SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LIGNOSPAN SPECIAL 20 mg/ml + 12.5 micrograms/ml, solution for injection
UTILYCAINE – LIGNOKENT – EUROCAINE - REXOCAINE

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains:
Lidocaine hydrochloride 20 mg
Adrenaline 12.5 micrograms (as tartrate) (1:80,000).

One cartridge of 1.8 ml of solution for injection contains 36 mg of lidocaine hydrochloride and 22.5 micrograms of adrenaline (as tartrate).

One cartridge of 2.2 ml of solution for injection contains 44 mg of lidocaine hydrochloride and 27.5 micrograms of adrenaline (as tartrate).

Excipient(s) with known effect:
This medicinal product contains 1.20 mg/ml potassium metabisulfite (E224) (equivalent to 0.422 mg/ml potassium (0.0108 mmol/ml)), and 2.602 mg/ml sodium (0.11 mmol/ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Production of local anaesthesia for dental procedures by infiltration or nerve block injection.

LIGNOSPAN SPECIAL is indicated in adults, children and adolescents.

4.2 Posology and method of administration

For professional use by dentists and stomatologists only.

Posology:

As with any anaesthetic, 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 used. The necessary dosage must be determined on an individual basis.

- **Adults:**

The maximum recommended dose is 7 mg/kg of body weight for a healthy adult above 50 kg of body weight with an absolute maximum dose of 500 mg of lidocaine or 200 micrograms of adrenaline. However, due to this product's fixed component of adrenaline 1:80,000, the latter will determine the maximum administered quantity to be 16 ml solution (containing 200 micrograms of adrenaline) which must not be exceeded.

				Equivalent in cartridges numbers
Lidocaine dose (mg)	Adrenaline dose (mg)	Volume (ml)	1.8 ml	2.2 ml
320	0.200	16	8.9	7.3

- **Adolescents (12 to 18 years of age) and children (4 to 11 years of age)**

Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.

The average dose to be used is in the range of 20mg to 30mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child's weight (in kilograms) x 1.33.

Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.

The number of cartridges corresponding to the maximum dose of 5 mg/kg can be calculated as follows:

Patient weight (kg) x Maximum lidocaine dose (mg/kg) / Quantity of lidocaine per cartridge (mg)

				Equivalent in cartridges numbers	
Weight (kg)	Lidocaine dose (mg)	Adrenaline dose (mg)	Volume (ml)	1.8 ml	2.2 ml
20	100	0.0625	5	2.8	2.3
30	150	0.09375	7.5	4.2	3.4

40	200	0.125	10	5.6	4.5
50	250	0.15625	12.5	6.9	5.7

- **Special populations**

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

Method of administration:

Infiltration or nerve block injection.

Before injection, aspiration should always be performed to avoid intravascular injection and if required, the needle repositioned until no return of blood can be elicited by aspiration. The absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Major systemic reactions as a result of accidental intravascular injection can be avoided in most cases by an injection technique after aspiration with a slow injection: the rate of injection should not exceed 1 ml of solution per minute.

To avoid risk of infection (e.g. hepatitis transmission), syringe and needles used to draw up the solution must always be fresh and sterile.

For single use. Any unused solution should be discarded.

The medicinal product should not be used if cloudy or discoloured.

For information relevant to the handling of the product, see section 6.6.

4.3 Contraindications

- Hypersensitivity to lidocaine (or to any local anaesthetic agent of the amide type) or to adrenaline or to any of the excipients listed in section 6.1.

Due to lidocaine:

- Severe conduction disturbances (e.g., severe bradycardia, 2nd / 3rd degree AV blocks)
- Acute intermittent porphyria;

Due to adrenaline:

- Uncontrolled /severe hypertension,
- Persistent / refractory tachyarrhythmia
- Pheochromocytoma.

4.4 Special warnings and precautions for use

Before using this medicinal product, 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).

Special warnings

This product must be used with caution in:

Patients with cardiovascular disorders:
- Peripheral vascular disease.
- Arrhythmias particularly of ventricular origin;
- Heart failure;
- Hypotension.

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

Patients with *myasthenia gravis*:
The lowest dose leading to effective anaesthesia should be used as these patients are particularly sensible to the effect of local anaesthetics.

Patients with epileptic disease:
Because of their convulsive actions, all local anaesthetics should be used very cautiously.

Patients with hepatic disease:
The lowest dose leading to efficient anaesthesia should be use, see section 4.2.

Patients with renal disease:
The lowest dose leading to effective anaesthesia should be used.

Patients with thyrotoxicosis:
The lowest dose leading to effective anaesthesia should be used.

Patients with coronary artery disease and valvular cardiac disease:
The lowest dose leading to effective anaesthesia should be used.

Patients receiving treatment with antiplatelets / anticoagulants:
The increased risk of severe bleeding after accidental vessel puncture and during oro-maxillo-facial surgery should be considered. INR monitoring should be increased in patients under anticoagulants.

Patients with uncontrolled diabetes:
This product should be used cautiously due to hyperglycemic effect of adrenaline.

Patients with susceptibility of acute angle-closure glaucoma:
This product should be used cautiously due to the presence of adrenaline.

Patients under the influence of illicit drug:
The efficacy of this product may be decreased in these patients.

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

The product must be used safely and effectively under appropriate conditions:

Adrenaline impairs the flow of blood in the gums, potentially causing local tissue necrosis.

The local anaesthetic effects may be reduced if the product is injected into an inflamed or 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 sensation is restored.

Precautions for use

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, e.g., convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest, due to the sudden high level of adrenaline and / or lidocaine in the systemic circulation.

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's potential chemical neurotoxicity and the presence of adrenaline as it may impair the perineural blood supply and prevent lidocaine local wash-out.

Risk of Takotsubo cardiomyopathy or stress-induced cardiomyopathy:

Stress cardiomyopathy induced by injected catecholamines has been reported.

Because of the presence of adrenaline, precautions and monitoring should be enhanced in the following situations: patients stressed prior to dental procedure or conditions of use which may contribute to induce a systemic passage of adrenaline e.g. an administered dose higher than recommended or in case of an accidental intravascular injection.

Any previous knowledge of such underlying conditions in patients requiring dental anaesthesia should be minded and a minimal dose of local anaesthetic with vasoconstrictor used.

The medicinal product contains potassium metabisulfite, a sulfite that may rarely cause hypersensitivity reactions and bronchospasm.

The medicinal product contains potassium, less than 1 mmol (39 mg) for a maximal dose of 16 ml, i.e. essentially 'potassium-free'.

The medicinal product contains 0.1132 mmol/ml (2.602 mg/ml) sodium (main component of cooking/table salt). This is equivalent to approximately 0.665% of the recommended maximum daily dietary intake of sodium for an adult. The maximum recommended dose of this medicinal product (16 ml) contains 1.8112 mmol (41.632 mg) sodium, which is equivalent to 10.65% of the recommended maximum daily intake of sodium for an adult.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions that are not recommended

Postganglionic adrenergic blocking agents (e.g., guanadrel, guanethidine, and rauwolfia alkaloids):

Reduced dose of this product should be used under strict medical supervision followed by careful aspiration due to possible increased response to adrenergic vasoconstrictors: risk of hypertension and other cardiovascular effects.

Interactions requiring precautions for use

Additive interactions with other local anaesthetics

Toxicity of local anaesthetics is additive.

This point is considered as not relevant with regard to dental anaesthesia doses and blood levels in adults, but it is a concern in children.

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

Opioid sedatives (central nervous system depressants)

Reduced doses of this product should be used due to potential additive CNS effects of lidocaine and sedatives.

Inhibitors of metabolism (e.g. cimetidine)

Increased serum levels of amide anaesthetics have been reported after concomitant administration of cimetidine.

Halogenated volatile anaesthetics (e.g.: halothane):

Reduced doses of this product should be used due to sensitization of the heart to the arrhythmogenic effects of catecholamines: risk of severe ventricular arrhythmia.

The patient's hemodynamic status should be closely monitored.

Non-selective beta-adrenergic blockers **(**e.g., propranolol, nadolol):

Reduced doses of this product should be used due to possible increase in blood pressure.

Close cardiovascular monitoring is recommended.

(TCAs) Trycyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, maprotiline and protriptyline):

Dose and rate of administration of this product should be reduced due to strengthening of adrenaline activity.

Close cardiovascular monitoring is recommended.

MAO inhibitors *[both A-selective MAO inhibitors* (e.g., brofaromine, moclobemide, toloxatone) *and non-selective MAO inhibitors* (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.

Drugs with combination of adrenergic-serotoninergic effect (e.g., venlafaxine, milnacipran, sertraline):

Dose and rate of administration of this product 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 in combination with adrenaline (e.g., antiarrhythmics like digitalis, quinidine):

Dose of administration of this product 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 this product 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) ***and other sympathomimetics (***e.g., isoproterenol, levothyroxine, methyldopa, antihistamines (such as chloropheniramine, diphenhydramine):

Risk of adrenergic toxicity. Reduced doses of this product should be used.

If cocaine has been used within 24 hours, the planned dental treatment should be postponed

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

Pregnancy

No effects during pregnancy are anticipated, since systemic exposure to lidocaine and adrenaline is negligible. This product can be used during pregnancy. Refer to section 5.3

Breastfeeding

Lidocaine/metabolites are excreted in human milk, but at therapeutic doses of this product no effects on the breastfed newborns/infants are anticipated.

Fertility

No adverse effects on fertility were observed in preclinical studies.

4.7 Effects on ability to drive and use machines

Lidocaine in combination with adrenaline solution may have minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of this product (see section 4.8). Patients should not leave the dental office within 30 minutes following the dental procedure.

4.8 Undesirable effects

a) Summary of the safety profile

Adverse reactions following administration of the product are similar to those observed with other amide local 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 the specific patient. Nervous system disorders, cardiac disorders and vascular disorders are the most frequently occurring adverse reactions.

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

b) Tabulated list of adverse reactions

The reported adverse reactions come from spontaneous reporting, clinical studies and literature.

By convention, frequency of initial signs of CNS or CVS toxicity is considered as rare.

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

MedDRA system Organ Class	**Frequency**	**Adverse Reactions**
Infections and infestations	Not known	Gingivitis
Immune system disorders	Rare	Hypersensitivity[1] Anaphylactic / anaphylactoid reactions[1]
Psychiatric disorders	Rare	Confusional state
	Very rare	Euphoric mood Anxiety/Nervousness/Agitation/Restlessness
Nervous system disorders	Common	Neuropathy peripheral[2]: Neuralgia (neuropathic pain) Headache Dizziness (light headedness) Tremor
	Rare	Deep CNS depression: Loss of consciousness

		Convulsion (including tonic clonic seizure) Somnolence
Eye disorders[4]	Rare	Visual impairment Vision blurred Accommodation disorder
Ear and labyrinth disorders	Very rare	Tinnitus
Cardiac disorders	Common	Palpitations Tachycardia
	Very rare	Conduction disorders, atrioventricular block Bradyarrhythmia Cardiac arrest Tachyarrhytmia (including ventricular extrasystoles and ventricular fibrillation)[5]
Vascular disorders	Common	Hypotension (with possible circulatory collapse) Hypertension Pallor (local, regional, general)
	Very rare	Vasodilatation Vasoconstriction Hot flush
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Rare	Bronchospasm / asthma
	Not known	Respiratory depression[3] Apnoea (respiratory arrest)
Gastrointestinal disorders	Uncommon	Nausea Vomiting
	Not known	Gingival/oral mucosal exfoliation (sloughing)/ ulceration/ necrosis[6] Dysphagia[1]Recurrent aphthous stomatitis, glossitis[7] Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Rash (eruption) Pruritus (itching)
	Rare	Angioedema[1] (oedema of face / tongue / lip / throat / larynx / periorbital oedema) Urticaria
	Very rare	Hyperhidrosis Swelling face
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia Arthralgia
General disorders and administration site conditions	Common	Injection site reaction[8]
	Very rare	Injection site pain
	Not known	Injection site swelling Malaise Pyrexia

c) Description of selected adverse reactions

[1] Hypersensitivity (anaphylactic or anaphylactoid reactions) may characteristically occur with various symptoms of rash (eruption), urticarial, pruritus, bronchospasm/asthma, wheezing, and angiodema. Angioedema include oedema of face / tongue / lip / throat / larynx / periorbital oedema. Laryngo-pharyngeal oedema may characteristically occur with hoarseness and / or dysphagia. Bronchospasm (bronchoconstriction) may characteristically occur with dyspnoea;

[2] These neural pathologies may occur with the various symptoms of abnormal sensations of the lips, tongue, and oral tissues.

[3] Respiratory depression may characteristically occur with various symptoms such as apnoea (respiratory arrest);

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

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

[6] Necrosis is due to excessive local effect of the vasoconstrictor and mostly occurs in patients with underlying ischemic diseases;

[7] This may be the sign of an injury to the lingual nerve

[8] Procedural pain, post procedural pain and contusion are symptoms that may be associated to injection site reaction

Because of the presence of adrenaline, precautions and monitoring should be enhanced in the following situations: patients stressed prior dental procedure.

Any previous knowledge of such underlying conditions in patients requiring dental anaesthesia should be minded and a minimal dose of local anaesthetic with vasoconstrictor used.

d) Paediatric population

The safety profile was similar in children and adolescents from 4 to 18 years old compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

- ***Types of overdose***

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

- Absolute overdose
- Relative overdose
  - inadvertent injection into a blood vessel, or
  - abnormal rapid absorption into the systemic circulation, or
  - delayed metabolism and elimination of the product.

- ***Symptomatology***
  - Due to lidocaine:
    The symptoms are dose-dependent and have progressive severity in the realm of neurological manifestations, followed by vascular, respiratory, and finally cardiac toxicity (detailed in section 4.8).
  - Due to adrenaline:
    Overdose of adrenaline may cause cardiovascular effects.

- ***Treatment of overdose***

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

  If signs of acute toxicity are suspected, the injection of this product must immediately be stopped.

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

  In case of cardiac arrest, immediate initiation of cardiopulmonary resuscitation is necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous System / Local Anaesthetics / Anaesthetics, local / Amides / Lidocaine, combinations

ATC Code: N01BB52

Mechanism of action:

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anaesthetic action.

Since lidocaine, as most agents currently used for local anaesthesia, is not a vasoconstrictor, adrenaline is included in the solution with the anaesthetic:

- by localizing the solution at the site of the injection, this vasoconstrictor intensifies and prolongs the anaesthetic effect and decreases the rate at which the anaesthetic drug enters the systemic circulation,
- the presence of a vasoconstrictor also decreases surgical haemorrhage in the immediate area of injection.

Onset duration of anaesthesia:

- When used for infiltration anaesthesia in dental patients, the time of onset averages less than two minutes. LIGNOSPAN SPECIAL provides an average pulp anaesthesia of at least sixty minutes with an average duration of soft tissue anaesthesia of approximately two and a half hours.
- When used for nerve blocks in dental patients, the time of onset averages two to four minutes. LIGNOSPAN SPECIAL provides pulp anaesthesia averaging at least ninety minutes with an average duration of soft tissue anaesthesia of three to three and a quarter hours.
- Hemodynamics:
- Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. These changes may be attributable to a direct depressant effect of the local anaesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of adrenaline when present.

5.2 Pharmacokinetic properties

Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administrations, its rate of absorption depending upon various factors, such as the site of administration, and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

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

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.

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 metabolized, any condition that affects liver function may alter lidocaine kinetics. 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.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per ml. In the rhesus monkey, arterial blood levels of 18-21 mcg/ml have been shown to be threshold for convulsive activity.

5.3 Preclinical safety data

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) and water for injections.

6.2 Incompatibilities

None stated.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25ºC.

Keep the cartridges in the outer carton tightly closed, in order to protect from light.

Do not freeze.

6.5 Nature and contents of container

- Glass cartridges with rubber closures.
- 50 dental cartridges of 1.8 ml or 2.2 ml in blister packs grouped in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

7 MARKETING AUTHORISATION HOLDER

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