PRIMACAINE™

A certain anesthesia

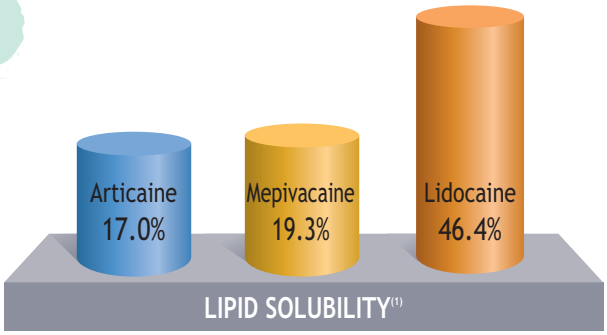
PIERRE ROLLAND ACTEON

PRIMA

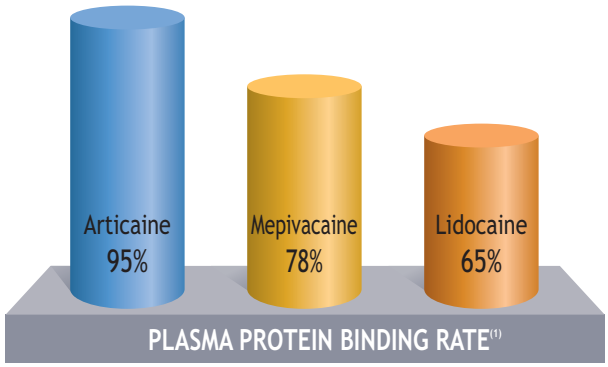
Injectable articaine hydrochlorid

Why Primacaine is the preferred anesthetic?

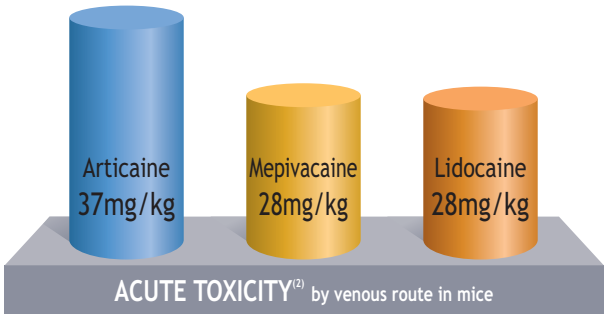
In Europe, Articaine has proven its qualities as local anesthetic in dental practice for 25 years. Articaine belongs to the amide-type family but differs from lidocaine and derivates by a different chemical structure which makes it superior.



Lower toxicity - Safer: Articaine is less liposoluble compared to Lidocaine or Mepivacaine based solutions.Thus the toxicity of Articaine is inferior, particularly its toxicity toward the Central Nervous System.



Higher efficacy - Reliable: Articaine, as other anesthetics, acts by binding to specific receptors. The ability to react with these specific receptors is directly correlated with the Plasma Protein Binding rate. Articaine with the highest PPB is the anesthetic which gives the deepest and longest-lasting anesthesia. Articaine has proven to be 1.5 times more potent compared with lidocaine.



Lower toxicity: The acute toxicity is the lowest; this greater safety is the direct consequence of its lower liposolubility and its higher Protein Binding capacity. In addition, if repeated administrations become necessary during a difficult procedure, the risk of accumulation is lower because of its faster elimination (Half-life: Articaine 20 min versus Lidocaine: 45 min). The maximum recommended dose is 7mg/kg in adults. As a cartridge contains 68 mg, the margin of safety is wide.

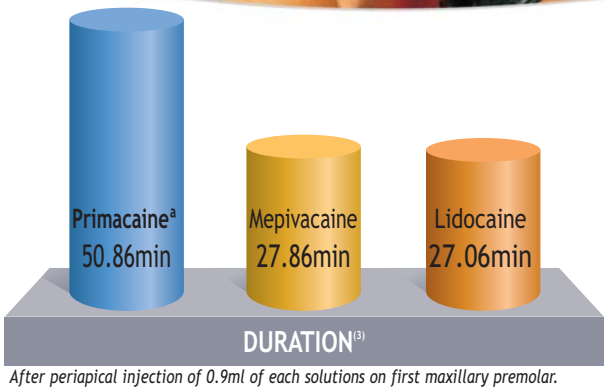
(1) *From Borchard U. Pharmacologie des articain und der vasokonstriktorshen zusätze in: Zahnärlihe lokalanästhesie heute - zwei jahrzehnte articain.(Aktuelle Wissen hoescht, 1990) Conseiller Ch.Guesnon P., Leoni J.Anésthesiques locaux.In Giroud P., Marthe G. Pharmacologie clinique. Bases de la thérapeutique.(Seconde édition, Paris, Expansion Scientifique Française, 1988).*

(2) *Muschaweck R,Rippel R. : Ein neues Lokalanästhetikum (articain) aus der Thiophenreihe-Prakt Anästh 1974;9:135-146.*

(3) *Journal of dental research 77 (5) 1998 ; 472.1266 W-J Pertot, E.Atlan, J. Dejou, J-P Proust Faculté d'odontologie, laboratoire IMEB, Marseille,France. A comparison between the efficiency of four anaesthetic solutions (formulated with Adrenaline 1/100 000).*

CAINE™

solution for dental anesthesia



After periapical injection of 0.9ml of each solutions on first maxillary premolar.

Primacaine™ adrenaline 1/100 000 - Pierre Rolland - Mérignac - France
Lidocaine 2% with adrenaline 1/100 000
Mepivacaine 2% with adrenaline 1/100 000

The duration of anesthesia is markedly superior: "Lidocaine or Mepivacaine with epinephrine solutions gave similar results, indicating that these 2 molecules have very close potencies. The articaine with epinephrine solution gave the longest duration of action.The difference between the tested solutions is more probably due to the degree of protein binding of the tested solutions" PRIMACAINE proves to be more effective.

Anesthesia performed with PRIMACAINE is deeper and longer-lasting. The blockade of the nerve endings is faster. These clinical results are reached eventhough PRIMACAINE has proven its safety compared with other amide-type anesthetics. PRIMACAINE is preferred: by respecting the techniques of anesthesia, with low quantities of PRIMACAINE, the results are exceptional.

PRIMACAINE *adrenaline 1/100 000* & PRIMACAINE *adrenaline 1/200 000*

1 - DENOMINATION

PRIMACAINE ADRENALINE 1/100 000, injectable solution for dental use.

2 - QUALITATIVE AND QUANTITATIVE COMPOSITION

Articaïne	60.277 mg in the form of articaine hydrochloride
Adrenaline	0.017 mg in the form of adrenaline tartrate

for one cartridge of 1.7 ml.
For the complete list of excipients, see 6.1

3 - PHARMACEUTICAL FORM

Injectable solution for dental use.

4 - CLINICAL DATA

4.1 Therapeutic indications

Local or loco-regional anaesthesia in odonto-stomatological practice. This presentation is particularly adapted when procedures require a high ischemia.

8 - FRENCH REGISTRATION ID NUMBER

3400956469659: 1.7 ml in cartridge (glass) with a stopper (bromobutyle). Box of 50.

9 - DATE OF FIRST AUTHORIZATION/OF RENEWAL OF AUTHORIZATION IN FRANCE

24 December 2002/24 December 2007

10 - DATE OF UPDATING OF THE TEXT

19 April 2010

1 - DENOMINATION

PRIMACAINE ADRENALINE 1/200 000, injectable solution for dental use.

2 - QUALITATIVE AND QUANTITATIVE COMPOSITION

Articaïne	60.277 mg in the form of articaine hydrochloride
Adrenaline	0.0085 mg in the form of adrenaline tartrate

for one cartridge of 1.7 ml.
For the complete list of excipients, see 6.1

3 - PHARMACEUTICAL FORM

Injectable solution for dental use.

4 - CLINICAL DATA

4.1 Therapeutic indications

Local or loco-regional anaesthesia in odonto-stomatological practice.

8 - FRENCH REGISTRATION ID NUMBER

3400956469710: 1.7 ml in cartridge (glass) with a stopper (bromobutyle). Box of 50.

9 - DATE OF FIRST AUTHORIZATION/OF RENEWAL OF AUTHORIZATION IN FRANCE

24 December 2002/24 December 2007

10 - DATE OF UPDATING OF THE TEXT

19 April 2010

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4 - CLINICAL DATA (continuation)

4.2 Dose and mode of administration

Reserved for adult and child over 4 as this type of anaesthesia is unsuitable before this age.

Dose

Adult • The quantity to be injected must be adapted according to the extent of the procedure. • Usually, half to one cartridge for a common procedure. • Do not exceed the dose of 7 mg of articaine hydrochloride per kilogram of bodyweight.

Child (over 4) • The injected quantity depends on the child's age, weight and the type of procedure performed. • The maximal dose is 5 mg of articaine hydrochloride (0.125 ml of anaesthetic solution) per kilogram of bodyweight. • The mean dose in mg of articaine hydrochloride that can be administered in a child can be calculated as follow: Child's weight (in kilograms) x 1.33

Elderly subject • Administer half of the dose indicated for adults.

Mode of administration

LOCAL OR REGIONAL INTRA-ORAL SUBMUCOSAL INJECTION. Verify the absence of vascular effraction by repeated aspiration tests, particularly during regional anaesthesia (nerve blocks). The injection rate must not exceed 1 ml of solution per minute.

4.3 Contraindications

This medicine is CONTRAINDICATED

• in the case of hypersensitivity to local anaesthetics or to one of the constituents, and in the following situations: severe disorders of atrioventricular conduction without a pacemaker / epilepsy not controlled by treatment / porphyria.

This medicine is USUALLY UNADVISED in association with sibutramine (see 4.5).

4.4 Special warnings and precautions for use

Warnings : THIS PRODUCT CONTAINS 1/100 000 ADRENALINE (for Primacaine Adrenaline 1/100 000) AND CONTAINS 1/200 000 ADRENALINE (for Primacaine Adrenaline 1/200 000). Take the risk of local necrosis into account in hypertensive or diabetic subjects. Anaesthesiophagy risks: all kind of bites (lips, cheeks, mucous, tongue); advise patients to avoid the use of chewing gum or eating food as long as the insensitivity persists. The use of this product is not recommended in children under the age of 4 years, as this type of anaesthesia is unsuitable before this age. Avoid injection into infected and inflamed areas (decreased efficacy of the local anaesthetic). Sportsmen must be advised that this medicine contains an active substance that can cause a positive reaction on anti-doping control tests.

Precautions for use The use of this product requires imperatively and previously: • to conduct a clinical interview to determine the clinical context, concomitant treatments and the patient's past history; • to perform a test injection of 5 to 10 % of the dose in the case of a risk of allergic reaction; • to perform the injection slowly and strictly outside of the vessels, verifying by repeated aspirations; • to maintain verbal contact with the patient.

Increased surveillance is required in subjects treated with anticoagulants (surveillance of the INR).

Due to the presence of adrenaline, precautions and increased surveillance in case of: • all rhythm abnormalities, except bradycardia; • coronary insufficiency; • severe arterial hypertension.

The dose of articaine may need to be decreased in case of severe hepatocellular insufficiency, due to the mainly hepatic metabolism of amide local anaesthetics. The dose must also be decreased in case of hypoxia, hyperkalaemia or metabolic acidosis. The simultaneous administration of this anaesthetic with some products (see 4.5) requires a close monitoring of the patient's clinical and biological state.

4.5 Interactions with other drugs or other forms of interactions

Associations not recommended

Due to the presence of adrenaline:

+ **Sibutramine**: Paroxystic hypertension with possibility of rhythm abnormalities (inhibition of the adrenaline or nor-adrenaline' s entrance in the sympathetic fibre).

Associations with precautions for use

Due to the presence of adrenaline:

+ **Halogenated volatile anaesthetics**: Serious ventricular rhythm abnormalities (increase of the cardiac reactivity).

Limit the dose, for example: less than 0.1 mg of adrenaline in 10 minutes or 0.3 mg in one hour in adult.

+ **Imipraminic anti-depressors**: Paroxystic hypertension with possibility of rhythm abnormalities (inhibition of the adrenaline or nor-adrenaline' s entrance in the sympathetic fibre). Limit the dose, for example: less than 0.1 mg of adrenaline in 10 minutes or 0.3 mg in one hour in adult.

+ **Serotoninergic-noradrenergic anti-depressors** (described for minalcipran and venlafaxine): Paroxystic hypertension with possibility of rhythm abnormalities (inhibition of the adrenaline or nor-adrenaline's entrance in the sympathetic fibre). Limit the dose, for example: less than 0.1 mg of adrenaline in 10 minutes or 0.3 mg in one hour in adult.

+ **Non selective MAOI** (iproniazide): Increase of the adrenaline and nor-adrenaline's pressive action, more often moderated. Use only under strict medicinal control.

+ **"A" Selective MAOI** (moclobemide, toloxatone) by extrapolation from the non selective MAOI: Risk of increase of the pressive action. Use only under strict medicinal control.

Associations to take into account

+ **Guanethidine**: High increase of the blood pressure (hyper reactivity due to the reduction of the sympathetic tonus and/or to the inhibition of the adrenaline or nor-adrenaline's entrance in the sympathetic fibre).

4.6 Pregnancy and breastfeeding

Pregnancy The studies carried out on animals do not show any teratogenic effect. Due to the absence of teratogenic effect on animals, a malformative effect on mankind is not expected. Indeed, until today, the substances responsible of malformations on mankind have been teratogenics on animals during studies carried out on two species. In clinical practice, there are actually not enough relevant facts to estimate an eventual malformative or foetotoxic effect of the articaine when administered during pregnancy. Consequently, in the odonto-stomatological indications, articaine should only be used during pregnancy if necessary.

Breastfeeding : Like other local anaesthetics, articaine diffuses into breast milk in very small quantity; however, breastfeeding can be continued following the anaesthetic procedure.

4.7 Effects on ability to drive and use machines

This product can modify the ability to drive and use machines.

4.8 Undesirable effects

Like with all the anaesthetics used in odonto-stomatology, lipothymies can occur. This product contains sodium metabisulphite, which can involve or worsen anaphylactic reactions.

In the case of overdose or in certain predisposed patients, the following clinical signs may be observed: • on the central nervous system: nervousness, agitation, yawning, tremor, apprehension, nystagmus, logorrhoea, headache, nausea, ringing in the ears. In the presence of these warning signs, the patient must be asked to hyperventilate, and attentive surveillance is required to prevent possible deterioration with seizures followed by CNS depression. • on the respiratory system: tachypnoea, then bradypnoea, possibly leading to apnoea. • on the cardiovascular system: tachycardia, bradycardia, cardiovascular depression with arterial hypotension, possibly leading to collapse, arrhythmias (premature ventricular complexes, ventricular fibrillation), disorders of conduction (atrioventricular block). These cardiac manifestations can lead to cardiac arrest.

4.9 Overdose

Toxic reactions, witnesses of an overdose in local anaesthetic, can occur in two situations: either immediately, due to relative overdose resulting from accidental intravenous injection, or more delayed, corresponding to true overdose due to the use of an excessive quantity of anaesthetic.

Action in case of overdose : As soon as warning signs are observed, ask the patient to hyperventilate, place the patient in the supine position, when necessary. In the case of clonic seizures, oxygenation and injection of a benzodiazepine. Treatment may require intubation with assisted ventilation.

5 - PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: LOCAL ANAESTHETICS
ATC Code: N01 BB 58

The articaïne hydrochloride is a local anaesthetic with an amide function, which interrupts the nerve impulse along the nerve fibre at the injection site. The addition of adrenaline diluted at 1/100 000 (Primacaine adrenaline 1/100 000) or at 1/200 000 (Primacaine adrenaline 1/200 000) to the solution of articaine delays the passage of the articaine into the systemic circulation and maintains an active tissue concentration, allowing to obtain a little hemorrhagic operative field. The anaesthesia is achieved within 2 to 3 minutes. The duration of anaesthesia allowing the surgical procedure is about 60 minutes. It is 2 to 3 times shorter for a pulpar anaesthesia.

5.2 Pharmacokinetic properties

Injected in the buccal mucosa, the articaine blood concentration pick is obtained within 30 minutes after the injection. The elimination half-life of articaine hydrochloride is about 110 minutes. Articaine hydrochloride metabolism is mainly hepatic; 5 to 10 % of the dose are eliminated under unchanged form in the urine.

5.3 Preclinical safety data

Studies carried out on animals have shown the good tolerance of articaine. Like other amide local anaesthetics, high doses of the active substance can induce toxic reactions on the central nervous system and/or cardiovascular system (see 4.8).

6 - PHARMACEUTICAL DATA

6.1 List of excipients

Sodium chloride, sodium metabisulphite, hydrochloric acid, sodium hydroxide, water for injectable preparations.

6.2 Incompatibilities

In the absence of compatibility studies, this drug should not be mixed with other drugs.

6.3 Shelf life

Before opening: 2 years. After opening: the product must be used immediately.

6.4 Special storage precautions

Store at a temperature not exceeding + 25 °C. Store cartridges in the external packing and protected from light.

6.5 Nature and contents of external packing

1.7 ml in cartridge (colourless glass of type I) with a stopper (bromobutyle) and capsule (aluminium) with seal (bromobutyle). Box of 50.

6.6 Instructions for use, handling and disposal

Like for all cartridges, the diaphragm will be disinfected just before use. It will be carefully plugged: either with ethyl alcohol at 70 %, or with pure isopropyl alcohol at 90 % for pharmaceutical use.

The cartridges must never be plunged in any solution.

Do not mix the injectable solution with other products in the same syringe. Any opened cartridge of anaesthetic solution must not be re-used.

7 - HOLDER OF MARKETING AUTHORIZATION

LABORATOIRE PRODUITS DENTAIRES PIERRE ROLLAND
Zone Industrielle du Phare - 17 avenue Gustave Eiffel
33700 MERIGNAC CEDEX - FRANCE

CONDITIONS OF PRESCRIPTION AND DELIVERY IN FRANCE

List I.

RESERVED FOR PROFESSIONAL DENTAL USE.

Ref. : 299130 (03/11)

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