessive concentrations regionally or in the systemic circulation;

[6] This mostly occurs in patients with underlying cardiac disease or those receiving certain drugs (section 4.5);

[7] This is due to excessive local effect of the vasoconstrictor;

[8] This occurs by accidental biting or chewing of the lips or tongue while the anaesthesia persists.

4.9 Overdose

4.9.1 Types of overdose

Local anaesthetic overdose in the largest sense is often used to describe:

- absolute overdose,
- relative overdose such as:
  - inadvertent injection into a blood vessel, or

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- abnormal rapid absorption into the systemic circulation, or
- delayed metabolism and elimination of LIGNOSPAN SPECIAL.

4.9.2 Symptomatology

- *Due to lidocaine:*

The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations, followed by vascular toxicity, respiratory toxicity and finally cardiac toxicity (detailed in section 4.8).

- *Due to adrenaline:*

Overdose of adrenaline may cause cardiovascular effects.

4.9.3 Treatment of overdose

The availability of resuscitation equipment should be ensured before the onset of dental anaesthesia with local anaesthetics.

If acute toxicity is suspected, the injection of LIGNOSPAN SPECIAL must immediately be stopped.

Oxygen should rapidly be administered, if necessary assisted ventilation should be used. Change patient position to supine position if necessary.

In case of cardiac arrest, immediate initiation of cardiopulmonary resuscitation should be performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous System/ Anaesthetics/ Local Anaesthetics/ Amides/ Licocaïne, combinations.

ATC Code: N01BB52

The mechanism underlying the anaesthetic action of lidocaine is similar to that of other commonly used anaesthetics. It decreases pain nerve conduction by inducing dose-dependent blocking of sodium channels.

Adrenaline potentiates the local anaesthetic effect of lidocaine by enhancing its retention at the injection site.

5.2 Pharmacokinetic properties

Absorption:

Peak plasma levels of lidocaine 20 mg/ml following peri-oral injections of adrenaline combined solutions during dental usual procedures were determined in various clinical studies. Cmax was 1.9 mg/ml of lidocaine following injection 160 mg of lidocaine.

Distribution:

Lidocaine is bound to plasma proteins, including α_1-acid glycoprotein (AAG). The extent of

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binding is variable but is about 66%.

Metabolism:

As all amide-type local anaesthetics, lidocaine is largely metabolised in the liver. Hepatic metabolism is rapid and about 90% of a given dose is mainly dealkylated to form monoethyl-glycinexylidide and glycinexylidide. Both of these metabolites may contribute to the therapeutic and toxic effects of lidocaine. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than those of lidocaine. Although some concerns were risen about 2,6-DMA and its carcinogenicity potential, as a single dose is injected with LIGNOSPAN SPECIAL, there is no toxicity concern to the best of our knowledge.

Elimination:

Plasma concentrations decline rapidly after an intravenous bolus injection with an initial half-life of less than 30 minutes; the half-life of lidocaine following an intravenous injection is 1.5 to 2 hours. Metabolites are excreted in the urine with less than 10% of unchanged lidocaine

5.3 Preclinical safety data

General toxicity studies were performed with lidocaine, adrenaline and lidocaine with adrenaline. No teratogenic effects were observed with lidocaine. However, some effects on fertility and teratogenicity were observed in animals treated with adrenaline at doses much higher than those recommended for dental treatments in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Potassium metabisulfite (E224)

Disodium edetate

Sodium hydroxide (for pH-adjustment)

Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, LIGNOSPAN SPECIAL must not be mixed with any other medicinal products.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C.

In order to protect from light, keep the cartridge in the tightly closed outer carton.

Do not freeze.

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6.1 Nature and contents of container

Type I glass cartridge sealed at its base by a mobile type I synthetic rubber and at the top by a type I synthetic rubber seal kept in place by a metal cap.

Cartridges of 1.8 ml.

Box containing 50 cartridges.

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

As for any cartridge, the diaphragm should be disinfected just prior to use. It should be carefully swabbed:

- either with 70% ethyl alcohol
- or with 90% pure isopropyl alcohol for pharmaceutical use.

The cartridges should under no circumstances be dipped into any solution whatsoever.

One cartridge can only be used for one single patient during one single session.

No opened cartridge of anaesthetic solution should be reused. If only a part is used, the remainder must be discarded.

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

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