1. NAME OF THE MEDICINAL PRODUCT

XILONIBSA 2% solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 20 mg lidocaine hydrochloride and 0.0125 mg epinephrine

Excipients: 4.75 mg/ml sodium chloride and 0.50 mg/ml sodium metabisulfite

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear, colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Local dental anaesthesia by infiltration and nerve blockade.

4.2 Posology and method of administration

Posology

The dosage varies in accordance with the area to be anaesthetised, the extent of tissue vascularisation and the anaesthetic technique to be applied.

The recommended doses are listed in the following table according to the technique used.

Anaesthetic technique	Recommended dose	Adults (70 kg)	Children	
			20 kg	40 kg
Infiltration anaesthesia (terminal)	in ml of solution	1 ml	0.3 ml	0.6 ml
	in mg lidocaine HCl	20 mg	6 mg	12 mg
Block anaesthesia	in ml of solution	1.5 - 2 ml.	0.4 - 0.6 ml.	0.8 - 1 ml.
	in mg lidocaine HCl	30 - 40 mg	8 - 12 mg	16 - 20 mg

Adults
The maximum dose in 24 hours is 490 mg lidocaine (calculated for a person weighing 70 kg), and a dose of 7 mg/kg body weight must never be exceeded.

Paediatric population:
XILONIBSA 2% solution for injection is indicated for use in adults and in children older than 4 years of age. The amount to be injected should be determined by the age and weight of the child and the scale of the operation. The anaesthetic technique must be carefully selected. Painful anaesthetic techniques should be avoided. The behaviour of children must be monitored carefully during treatment. The mean dose for use is in the range 20 mg to 30 mg lidocaine hydrochloride per session. Alternatively, the dose in mg of lidocaine hydrochloride that can be administered in children can be calculated using the expression: weight of child (in kilogrammes) x 1.33. Do not exceed the equivalent of 5 mg lidocaine hydrochloride per kilogramme body weight.

Special populations:
Elevated XILONIBSA 2% levels in plasma may occur in elderly patients due to a reduction in metabolic processes and a lower volume of distribution.
The risk of accumulation is greater in the case of repeated administration and in patients with altered liver function (see section 4.4), therefore it is recommended to administer a lower dose in such cases.

Method of administration

Local injection / Oromucosal use.
For use in dental anaesthesia only.
Injections must always be administered slowly and with prior aspiration in at least two planes (by rotation of the needle by 180º) to prevent accidental intravascular injection.
The injection rate must not exceed 0.5 ml in 15 seconds, which is equivalent to one cartridge per minute.

4.3 Contraindications

XILONIBSA 2% is contraindicated in the event of hypersensitivity to the active substances, amide-type anaesthetics or any of the excipients listed in section 6.1.

The use of XILONIBSA 2% is contraindicated in children under 4 years of age.

Due to the lidocaine content, XILONIBSA 2% is contraindicated in the event of:

- A known hypersensitivity to amide-type local anaesthetics.
- Severe atrioventricular conduction defects not compensated by a pacemaker.
- A deficiency in plasma cholinesterase activity.
- Severe clotting disorders
- Degenerative nerve disease

Due to the epinephrine (adrenaline) content, XILONIBSA 2% is contraindicated in the event of:

- Unstable angina pectoris
- Recent myocardial infarction
- Recent coronary artery bypass surgery
- Refractive arrhythmias and paroxysmal tachycardia or continuous high-frequency arrhythmia
- Severe untreated or uncontrolled hypertension
- Untreated or uncontrolled congestive heart failure
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (see section 4.5).

Due to the metabisulfite content, XILONIBSA 2% is contraindicated in the event of:

- Allergy or hypersensitivity to sulfite.
- Severe bronchial asthma

4.4 Special warnings and precautions for use

Accidental intravascular injections may be associated with seizures followed by central nervous system failure or cardiopulmonary arrest. Resuscitation equipment, oxygen and other medicinal products for resuscitation must be immediately available.

It must be taken into consideration that during treatment with clotting inhibitors (e.g. heparin or acetylsalicylic acid), accidental intravascular injection when administering a local anaesthetic may cause severe bleeding with increased haemorrhagic tendency (see section 4.5)

The injection of local anaesthetics into infected or inflamed regions must be avoided.

The patient must be warned of the possibility of injuries due to involuntary biting of the lips, tongue and buccal mucosa while these structures are anaesthetised. Consequently, food intake must be postponed until sensitivity returns.

The presence of sodium metabisulfite as excipient may cause the onset of allergic-type reactions, including anaphylactic-type reactions and bronchospasm, especially in patients with a history of asthma or allergies.

This medicine contains less than 1 mmol (23 mg) sodium per ml, and is thus considered to be essentially "sodium-free".

The product should be administered with caution in patients with impaired cardiovascular function since they are less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs (see section 4.3).

XILONIBSA 2% must be used with special caution in the case of:

- Angina pectoris
- Arteriosclerosis
- Clotting disorders
- Diabetes mellitus
- Severe liver dysfunction
- Lung diseases, particularly allergic asthma
- Epilepsy
- Phaeochromocytoma
- Narrow-angle glaucoma
- Thyrotoxicosis
- Acute porphyria XILONIBSA 2% solution for injection is probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its lidocaine content, XILONIBSA 2% must be used with care in patients who are also receiving drugs that present structural similarities to local anaesthetics (for example, class Ib antiarrhythmic agents) as their toxic effects are additive in nature.

Due to its epinephrine content, XILONIBSA 2% must be used with care in patients simultaneously receiving one of the following drugs:

- Coagulation inhibitors (heparin), non-steroidal anti-inflammatories (NSAIDs), plasma substitutes (dextran), phenothiazines, butyrophenones: decrease in the vasopressor effect of epinephrine, possibly causing hypotension, tachycardia and an increased haemorrhagic tendency.

- Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), ergotamine-type oxytocic drugs, non-selective beta-blockers (propranolol): increase in the vasopressor effect of epinephrine, possibly causing severe hypertension and bradycardia.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
Although there is no evidence from animal studies of harm to the foetus, XILONIBSA 2% should not be used during pregnancy unless clearly necessary.

The administration of XILONIBSA 2% during pregnancy may cause foetal bradycardia due to the local anaesthetic content, as well as decreased intrauterine blood flow due to the epinephrine content, especially in the case of accidental intravascular injection.

<u>Breast-feeding</u>

Lidocaine is excreted in breast milk but in such low quantities that, in general, there is no risk to the newborn. There are no data regarding epinephrine excretion in breast milk, although it is unlikely to affect the newborn, therefore XILONIBSA 2% can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Depending on the dose and site of administration, local anaesthetics may affect mental functions and temporarily alter locomotion and coordination. When administering this medicine, the doctor or dentist must evaluate in each particular case whether the ability of the patient to react has been compromised and whether the patient can drive or use machines. The patient must remain in the consulting room for at least 30 minutes after the intervention.

4.8 Undesirable effects

The adverse reactions strictly attributable to the local anaesthetic are limited. However, the physiological effects of nerve blockade are common, although they vary considerably depending on the type of blockade administered.

The following adverse reactions can occur as a result of the content of lidocaine as local anaesthetic:

FREQUENCY	**DISORDERS**	**EFFECTS**
Rare (≥1/10,000 to <1/1000)	Heart disorders	Hypotension, arrhythmias, bradycardia, cardiac arrest.
	Nervous system disorders	Metallic taste, tinnitus, feeling of dizziness, nausea, vomiting, anxiety, tremors, nystagmus, headaches, increased breathing rate. Paresthesia (numbness accompanied by a burning sensation) of the lip and/or tongue . Unconsciousness and seizures, coma and respiratory arrest (in the event of overdose).
	Respiratory disorders	Tachypnoea followed by bradypnoea, possibly causing apnoea.
Very rare (< 1/10,000)	General disorders and administration site conditions	Allergic reactions, skin rash, erythema, pruritus, oedema of the tongue, mouth, lips or throat and, in the most severe cases, anaphylactic shock.

The following adverse reactions can occur as a result of the content of epinephrine as a vasoconstrictor:

FREQUENCY	DISORDERS	EFFECTS
Rare (≥1/10,000 to <1/1000)	Heart disorders	Hot sensation, sweating, migraine-type headaches, increased blood pressure, angina pectoris disorders, tachycardias, tachyarrhythmias, and cardiac arrest, as well as oedematous swelling of the thyroids.

The following adverse reactions can occur as a result of the content of metabisulfite as an excipient:

FREQUENCY	DISORDERS	EFFECTS
Very rare (< 1/10,000)	General disorders and administration site conditions	Particularly in bronchial asthmatics, allergic reactions which manifest as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of the consciousness or anaphylactic shock may occur.

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 Spanish Pharmacovigilance System for Medicinal Products for Human Use website: https://www.notificaram.es.

4.9 Overdose

Systemic toxic reactions appear immediately after accidental intravascular injection and within 15 to 60 minutes after overdose of the local anaesthetic. Toxicity manifests initially in the central nervous system, followed by the cardiovascular system. In paediatric patients, if the local anaesthetic is administered under general anaesthesia, it is difficult to detect the first signs of toxicity to the local anaesthetic.

Central nervous system toxicity
Initial symptoms include agitation, a feeling of intoxication and numbness of the lips and tongue, paresthesia around the mouth, dizziness, visual problems and ringing in the ears. The onset of speaking difficulties, muscle rigidity and spasms are symptoms that precede major seizures. Respiratory arrest may occur in the most serious cases. Acidosis increases the toxic effects of local anaesthetics. Recovery depends on metabolism of the local anaesthetic and its distribution outside the central nervous system. This occurs rapidly provided large quantities of the medicinal product are not administered.

Cardiovascular system toxicity
The symptoms associated with the local anaesthetic may include a drop in blood pressure, bradycardia, arrhythmia and cardiac arrest as a result of high systemic concentrations of local anaesthetic.
The symptoms associated with epinephrine are a hot sensation, sweating, headaches, increased blood pressure, tachycardias, tachyarrhythmias and cardiac arrest.

General measures
If these adverse reactions appear, the administration of anaesthetic must be interrupted immediately. Measures will be based on the maintenance or restoration of the vital functions of respiration and circulation, administration of oxygen and intravenous access.

Special measures
- Hypertension: raise the upper part of the body; administer sublingual nifedipine if necessary.
- Seizures: protect the patient from injury; administer benzodiazepines (e.g. diazepam IV) if necessary.
- Hypotension: raise the legs; administer a complete electrolyte IV solution, vasopressors (e.g. etilefrine IV).
- Bradycardia: administer atropine IV.
- Anaphylactic shock: administer a complete electrolyte IVsolution, epinephrine IV, cortisone IV; contact the emergency department.
- Cardiac arrest: apply cardiopulmonary resuscitation; contact the emergency department.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics, local – amides – lidocaine; ATC Code: N01B B52.

As is the case with other local anaesthetics, lidocaine exerts a reversible blockade of impulse propagation along the nerve fibres, thereby preventing the movement of sodium ions through the nerve membrane.

Local anaesthetics may exert a similar effect on the excitable membranes of the heart and brain. At high concentrations, lidocaine possesses a quinidine-type action on the myocardium, acting as a cardiac depressor. All local anaesthetics stimulate the CNS and may produce anxiety, restlessness and spasms.

The onset and duration of action of lidocaine are increased by the addition of epinephrine as a vasoconstrictor. This delays absorption of the anaesthetic and results in a greater concentration at

the site of administration over a longer period of time, as well as a reduction in the possible occurrence of systemic adverse side effects.

5.2 Pharmacokinetic properties

ABSORPTION
The information obtained from different formulations, concentrations and uses shows that lidocaine is absorbed completely upon parenteral administration and that its absorb ration depends, for example, on various factors such as the site of administration and the presence or absence of a vasoconstrictor. Except for intravascular administration, the highest blood concentrations are obtained via intercostal nerve blockade and the lowest levels after subcutaneous administration.

DISTRIBUTION
The binding of lidocaine to plasma proteins is dependent on the concentration of the drug and the bound fraction decreases with increasing concentration. At concentrations of between 1 and 4 µg free fraction per ml, between 60% and 80% of lidocaine is bound to proteins. Binding is also dependent on the plasma concentration of alpha-1-acid glycoprotein.
Lidocaine crosses the blood-brain barrier and placenta, supposedly by passive diffusion.

BIOTRANSFORMATION
Lidocaine is rapidly metabolised by the liver, with metabolites and non-metabolised drug being excreted via the kidneys. Biotransformation includes oxidative N-dealkylation, aromatic hydroxylation, cleavage of the amide bond and conjugation. N-dealkylation results in the monoethylglycinexylidide and glycinexylidide metabolites. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of the 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.

ELIMINATION
Studies of lidocaine metabolism after injection of an intravenous bolus have shown that the elimination half-life of this agent is between 1.5 and 2 hours. Due to the high metabolisation rate of lidocaine, any condition that affects hepatic function may alter lidocaine kinetics. The half-life may be prolonged twofold or more in patients with hepatic impairment. Renal impairment does not affect lidocaine kinetics but may increase the accumulation of metabolites.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional safety pharmacology studies, repeated dose toxicity, genotoxicity, carcinogenic potential, reproductive toxicity.
As is the case for other amide-type local anaesthetics, the active substance may produce central nervous system and cardiovascular system reactions at high doses (see section 4.8. *Undesirable effects*).

A metabolite of lidocaine, 2,6-dimethylaniline, showed weak evidence of activity in some genotoxicity tests. The metabolite 2,6-dimethylaniline has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium metabisulfite
Hydrochloric acid (to alter the pH)
Sodium hydroxide (to alter the pH)
Citric acid monohydrate
Water for injectable preparations

6.2 Incompatibilities

In solutions with epinephrine, mixing with alkaline solutions may cause rapid degradation of the vasoconstrictor and a greater tendency to precipitate.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store below 30ºC and protected from light.

6.5. Nature and contents of container

Neutral, colourless type I glass cartridges, stopper and discs of bromobutyl rubber and capsule of aluminium with a double bromobutyl disc.
XILONIBSA 2% is presented in boxes containing 50 or 100 cartridges of 1.8 ml for self-aspiration.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Cartridges **for single use only.**
Previously opened cartridges must not be used in other patients. Unused product must be discarded.
Any unused medicinal product or material that has been in contact with it should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT