1. NAME OF THE MEDICINAL PRODUCT

ARTINIBSA 40 mg/ml + 0,005 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains:
- Articaine hydrochloride 40.00 mg
- Epinephrine (tartrate) 0.005 mg
- Sodium chloride 1.00 mg
- Sodium metabisulfite 0.50 mg

One cartridge (1.8 ml) contains:
- Articaine hydrochloride 72.00 mg
- Epinephrine (tartrate) 0.009 mg
- Sodium chloride 1.8 mg
- Sodium metabisulfite 0.90 mg

Each 1.8 ml cartridge contains: 0.71 mg of sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is a clear, non-opalescent, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARTINIBSA 40 mg/ml + 0,005 mg/ml is indicated in adults and children of 4 years of age or older for local anaesthesia (by infiltration and nerve block) in dentistry during minor procedures.

4.2 Posology and method of administration

Posology:

The smallest possible volume of solution which will lead to effective anaesthesia should be used.

For extraction of maxillary teeth, 1.8 ml of ARTINIBSA 40 mg/ml + 0,005 mg/ml per tooth is sufficient in most cases; painful palatal injections can thus be avoided.

In the case of successive extractions of neighbouring teeth, it is often possible to reduce the injection volume.

If a cut or suture is required in the palate, a palatal injection of approximately 0.1 ml per puncture is indicated.

In the case of simple mandibular premolar extractions, infiltration anaesthesia of 1.8 ml of ARTINIBSA 40 mg/ml + 0,005 mg/ml per tooth is sufficient in most cases; in some cases a buccal reinjection of 1 to 1.8 ml is required. An injection into the mandibular foramen may be indicated in rare cases.
Vestibular injections of 0.5 - 1.8 ml of ARTINIBSA 40 mg/ml + 0,005 mg/ml per tooth enable cavity and coronal pulp preparations.

Nerve block anaesthesia should be used in the treatment of mandibular molar teeth.

In surgical procedures, ARTINIBSA 40 mg/ml + 0,005 mg/ml should be dosed individually depending on patient-related factors and the type and duration of the intervention.

Paediatric population:
Generally, a dose of 0.25 - 1 ml is sufficient for children weighing between 20 - 30 kg. Children weighing between 30 - 45 kg need 0.5 - 2 ml.

ARTINIBSA 40 mg/ml + 0,005 mg/ml should not be used in children under 4 years of age.

Dosing in elderly patients and in patients with underlying diseases:
In elderly patients increased plasma levels of ARTINIBSA 40 mg/ml + 0,005 mg/ml can occur, due to diminished metabolic processes and a smaller volume of distribution. The risk of accumulation of ARTINIBSA 40 mg/ml + 0,005 mg/ml is increased particularly after repeated application (for example, reinjection). A similar effect is observed in weakened patients or those with severely diminished renal or hepatic function (see also section 4.4 "Special warnings and precautions for use"). Therefore, the lowest possible dose range is recommended in all such cases (the minimum amount to achieve a sufficiently deep anaesthetic effect).

The dose must also be reduced in patients with certain underlying diseases (angina pectoris, arteriosclerosis) (see also section 4.4 "Special warnings and precautions for use").

Maximum recommended dose:

Adults:
The maximum dose for healthy adults is 7 mg/kg of body weight of articaine (500 mg for a patient weighing 70 kg), equivalent to 12.5 ml of ARTINIBSA 40 mg/ml + 0,005 mg/ml. The maximum dose represents 0.175 ml of solution per kg of body weight.

Children:
The amount to be injected should be determined by the age and weight of the child and the scale of the operation. The equivalent of 7 mg of articaine (0.175 ml of ARTINIBSA 40 mg/ml + 0,005 mg/ml) per kg of body weight should not be exceeded.

ARTINIBSA 4% with Epinephrine 1:100,000 can also be used and may be more appropriate for longer procedures and when there is risk of significant bleeding in the operative field (see section 5.1 "Pharmacodynamic properties" for more information on the duration of analgesia).

Method of administration:
Local injection in the oral mucosa.
ONLY FOR USE IN DENTAL ANAESTHESIA

To avoid intravascular injection, aspiration control in at least two planes (rotation of the needle by 180º) must always be carried out, although a negative aspiration result does not safely rule out an unintentional and inadvertent intravascular injection.

The injection rate should not exceed 0.5 ml in 15 seconds, i.e., 1 cartridge/minute.

Major systemic reactions as a result of accidental intravascular injection can be avoided in most cases by the following injection technique: after aspiration, slow injection of 0.1-0.2 ml and slow application of the remainder no sooner than 20-30 seconds later.
For single use only Previously opened cartridges must not be used in other patients. Any unused solution must be disposed of.

4.3. Contraindications

Hypersensitivity to articaine hydrochloride, epinephrine or any of the excipients included in section 6.1.

Due to the local anaesthetic component articaine, ARTINIBSA 40 mg/ml + 0.005 mg/ml must not be used in patients with:
- A known allergy or hypersensitivity to amide-type local anaesthetics.
- A serious deterioration of cardiac impulse initiation and of the heart conduction system (for example, grade II or IIIAV block, pronounced bradycardia).
- Acute decompensated heart failure (acute congestive heart failure).
- Severe hypotension.
- Known cholinesterase activity deficiency
- Haemorrhagic diathesis, particularly with nerve block anaesthesia.
- Do not inject into inflamed areas

Due to the content of adrenaline as a vasoconstrictor component, ARTINIBSA 40 mg/ml + 0.005 mg/ml must not be used in patients with:
- Heart diseases such as:
  - Unstable angina pectoris.
  - Recent myocardial infarction.
  - Recent coronary artery bypass surgery.
  - Refractory arrhythmias and paroxysmal tachycardia or high-frequency, continuous arrhythmia.
  - Untreated or uncontrolled severe hypertension.
  - Untreated or uncontrolled congestive heart failure.
  Concomitant treatment with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants (see section 4.5 "Interactions").

Due to the content of sulphite as excipient, the use of ARTINIBSA 40 mg/ml + 0.005 mg/ml is not permitted in the case of:
- Allergy or hypersensitivity to sulphite.
- Severe bronchial asthma.

In these persons, ARTINIBSA 40 mg/ml + 0.005 mg/ml may trigger acute allergic reactions with anaphylactic symptoms, such as bronchospasm.

4.4 Special warnings and precautions for use

Special warnings

ARTINIBSA 40 mg/ml + 0.005 mg/ml must be used with special caution in the case of:
Severe impairment of the renal function.
Angina pectoris (see section 4.2 "Posology and method of administration" and 4.3 "Contraindications").
Arteriosclerosis
Considerably impaired blood coagulation (see section 4.5 "Interactions").
Thyrotoxicosis.
Narrow-angle glaucoma.
Diabetes mellitus.
Lung diseases - particularly allergic asthma.
Phaeochromocytoma.
Accidental injections may be associated with convulsions followed by central nervous system failure or cardiopulmonary arrest. Resuscitation equipment, oxygen and other resuscitative drugs must be available for immediate use.

Since amide-type local anaesthetics are also metabolised by the liver, ARTINIBSA 40 mg/ml + 0.005 mg/ml should be used with caution in patients with liver diseases. Patients with severe liver diseases are at greater risk of developing toxic plasma concentrations.

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.

The product should be administered with caution in patients with a history of epilepsy.

It must be taken into account that during treatment with blood coagulation inhibitors (for example, heparin or acetylsalicylic acid), an inadvertent vasopuncture on administering the local anaesthetic may cause severe haemorrhage. In general, these inhibitors increase the overall risk of bleeding. (See section 4.5 “Interactions”).

Inadvertent intravascular injection should be avoided (see section 4.2 "Posology and method of administration”).

With regard to oral cavity or crown preparations, when examining an open pulp, the lower blood flow in the pulp tissue due to the adrenaline content, and the risk it entails, should be considered.

**Precautions for use**

The following drugs/therapies should be available every time a local anaesthetic is used:

- Anticonvulsant medicines (benzodiazepines or barbiturates), muscle relaxants, atropine and vasopressors or adrenaline for a severe allergic or anaphylactic reaction.
- Resuscitation equipment (especially an oxygen supply) that can be used for artificial ventilation if required.
- Careful and constant monitoring of cardiovascular and respiratory (adequate ventilation) vital signs, and the state of consciousness of the patient should be monitored after each local anaesthetic injection. Restlessness, anxiety, tinnitus, vertigo, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity (see section 4.9 "Overdose”).

Although age-dependent adjustments are not required, it is advisable to take particular care when giving an injection to elderly patients and children.

**Patients taking phenothiazines**

Phenothiazines can reduce or reverse the pressor effect of adrenaline. Concurrent use of these agents should be avoided. In situations where concurrent therapy is necessary, careful monitoring of the patient is essential.

**Patients taking non-selective beta-blockers**

The concomitant administration of non-cardioselective -blockers may lead to an increase in blood pressure due to adrenaline (see section 4.5 "Interactions").

This medicinal product contains sodium metabisulfite, which can cause allergic reactions (possibly delayed) and, on occasions, bronchospasm.

This medicinal product also contains 0.71 mg of sodium per cartridge. This may be harmful for patients on low-sodium diets.
Paediatric population

Carers of small children must be informed that due to prolonged soft tissue insensitivity there is a risk that children may accidentally bite themselves.

4.5 Interaction with other medicinal products and other forms of interaction

The sympathomimetic effect of adrenaline can be intensified by the simultaneous intake of MAO inhibitors or tricyclic antidepressants (see section 4.3 "Contraindications").

Adrenaline can inhibit the release of insulin in the pancreas and therefore diminish the effect of oral antidiabetics.

Phenothiazines can reduce the pressor effect of adrenaline (see section 4.4 "Special warnings and precautions for use").

Concomitant administration of antiarrhythmic drugs (e.g. quinidine) can increase the potential cardiac effects of local anaesthetics.

The simultaneous administration of non-cardioselective β-blockers can lead to an increase in blood pressure due to the adrenaline component of ARTINIBSA 40 mg/ml + 0,005 mg/ml.

Certain inhalational anaesthetics, such as halothane, can sensitise the heart to catecholamines and, therefore, induce arrhythmias following administration of ARTINIBSA 40 mg/ml + 0,005 mg/ml.

Haemorrhaging tendency is increased during treatment with blood coagulation inhibitors (see also section 4.4 "Special warnings and precautions for use").

4.6 Fertility, pregnancy and lactation

No clinical experience of use in pregnant and lactating women is available.

Pregnancy
Safe use of local anaesthetic during pregnancy has not been established with respect to adverse effects on foetal development: ARTINIBSA 40 mg/ml + 0,005 mg/ml should only be administered during pregnancy when it is considered that the benefits outweigh the risks.

Breast-feeding
The excretion of articaine and its metabolites in human milk is unknown. However, preclinical safety data suggest that the concentration of articaine in human milk does not reach clinically relevant concentrations. Therefore, lactating mothers should discard the first milk following anaesthesia with articaine.

4.7. Effects on ability to drive and use machines

It has been observed that local anaesthesia with articaine does not perceivably hinder normal ability to drive a vehicle. The dentist has to decide whether the patient is capable of returning to operate a machine or drive a vehicle. The possible apprehension and stress resulting from the intervention could affect the patient’s ability to function as usual.

4.8 Undesirable effects

The following adverse reactions can occur as a result of the local anaesthetic component articaine:

Cardiovascular disorders:
Rare (≥1/10,000 to < 1/1,000)
Decreased heart rate, hypotension.
Drop in blood pressure, cardiac impulse conduction disorders, bradycardia, asystole, cardiovascular arrest.

**Nervous system disorders:**
*Rare (≥1/10,000 to < 1/1,000)*
Metallic taste, tinnitus, vertigo, nausea, vomiting, restlessness, anxiety, yawning, agitation, nervousness, nystagmus, logorrhea, headache, increased respiratory rate.
Paresthesia (loss of sensitivity, burning, tingling) of the lips, tongue or both.
When these signs appear, rapid corrective measures are required to prevent possible worsening.
Drowsiness, confusion, tremors, muscle spasms, tonic-clonic seizure, coma and respiratory paralysis.

**Respiratory disorders:**
*Rare (≥1/10,000 to < 1/1,000)*
Tachypnea, after bradypnea, which can lead to apnoea.

**Allergic reactions:**
*Very rare (<1/10,000), unknown frequency (cannot be estimated based on the data available)*
Manifestations of hypersensitivity to articaine such as: rash, pruritus, edematous pruritus and erythema, as well as nausea, diarrhoea, wheezing or anaphylaxis. Cross-reactivity to articaine has been reported in a patient with delayed hypersensitivity to prilocaine.
In general, patients who have demonstrated hypersensitivity to articaine or other amides should receive an ester local anaesthetic for subsequent procedures.
Administration of large doses of articaine may produce methaemoglobinemia in patients with subclinical methaemoglobinemia.

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

**Cardiovascular disorders:**
*Rare (≥1/10,000 to < 1/1,000)*
Hot sensation, sweating, accelerated pulse, migraine headaches, increased blood pressure, angina pectoris disorders, palpitations, tachyarrhythmias and cardiac arrest; oedematous swelling of the thyroid should also not be excluded.

The following adverse reactions can occur in isolated cases as a result of the content of sulfite as excipient:
Particularly in bronchial asthmatics, allergic or hypersensitivity reactions which are manifested as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of the consciousness or shock may occur.

The following adverse reactions can occur as a result of the articaine and adrenaline content

**Nervous system disorders:**
Two weeks after use of articaine/epinephrine, the appearance of facial nerve paralysis has been reported, persisting up to 6 months after the event.

The simultaneous occurrence of several complications and adverse reactions may interfere with the clinical picture.

4.9 Overdose

Adverse reactions (showing an abnormally high concentration of local anaesthetic in the blood), may appear either immediately, as a result of accidental intravascular injection or abnormal absorption conditions, for example in inflamed or intensely vascularised tissue, or later, caused by true overdose following injection of an excessive amount of the anaesthetic solution, manifesting itself as central nervous and/or vascular symptoms.
Symptoms caused by the local anaesthetic component articaine:
Mild central nervous symptoms include metallic taste, tinnitus, vertigo, nausea, vomiting, restlessness, anxiety, initial increase in respiratory rate.
More serious symptoms are: drowsiness, confusion, tremors, sudden muscle spasms, tonic-clonic seizures, coma and respiratory paralysis.
Severe cardiovascular episodes may occur in the form of a drop in blood pressure, cardiac impulse conduction disorders, bradycardia, cardiovascular arrest.

Symptoms caused by adrenaline as vasoconstrictor:
Cardiovascular symptoms such as hot sensation, sweating, accelerated heart rate, headaches, increased blood pressure, angina pectoris disorders, tachycardia, tachyarrhythmias and cardiovascular arrest.

The simultaneous occurrence of several complications and adverse reactions may interfere with the clinical picture.

Therapy

Basic general measures:
In the event of an adverse reaction, application of the local anaesthetic must be interrupted.
Diagnosis (respiration, circulation, consciousness), maintenance/restoration of the respiratory and circulatory vital signs, administration of oxygen, intravenous access.

Special measures:
Hypertension: Raise the upper part of the body, sublingual administration of nifedipine if necessary.
Convulsions: Protect the patient from concomitant damage, administer benzodiazepines (for example iv diazepam) if necessary.
Hypotension: Horizontal position, intravascular infusion of a whole electrolyte solution, vasopressor (for example iv ethilefrine), if necessary.
Bradycardia: Atropine i.v. Anaphylactic shock: Contact an emergency doctor, in the meantime place the patient in the shock position, give generous infusion of a complete electrolyte solution, iv adrenaline and/or iv cortisone if necessary.
Cardiovascular arrest: Immediate cardiopulmonary resuscitation, contact an emergency doctor.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Local anaesthetics, ATC code: N01B B58.
ARTINIBSA 40 mg/ml + 0,005 mg/ml contains articaine, which is an amide-type local anaesthetic for use in dentistry and produces a reversible inhibition of the irritability of vegetative, sensory and motor nerve fibres. It is thought that articaine acts by blocking the voltage dependent Na+ channels on the nerve fibre membrane.

It is characterized by a rapid onset of the anaesthetic effect - latency period of 1-3 minutes- intense analgesic effect and good local tolerability. The duration of the effect of ARTINIBSA 40 mg/ml + 0,005 mg/ml in pulpal anaesthesia is at least 45 minutes, 120 - 240 minutes in soft tissue anaesthesia.

Adrenaline causes local vasoconstriction, delaying the absorption of articaine. The result is a greater concentration of local anaesthetic 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
ARTINIBSA 40 mg/ml + 0.005 mg/ml is rapidly and almost completely absorbed. The peak plasma concentration of articaine, after an intraoral injection, is reached after about 10-15 minutes. The distribution volume is 1.67 l/kg, the elimination half-life is approximately 20 minutes and the Cmax value is between 400 and 2100 μg/l.

Up to 95% of articaine is bound to plasma proteins.

Articaine is rapidly hydrolyzed by plasma cholinesterases to its primary metabolite, articainic acid, which is subsequently metabolised to articainic acid glucoronide. Articaine and its metabolites are eliminated primarily in the urine.

Adrenaline is catabolised rapidly in the liver and other tissues. The metabolites are excreted via the kidneys.

5.3. Preclinical safety data
The toxic symptoms of articaine were independent of the administration route (iv, im, sc or oral) or the animal species, and included tremors, vertigo and tonic-clonic seizures. The duration and intensity of these symptoms were dose-dependent; at high doses (single dose of approximately 50-100 mg/kg) convulsions led to death and at low doses, all symptoms disappeared in 5 - 10 minutes. Lethal doses of articaine produced a pulmonary oedema in mice (iv and sc) and in rats (iv, im, and sc and oral).

In rats, rabbits and cats, it showed no effect on embryo or foetal development in the uterus and there were no organ or skeletal abnormalities. Young being weaned by mothers who received a high dose (80 mg/kg/day) of articaine, which led to maternal toxicity, showed delayed eye opening and were more likely to fail the passive avoidance test.

Adrenaline was potentially teratogenic in albino rats at doses 25 times the human therapeutic dose.

After iv administration, the presence of 1:200,000 adrenaline increased articaine toxicity in rats and mice but not in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium metabisulfite (E-223)
Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injectable preparations

6.2. Incompatibilities
Not applicable

6.3. Shelf Life
2 years

6.4 Special precautions for storage
Keep in the original package to protect it from light.

6.5 Nature and contents of container
Type I neutral colourless glass cartridges.
Bromobutyl rubber discs and stopper.

The aluminum capsule is made with a bromobutyl double-disc.

Pack containing 1 x 1.8 ml cartridge with flat plunger for self-aspiration.
Pack containing 1 x 1.8 ml cartridge with cavity plunger for manual aspiration.
Pack containing 100 x 1.8 ml cartridge with flat plunger for self-aspiration.
Pack containing 100 x 1.8 ml cartridge with cavity plunger for manual aspiration.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product must be visually inspected to detect particles, discoloration or damage to the container prior to administration. The product must not be used if these defects are detected.

This product is for single use only. Any amount of unused product must be discarded immediately after use.

The disposal of unused product and any material that has been in contact with it should be carried out in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

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