SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xilonibsa 10 mg/pulse, cutaneous spray solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Every pulse of the dispenser releases a dose of 10 mg of lidocaine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous spray solution.
Clear or practically clear liquid with a characteristic smell.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xilonibsa 10 mg/pulse is indicated as topical anaesthesia for mucous membranes in surgery, obstetrics, dentistry and otorhinolaryngology.

4.2 Posology and method of administration

Posology

The dosage can be adjusted depending on the patient's response and the site to be anaesthetised, evaluating the extent of tissue vascularisation and the anaesthetic technique to be applied. It should be administered at the lowest dose possible that provides the anaesthetic effect required, avoiding the use of excessive doses (see *Section 4.4 Special warnings and precautions for use*).

The administration of lidocaine should be adjusted when used concomitantly with other drugs that reduce its clearance (see section *4.5 Interaction with other medicinal products and other forms of interaction*).

No more than 20 pulses should be applied to produce the desired anaesthesia in adults.

Adults

<u>In dentistry</u>

1 to 5 applications are recommended for administration on the mucous membranes.

<u>In otorhinolaryngology</u>

When used for maxillary sinus puncture, 3 sprays are recommended.

In gynaecology and obstetrics

Applying 20 sprays (equivalent to 200 mg) is recommended.

Bear in mind that the maximum 24-hour dose for an adult weighing 70 kg is 200 mg (corresponding to 20 applications with the dosing valve). No more than 20 applications should be administered for adult patients. If dosed according to the weight of the patient, the dose must not exceed 3 mg/kg of body weight per day.

Special populations

Weakened or elderly patients
They may be more sensitive to the standard dose, so it is recommended to reduce the dose in this group of patients.

Patients with impaired cardiovascular function
In patients with cardiovascular disorders and cardiovascular insufficiency, it is recommended to reduce the dose, taking into account that the volume of distribution is low in such patients.

Patients with impaired renal function
In patients with nephritic syndrome, it is recommended to reduce the dose, taking into account the low capacity of plasma proteins to bind to lidocaine and its metabolites.

Patients with impaired liver function
In patients with liver problems, it is recommended to reduce the dose, taking into account that it is metabolised in the liver and there is a greater likelihood of occurrence of adverse reactions.

Patients with epilepsy
In patients who suffer from epilepsy, treated over a long period of time with phenytoin or barbiturates, it is recommended to adjust the dose.

Paediatric population
The dose of lidocaine in children should be adjusted according to the nature of the procedure and the patient's characteristics. In children over 6 years of age, the maximum dose shall be calculated according to body weight, using the dose of 3 mg/kg of body weight per day as the maximum recommended daily dose.
The use of Xilonibsa Spray 10% in children under 6 years of age is not recommended (see section 4.4).

Method of administration

Cutaneous use.

4.3 Contraindications

- Hypersensitivity to lidocaine, amide-type anaesthetics or any of the excipients.

4.4 Special warnings and precautions for use

Lidocaine should be used with caution in weakened and elderly individuals.

Lidocaine should be used with caution in patients with epilepsy, hypovolaemia, atrioventricular block or other circulatory disorders, bradycardia or impaired respiratory function. Lidocaine is

metabolised in the liver and should be administered with caution in patients with impaired liver function. The plasma half-life of lidocaine may be extended under conditions that reduce hepatic blood flow, such as cardiac and circulatory insufficiency. In addition, lidocaine metabolites may accumulate in patients with renal impairment.

Avoid administering excessive doses, and avoid applying the drug to infected or inflamed tissues, as lidocaine absorption is very quick in these cases, which could lead to adverse reactions of a systemic nature. In addition, it should be noted that anaesthetic absorption is very quick in the trachea and bronchial tree, which could lead to systemic adverse reactions.

After any oropharyngeal anaesthesia application, the ingestion of solid or liquid food must be avoided for at least two hours to avoid false routing of the alimentary bolus, as well as lingual lesions due to bites.

Avoid lidocaine contact with the eyes. In case of eye contact, if necessary, remove contact lenses from the individual. Rinse immediately and flush with water for 15 minutes, keeping eyelids apart. Do not let water flow towards the unaffected eye. Immediately undergo further care under an ophthalmologist.

Patients treated with class III anti-arrhythmic drugs (e.g. amiodarone) should be closely monitored. Monitoring via electrocardiogram (ECG) should be considered, as cardiac effects may be additive.

Paediatric population
The use of Xilonibsa 10 mg/pulse is not recommended in children under 6 years of age due to the risk of very rapid absorption of the anaesthetic and the risk of laryngospasm in newborns.
Lidocaine should be used with caution in children over 6 years of age, never exceeding the maximum recommended dose.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Drugs that affect the use of lidocaine
The antagonists drugs of the ß-adrenergic receptors (propranolol) and H_2 antagonists (cimetidine) reduce the hepatic clearance of lidocaine. Propranolol-induced reduction seems to be mainly due to a direct inhibition of lidocaine metabolism; cimetidine-induced reduction is due to a reduction in liver metabolism of lidocaine and a decrease in hepatic blood flow. Although the clinical relevance of these interactions has not been established, it is recommended to reduce the dose of lidocaine when administered concomitantly with ß-blockers and H_2 receptor antagonists, especially when lidocaine is used at high doses repeatedly.

The use of halothane reduces hepatic blood flow, leading to a reduction in lidocaine clearance.

The use of phenytoin and other enzyme inducers in long-term treatments may make it necessary to increase the dose of lidocaine as a result of an enhanced liver metabolic effect.

Antiretroviral drugs used in AIDS treatment (atazanavir, darunavir) increase plasma concentrations of lidocaine.

Hypokalaemia caused by acetazolamide, loop diuretics and thiazides antagonize the effect of lidocaine.

Drugs affected by the use of lidocaine
Lidocaine may enhance the effect of neuromuscular blockers. High doses of lidocaine may reduce the release of acetylcholine and act directly on the muscle membrane.

Specific interaction studies on the interaction between lidocaine/prilocaine and class III anti-arrhythmic drugs (e.g. amiodarone) have not been conducted; therefore, caution is advised (see also section 4.4).

Lidocaine should be used with caution in patients who receive other local anaesthetics or amide-type drugs, as the toxic effects are additive.
The simultaneous administration of lidocaine and anti-psychotic drugs that extend the QT interval increases the risk of ventricular arrhythmias.

4.6 Fertility, pregnancy and lactation

Pregnancy

Using Xilonibsa 10 mg/pulse during pregnancy is not recommended.

Lidocaine crosses the placental barrier. Data in a limited number of pregnant women did not show evidence of congenital anomalies.

The use of Xilonibsa 10 mg/pulse during pregnancy shall be reserved exclusively for those cases in which the potential benefit justifies possible risks to the foetus.

Breast-feeding

Lidocaine is excreted in breast milk, but at the therapeutic doses of Xilonibsa 10 mg/pulse, effects on nursing newborns/infants are not expected.

Fertility

Although there are no systematic studies in humans on the influence of lidocaine on fertility, since its introduction to the market many years ago, there have been no unfavourable effects reported on fertility to date.

4.7 Effects on ability to drive and use machines

Xilonibsa 10 mg/pulse has a minor influence on the 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 drug, the doctor 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.

Typically, a single application of lidocaine does not cause adverse effects of a systemic nature. However, lidocaine may cause light-headedness, sedation, blurred vision and dizziness. If after the application of lidocaine, any of these adverse effects arises, the patient must wait until these symptoms cease before driving or using machinery.

4.8 Undesirable effects

Xilonibsa 10 mg/pulse may cause local irritation (coughing, sneezing) at the time of the application or immediately after.

The route of administration of the product, with external application on the skin or mucous membranes, excludes the risk of inadvertent intravascular administration.

Adverse reactions by group
Other adverse reactions that may occur with the use of lidocaine are:

FREQUENCY	DISORDERS	EFFECTS
Rare (≥1/10,000 to <1/1000)	Cardiac disorders	Hypotension, arrhythmias, bradycardia, cardiac arrest.
	Nervous system disorders	Metallic taste, tinnitus, felt faint, nausea, vomiting, anxiety, tremors, nystagmus, headaches, increased respiratory rhythm. Paraesthesia (sensory loss accompanied by a burning sensation) of the lip and/or tongue. Unconsciousness and convulsions, 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 eruption, erythema, pruritus, oedema of the tongue, mouth, lips or throat and, in the most severe cases, anaphylactic shock.

Paediatric population
Children are more prone than adults to the adverse effects of local anaesthetics such as lidocaine.

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: www.notificaram.es

4.9 Overdose

As with other local anaesthetics, excessive dosing, or rapid absorption, particularly through the trachea and bronchial tree, which can simulate a slow intravenous injection, may lead to systemic reactions that can affect the CNS and cardiovascular system. In these cases, treatment should consist of monitoring vital signs, and if seizures occur, administering short-acting barbiturates (for example, thiopental) or benzodiazepines (diazepam) intravenously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetics - amides - lidocaine;
ATC code: N01BB02.

Mechanism of action
As with all local anaesthetics, lidocaine blocks the transmission of nervous impulse, preventing the entry of Na^+ ions through the nerve membrane.

5.2 Pharmacokinetic properties

Absorption
Lidocaine is rapidly absorbed from the gastrointestinal tract, mucous membranes, and damaged skin, while lidocaine absorption through intact skin is low.

After a topical application of Xilonibsa 10 mg/pulse onto the mucous membranes, the analgesic effect begins between 1 and 3 minutes after application and lasts approximately 15 minutes.

Distribution
After an intravenous infusion, lidocaine disseminates widely and quickly through highly perfused tissues, subsequently redistributing in muscle and adipose tissue. Lidocaine binds to plasma proteins, including α-1-acid glycoprotein. The extent of binding is variable and approximately of 66%. The binding of lidocaine to plasma proteins depends in part on the concentrations of lidocaine and α-1-acid glycoprotein. For this reason, any change in the concentration of α-1-acid glycoprotein may significantly affect the plasma concentrations of lidocaine.

Lidocaine crosses the placenta and the blood-brain barrier, and passes into breast milk.

Metabolism
Lidocaine is metabolised widely in the liver and any alteration in liver function or hepatic blood flow may significantly affect its pharmacokinetics and the dosing requirement. First-pass metabolism is extensive. Approximately 90% of the lidocaine administered is transformed into monoethylglycinexylidine and glycinexylidine. Both metabolites may contribute to the therapeutic and toxic effects of lidocaine. The half-lives of these metabolites are greater than that of lidocaine.

Elimination
Plasma concentrations of lidocaine decline rapidly after an intravenous infusion. The elimination half-life is 1 to 2 hours, though it may be longer if infusions are administered for more than 24 hours or if hepatic blood flow is decreased.

The metabolites are excreted in the urine, with less than 10% excreted as lidocaine. Lidocaine clearance is reduced in patients with cardiovascular insufficiency, viral or chronic hepatitis, and alcohol-related liver diseases. Drugs that alter hepatic blood flow or induce the enzymatic metabolism of lidocaine may affect its clearance. In addition, lidocaine clearance may be affected when kidney damage exists, as this could result in an accumulation of metabolites.

5.3 Preclinical safety data

Local tolerance
Local tolerance studies in cats with the current formulation of Xilonibsa 10mg/pulse showed clinical signs of irritation in the respiratory tract (coughing, sneezing), which appeared at the time of administration or immediately after.

Reproduction toxicology
For the study of the effects of lidocaine on fertility, rat and rabbit models have been used.
In the rat model, the administration of 30 mg/kg (180 mg/m^2 body surface) on the reproductive organ did not produce alterations to fertilisation capacity or fertility.
In the rabbit model, there was no evidence of foetal damage at doses of 5 mg/kg (60 mg/m^2 body surface). At doses much higher than 25 mg/kg (300 mg/m^2), signs of toxicity appeared in the mother as well as signs of delayed foetal development, in the form of a non-significant (7%) reduction in weight and an increase in minor skeletal development defects and skull, sternum and phalanges ossification abnormalities.

The use of topical lidocaine in spray format is not contraindicated during childbirth.

Mutagenesis, genotoxicity and carcinogenesis
The mutagenic potential of lidocaine has been assessed using the Ames test on Salmonella, "in vitro" trials on chromosomal aberrations in human lymphocytes and "in vivo" estimations of the effects using the rat micronucleus test. No mutagenic effects were observed from the results of all of these.

In research on the genotoxic effects of lidocaine administered topically, no alterations appeared. However, one of the metabolites, 2,6-xylidine has demonstrated potential uterine genotoxicity under "in vitro" conditions.

In a study on the carcinogenic effects on rats exposed to the metabolite 2,6-xylidine in the uterus over a long period and at very high doses, tumours in the nasal cavity, liver and subcutaneous tissue did appear. The clinical relevance of this effect of the lidocaine metabolite, after its intermittent use as a local anaesthetic, has not been established.

There are no animal studies that have evaluated the carcinogenic potential of lidocaine administered as a spray, nor is there evidence of foetal damage from the subcutaneous administration of lidocaine at doses of 50 mg/kg (300 mg/m^2 body surface).

In conclusion, there are no properly formalised studies on the effects of lidocaine on pregnant women. Given that studies on the effects on reproduction in animals are not always predictive of the response in humans, lidocaine should be used in pregnancy only when clearly needed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96%, menthol, saccharin, macrogol 400, fragance of banana and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original package in order to protect it from light.

6.5 Nature and contents of container

Xilonibsa 10 mg/pulse comes in a 50 mL bottle. Each bottle contains a dosing valve that provides the dose of 10 mg of lidocaine in each pulse.

6.6 Special precautions for disposal and other handling

No special requirements.

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

Inibsa Dental, S.L.U.
Ctra. Sabadell a Granollers, km 14.5
08185 Lliçà de Vall
e-mail: info_medica@inibsa.com

8. MARKETING AUTHORISATION NUMBER(S)

56741

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

18/November/1987

10. DATE OF REVISION OF THE TEXT

May, 2016