1. NAME OF THE MEDICINAL PRODUCT

Inibsacain 5 mg/ml + 0.005 mg/ml solution for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5 mg of bupivacaine hydrochloride and 0.005 mg of epinephrine (adrenaline) (in bitartrate form).
Each 1.8 ml cartridge contains 9 mg of bupivacaine hydrochloride and 0.009 mg of epinephrine (adrenaline) (in bitartrate form).

Excipients with a known effect:
Each 1.8 ml cartridge contains 0.9 mg of sodium metabisulphite (E-223).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Local anaesthesia induction for dental procedures in adults, by injection or trunk blockade.

4.2 Posology and method of administration

Posology
The 0.5 mg/ml concentration with adrenaline is recommended for injection in order to achieve a prolonged local anaesthesia blockade in the upper and lower jaw regions for cases such as oral surgical procedures generally associated with severe postoperative pain.

As with other anaesthetics, the dose to be administered depends on the region requiring anaesthesia, the number of neuron segments to block, individual tolerability, and the anaesthetic technique to be used.

The smallest volume of solution to produce effective anaesthesia should be used. The dosage should be adjusted on an individual basis according to the age, weight and health condition of each patient.

Adults
An average dose of 1.8 ml (9 mg bupivacaine hydrochloride) per injection zone is usually enough to produce anaesthesia.

A second dose of 1.8 ml (9 mg bupivacaine hydrochloride) can sometimes be administered 2 to 10 minutes after the onset of action to produce adequate anaesthesia if required. Time must be left between injections.

Paediatric population
The safety and efficacy of Inibsacain among children and adolescents under the age of 18 years old have not been established, as such use on this population is not recommended.

Maximum recommended dose
The total recommended dose for a healthy adult when injected across all regions during a dental session should not exceed 90 mg (10 injections of 1.8 ml).

Method of administration
Route of administration: dental use.
Local injection (blockade or infiltration)
For dental anaesthesia use only. To avoid intravascular injection, always aspirate at least two planes beforehand (by rotating the needle by 180º), although a negative result does not rule out an unintentional and undetected intravascular injection.
The injection rate must not exceed 1 ml per minute.
Major systemic reactions, like those resulting from accidental intravascular injection, can be avoided in most cases by using an injection technique - after aspiration, slowly inject 0.1-0.2 ml and then slowly administer the remainder - but not before 30 seconds to 1 minute have passed.

Products containing parenteral drugs must be inspected visually to check for the absence of particles and discolouration prior to administration, provided the solution and packaging allow this (see section 6.6).

4.3 Contraindications

Solutions containing bupivacaine should not be used by patients with known hypersensitivity to bupivacaine hydrochloride or other amide-type local anaesthetics (such as articaine, lidocaine, mepivacaine, prilocaine, etc.), or to any of the excipients listed in section 6.1.

Due to its adrenaline content, its use is contraindicated for patients with:
- Paroxysmal tachycardia
- Atrial fibrillation with a rapid heart rate
- Narrow-angle glaucoma.

In general, the use of anaesthetics is contraindicated in the following cases:
- Patients with severe cardiac impulse conduction disorders, uncompensated heart failure and cardiogenic shock or hypovolaemia.
- Patients with active degenerative nerve disease.
- Patients with clotting defects.

The local anaesthetic must not be injected into infected regions.

Intravenous administration is contraindicated.

4.4 Special warnings and precautions for use

Local dental anaesthetics contain high concentrations of an active substance. This means that fast injection at high pressure may lead to complications, even when only small quantities are administered (see section 4.9). The risk is particularly high in the case of involuntary intravascular injections, as the injected medicinal product may be transported in a retrograde manner. Intra-arterial injection in the head and neck region derives in high concentrations of medicinal product, which reach the brain to a greater extent than through intravenous injection. Careful aspiration should be performed prior to injection to reduce the risk of intravascular injection.

In the case of intraneural injection, there is a risk that the medicinal product may be transported via the nerve in a retrograde manner due to the high pressure. To avoid intraneural injection and prevent nerve blockade related damage, the needle should be removed slowly if paraesthesia occurs during the injection.

Local anaesthesia procedures must always be performed by appropriately trained professionals with suitable resuscitation equipment available (especially a source of oxygen), as well as anticonvulsant medicinal products (benzodiazepines or barbiturates), atropine, and vasopressors or adrenalin in the event of an allergic or severe anaphylactic reaction. Verbal contact with the patient must always be maintained and cardiovascular signs monitored.
Patients with blood clotting problems or those receiving anticoagulant treatment must be monitored more closely.
A delay in the appropriate treatment of dose-related toxicity, decreased ventilation for any reason, and/or altered sensitivity, may lead to the onset of acidosis, cardiac arrest, and potentially death (see sections 4.8 “Undesirable effects” and 4.9 “Overdose”).

Solutions with adrenaline must be used with care among patients with severe or untreated hypertension, poorly controlled thyrotoxicosis, ischaemic heart conditions, heart block, cerebrovascular impairment, advanced diabetes, and any other pathological condition that may worsen due to the effects of adrenaline. Such solutions must be used with care and in limited quantities in distal arterial regions, such as the fingers and toes, or those with a compromised blood flow (see section 4.5 “Interaction with other medicinal products and other forms of interaction”).

In order to reduce the potentially harmful side-effects caused by local anaesthetics, special attention must be paid in some patients:

- Patients with partial or total heart block as the action of local anaesthetics may lead to myocardial conduction depression.
- Patients with advanced hepatic disease or severe renal dysfunction.
- Older or weakened patients in which there is a probability of systemic toxicity; moreover, repeated doses may result in accumulation of the drug or its metabolites or slow its metabolism. Consequently, lower doses must be used.

Paediatric population
The safety and efficacy of Inibsacain among children and adolescents under the age of 18 years old have not been established, as such use on this population is not recommended.

Excipients warning

- This medicinal product may cause severe allergic reactions and bronchospasm due to its sodium metabisulphite content.
- This medicinal product contains less than 1 mmol of sodium (23 mg) per 1.8 ml cartridge, meaning it is essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Solutions containing adrenaline must be avoided or used with care among patients receiving treatment with tricyclic antidepressants, as they may result in prolonged and severe hypertension. Moreover, the use of solutions containing adrenaline and ergotamine-type oxytocic drugs may cause severe and persistent hypertension, heart attacks and strokes. Phenothiazines and butyrophenones can reduce or reverse adrenaline's pressor effect.

Solutions containing adrenaline must be used with care among patients under general anaesthesia from inhaled agents, such as halothane, given the risk of severe cardiac arrhythmias.

Non-cardioselective beta-blockers, such as propranolol, augment adrenaline's pressor effect, which may lead to severe hypertension and bradycardia.

Bupivacaine must be used with care among patients receiving treatment with agents structurally similar to local anaesthetics (e.g. class Ib antiarrhythmic agents) as toxic effects may increase.

4.6 Fertility, pregnancy and lactation

Pregnancy
As is the case with most medicinal products, appropriate precautions must be taken when administering during pregnancy.

There are no reports of specific alterations to the reproductive process, for example, a higher incidence of malformations (see section 5.3).

It should only be administered during early pregnancy when the benefits are considered to outweigh the potential risks.
Adding adrenaline may enhance uterine blood flow reduction and contractability, especially after involuntary injection into maternal blood vessels.

Adverse effects on the foetus due to local anaesthetics, such as foetal bradycardia, appear to be more closely related to anaesthesia of the paracervical block. These effects may arise due to high concentrations of the anaesthetic reaching the foetus.

Breast-feeding
Only small amounts of bupivacaine appear to secrete into breast milk, but its precise distribution in breast milk is unknown. There are no reports of problems in human beings in this respect. As such, it should be used with caution by mothers 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 function and temporarily alter locomotion and coordination. When administering this medicinal product, the doctor must evaluate each individual case in terms of whether the ability to react has been compromised and whether the patient can drive or use machines.

4.8 Undesirable effects

In general, the adverse reactions profile for bupivacaine is similar to that for other long-acting local anaesthetics. The adverse reactions caused by drugs themselves are difficult to distinguish from the physiological effects of nerve blockade (e.g. reduced arterial pressure, bradycardia), and the effects caused either directly (e.g. by nerve damage) or indirectly (e.g. abscess) by the puncture needle.

Table of adverse reactions
The adverse reactions reported with use of bupivacaine are listed below by the frequency of their appearance.

	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)*
Immune system disorders				allergic reactions, anaphylactic reaction/shock
Nervous system disorders		paraesthesia, vertigo	signs and symptoms of CNS toxicity (seizure, circumoral paraesthesia, numbness of the tongue, hyperacusis, sight alterations, loss of consciousness, tremor, mild headache, tinnitus and dysarthria)	neuropathy, peripheral nerve damage, arachnoiditis
Eye disorders				diplopia
Cardiac disorders		bradycardia		cardiac arrest, arrhythmia
Vascular disorders	hypotension	hypertension		
Respiratory, thoracic & mediastinal disorders				respiratory depression

Gastrointestinal disorders	nausea	vomiting		
Renal and urinary disorders		urinary retention		

Systemic adverse reactions to adrenaline are related to the drug's vasoconstrictor effect, which can lead to cardiovascular alterations, hypertension, brain haemorrhage, etc.

However, at the dose contained in this medicinal product, and considering the route of administration (local injection), it is unlikely that the aforementioned toxicity phenomena will occur. Very high volumes of the substance must be administered intravenously for them to occur.

Adrenaline does not increase the toxicity of bupivacaine beyond the pharmacologically desirable effect of increasing the amount of the anaesthetic agent locally to prolong its period of action. Given the different action profiles (anaesthetic and vasoconstrictor) and the additive profile of both substances in achieving an anaesthetised and ischaemic anatomical region suitable for procedures, the toxicity of the combination is minimal and does not extend beyond the theoretical addition of the profiles for each of the drugs when considered separately.

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

Acute systemic toxicity
In the case of accidental intravascular injection, the toxic effects become clear within 1-3 minutes, whereas in the event of overdose, the peak plasma concentrations may not be reached for up to 20-30 minutes, depending on the site of injection, as such that the signs of toxicity are delayed. Toxic reactions mainly occur in the central nervous and cardiovascular system.

Central nervous system toxicity is a sudden response with signs and symptoms of severe intensity. The initial symptoms are paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual alterations and muscle tremors, which precede the onset of a major seizure, are important. These signs must not be confused with neurotic behaviour. Unconsciousness and epileptic seizures, which may last from a few seconds to several minutes, may then appear. Hypoxia and hypercapnia due to increased muscle activity, together with interference with normal respiration and decreased ventilation, appear rapidly after the seizures. The occasional case of severe apnoea may appear. Acidosis increases the toxic effects of local anaesthetics.

Recovery occurs due to redistribution of the local anaesthetic throughout the central nervous system and metabolism. Recovery is usually rapid even though a large quantity of drug has been injected.

Effects on the **cardiovascular system** may appear among severe cases. High systemic concentrations may lead to hypotension, bradycardia, arrhythmia and cardiac arrest.

Toxic cardiovascular reactions are generally related to the cardiac conduction system and the myocardium, leading to a decrease in cardiac output, hypotension, heart block, bradycardia and occasionally ventricular arrhythmia, including ventricular tachycardia, ventricular fibrillation and cardiac arrest. This is generally preceded, or accompanied, by major CNS toxicity, such as seizures, although cardiac arrest occasionally occurs in the absence of prodromic CNS effects. No prodromic CNS symptoms appear among heavily sedated patients or those under general anaesthesia.

The symptoms of acute toxicity due to adrenaline and its vasoconstrictor effect include cardiovascular reactions, such as feeling hot, sweating, accelerated heart rate, headache, higher blood pressure, angina pectoris, tachycardia, tachyarrhythmias and cardiovascular arrest.

Treatment of acute toxicity
In the event that signs of acute toxicity appear, administration of the local anaesthetic must be stopped immediately.

Treatment will be necessary if seizures occur. All drugs and equipment must be immediately available. Treatment aims to maintain oxygenation, stop the seizures and maintain circulation. If necessary, oxygen and assisted ventilation (mask and gas chamber) must be used. An anticonvulsant must be administered IV if the seizures do not disappear spontaneously within 15-20 seconds. Thiopentone 100-150 mg IV can be used to stop the seizures rapidly. As an alternative, diazepam 5-10 mg IV may be used, although its action is slower. Suxamethonium rapidly stops convulsions, but requires tracheal intubation and controlled ventilation, and therefore, must only be used if you are familiar with these procedures.

If cardiovascular depression (hypotension, bradycardia) is detected, ephedrine 5-10 mg IV must be administered and the dose repeated after 2-3 minutes if necessary.

In the event of circulatory arrest, cardiopulmonary resuscitation must be commenced immediately. Optimal oxygenation and ventilation, circulatory support and treatment of the acidosis are of prime importance, as hypoxia and acidosis may increase the systemic toxicity of the local anaesthetic.

In the event of anaphylactic shock, and when considered necessary, adrenaline must be administered (0.1-0.2 mg by intravenous or intracardiac injection), and the dose repeated should the administered dose prove insufficient.

In the event of cardiac arrest, a prolonged resuscitation effort must be applied to ensure a good outcome.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetics, amides, ATC code: N01BB51

Bupivacaine is an amide-type local anaesthetic. It is approximately four times more potent than lidocaine. At a concentration of 5 mg/ml, it has a long duration of action of more than 12 hours after blocking the peripheral nerve. The onset of the blockade is slower than for lidocaine, especially when anaesthetising long nerves.
Adding the adrenaline-type vasoconstrictor may decrease the absorption rate.

As with other local anaesthetics, bupivacaine blocks signal propagation in nerve fibres by preventing the influx of sodium ions through the nerve membrane. Amide-type local anaesthetics are known to act on the sodium channels in the nerve membrane.

Local anaesthetics exert a similar effect on the excitable membranes of the myocardium and brain. If excessive quantities of the drug rapidly reach systemic circulation, signs and symptoms of toxicity may appear, mainly in the central nervous system and cardiovascular system.

Central nervous system toxicity (see section 4.9 “Overdose”) generally precedes the cardiovascular effects, as is the case at low plasma concentrations. The direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and, occasionally, cardiac arrest.

5.2 Pharmacokinetic properties

Absorption

Bupivacaine has a pK_a of 8.1 and is more lipid soluble than lidocaine.

Systemic absorption depends on the dose, route of administration and vascularisation of the injection site. Subcutaneous administration leads to the lowest concentration.

Absorption is slower when adrenaline is added. From a pharmacokinetic viewpoint, adrenaline is used for its ability to reduce the bupivacaine absorption rate and for the possibility of extending the local anaesthetic’s duration of action.

Distribution

Bupivacaine has a distribution volume of 73 L. 96% of it binds to the plasma alpha-1-acid glycoprotein.

Biotransformation

It undergoes hepatic metabolisation by oxidation, N-dealkylation and other pathways. It has an intermediate hepatic extraction ratio of 0.40.

Elimination

Bupivacaine has a total plasma clearance of 0.58 L/min and an elimination half-life of 2.7 hours. Around 6% of bupivacaine is excreted unchanged through urine at 24 hours, and approximately 5% corresponds to the N-dealkylated metabolite pipecolylxylidine (PPX). The final elimination half-life in new-borns extends to up to 8 hours. The elimination half-life in children aged older than 3 months is similar to that among adults.

Bupivacaine crosses the placenta and reaches a steady state with respect to the free drug. The degree of plasma binding in the foetus is lower than in the mother, meaning the total plasma concentration is lower in the foetus than in the mother. However, the concentration of free drug is similar in both.

Bupivacaine is present in breast milk at concentrations lower than those in maternal plasma.

5.3 Preclinical safety data

In light of the conventional studies performed with bupivacaine, from a pharmacological safety, single- and repeat-dose toxicity, reproductive toxicity, mutagenic potential and local toxicity viewpoint, no risks to humans have been identified, other than those normally expected due to the pharmacodynamic action of high doses of this type of drug (e.g. central nervous system effects and cardiotoxicity).

Adding adrenaline to the medicinal product does not appear to modify the preclinical safety data; so the results for bupivacaine can be extrapolated to the combination of both drugs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium metabisulphite (E-223), hydrochloric acid to adjust the pH and water for injections.

6.2 Incompatibilities

The solubility of bupivacaine is limited at pH > 6.5. This should be considered if alkaline solutions like carbonates must be added, as a precipitate may form.
Mixing with alkaline solutions leads to rapid degradation of the adrenaline.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Glass cartridges containing 1.8 ml of solution for injection, sealed at one end with a bromobutyl plunger and with a bromobutyl disc covered with an aluminium capsule at the other end.

It is presented in cartons containing 1 x 1.8 ml cartridge or 100 x 1.8 ml cartridges (clinical container).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solutions must be used immediately after opening.

Cartridges for single use only. Any unused medicinal product or material that came into contact with it should be disposed of in accordance with local requirements.

Products containing adrenaline must not be sterilised due to its instability.

The solution is colourless, transparent and particle-free, therefore it must not be used if it exhibits a pink or darker than pale-yellow colour, or if it contains a precipitate.

Appropriate precautions must be taken to prevent prolonged contact between anaesthetic solutions containing adrenaline (low pH) and metal surfaces (e.g. needles and metallic parts of syringes), as the metal ions (mainly copper) dissolve, potentially causing local irritation (swelling, oedema) at the injection site and accelerated degradation of the adrenaline.

7. MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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